Abstract:

The invention provides a pharmaceutical product, kit or composition comprising a first active ingredient which is a selected muscarinic receptor antagonist, and a second active ingredient which is selected from a phosphodiesterase inhibitor, a modulator of chemokine receptor function, an inhibitor of kinase function, a protease inhibitor, a steroidal glucocorticoid receptor agonist, a non-steroidal glucocorticoid receptor agonist and a purinceptor antagonist, of use in the treatment of respiratory diseases such as chronic obstructive pulmonary disease and asthma.
The present invention relates to combinations of pharmaceutically active substances for use in the treatment of respiratory diseases, especially chronic obstructive pulmonary disease (COPD) and asthma.

The essential function of the lungs requires a fragile structure with enormous exposure to the environment, including pollutants, microbes, allergens, and carcinogens. Host factors, resulting from interactions of lifestyle choices and genetic composition, influence the response to this exposure. Damage or infection to the lungs can give rise to a wide range of diseases of the respiratory system (or respiratory diseases). A number of these diseases are of great public health importance. Respiratory diseases include Acute Lung Injury, Acute Respiratory Distress Syndrome (ARDS), occupational lung disease, lung cancer, tuberculosis, fibrosis, pneumoconiosis, pneumonia, emphysema, Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Among the most common of the respiratory diseases is asthma. Asthma is generally defined as an inflammatory disorder of the airways with clinical symptoms arising from intermittent airflow obstruction. It is characterised clinically by paroxysms of wheezing, dyspnea and cough. It is a chronic disabling disorder that appears to be increasing in prevalence and severity. It is estimated that 15% of children and 5% of adults in the population of developed countries suffer from asthma. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

COPD is a term which refers to a large group of lung diseases which can interfere with normal breathing. Current clinical guidelines define COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. The most important contributory source of such particles and...
gases, at least in the western world, is tobacco smoke. COPD patients have a variety of symptoms, including cough, shortness of breath, and excessive production of sputum; such symptoms arise from dysfunction of a number of cellular compartments, including neutrophils, macrophages, and epithelial cells. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased production of mucous and other changes. The patients' symptoms are cough and expectoration of sputum. Chronic bronchitis can lead to more frequent and severe respiratory infections, narrowing and plugging of the bronchi, difficult breathing and disability.

Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become enlarged. These enlarged areas trap stale air and do not effectively exchange it with fresh air. This results in difficult breathing and may result in insufficient oxygen being delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

Therapeutic agents used in the treatment of respiratory diseases include muscarinic antagonists. Muscarinic receptors are a G-protein coupled receptor (GPCR) family having five family members Mi, M2, M3, M4 and M5. Of the five muscarinic subtypes, three (Mi, M2 and M3) are known to exert physiological effects on human lung tissue. Parasympathetic nerves are the main pathway for reflex bronchoconstriction in human airways and mediate airway tone by releasing acetylcholine onto muscarinic receptors. Airway tone is increased in patients with respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), and for this reason muscarinic receptor antagonists have been developed for use in treating airway diseases. Muscarinic receptor antagonists, often called anticholinergics in clinical practice, have gained widespread acceptance as a first-line therapy for individuals with COPD, and their use has been extensively reviewed in the literature (e.g. Lee et al, Current Opinion in Pharmacology 2001,1, 223-229).
Whilst treatment with a muscarinic antagonist can yield important benefits, the efficacy of these agents is often far from satisfactory. Moreover, in view of the complexity of respiratory diseases such as asthma and COPD, it is unlikely that any one mediator can satisfactorily treat the disease alone. Hence there is a pressing medical need for new therapies against respiratory diseases such as COPD and asthma, in particular for therapies with disease modifying potential.

The present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a muscarinic antagonist selected from:

- \([2-((S)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium salt,}\]
- \([2-((R)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium salt,}\]
- \([2-((R)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-(2-phenethyloxy-ethyl)-ammonium salt,}\]
- \([2-((R)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium salt,}\]
- \([2-((R)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-[2-(3,4-dichlorobenzyloxy)-ethyl] dimethyl-ammonium salt, and}\]
- \([2-(4\text{-Chloro-benzyloxy)-ethyl}]\text{-[2-((R)\text{-Cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}] dimethyl-ammonium salt,}\]

and a second active ingredient which is selected from

- i) a phosphodiesterase inhibitor,
- ii) a modulator of chemokine receptor function,
- iii) an inhibitor of kinase function,
- iv) a protease inhibitor,
- v) a steroidal glucocorticoid receptor agonist,
- vi) a non-steroidal glucocorticoid receptor agonist, and
- vii) a purinoceptor antagonist.
A beneficial therapeutic effect may be observed in the treatment of respiratory diseases if a muscarinic antagonist according to the present invention is used in combination with a second active ingredient as specified above. The beneficial effect may be observed when the two active substances are administered simultaneously (either in a single pharmaceutical preparation or via separate preparations), or sequentially or separately via separate pharmaceutical preparations.

The pharmaceutical product of the present invention may, for example, be a pharmaceutical composition comprising the first and second active ingredients in admixture. Alternatively, the pharmaceutical product may, for example, be a kit comprising a preparation of the first active ingredient and a preparation of the second active ingredient and, optionally, instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The first active ingredient in the combination of the present invention is a muscarinic antagonist selected from:

- [2-((S)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-diethyl-(2-phenethyloxy-ethyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium salt, and
The muscarinic antagonists of the invention are selected members of a novel class of compound described in WO2007/017669 (PCT/GB2006/002956) which display high potency to the M3 receptor. The names of the muscarinic antagonists are IUPAC names generated by the Autonom 2000 plug in for IsisDraw Version 2.5, as supplied by MDL Information Systems Inc., based on the structures depicted in the examples, and stereochemistry assigned according to the Cahn-Ingold-Prelog system. For example, the name \[2-(((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl})-\text{dimethyl-(3-phenoxy-propyl})-\text{ammonium},\] was generated from the structure:

The muscarinic receptor antagonists of the present invention are ammonium salts. The salt anion may be any pharmaceutically acceptable anion of a mono or polyvalent (e.g. bivalent) acid. In an embodiment of the invention, the salt anion is selected from chloride, bromide, iodide, sulfate, benzenesulfonate, toluenesulfonate (tosylate), napadisylate (naphthalene-1,5-disulfonate), edisylate (ethane-1,2-disulfonate), isethionate (2-hydroxyethylsulfonate), phosphate, acetate, citrate, lactate, tartrate, oleic, mesylate (methanesulfonate), maleate ((Z)-3-carboxy-acrylate), fumarate, succinate (3-carboxy-propionate), malate ((S)-3-carboxy-2-hydroxy-propionate), xinafoate and p-acetamidobenzoate.

In an embodiment of the invention, the muscarinic receptor antagonist is selected from

- \[2-(((S)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl})-\text{dimethyl-(3-phenoxy-propyl})-\text{ammonium bromide},\]
- \[2-(((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl})-\text{dimethyl-(3-phenoxy-propyl})-\text{ammonium bromide},\]
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium tosylate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium maleate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium succinate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium malate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethoxy-ethyl)-ammonium bromide,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethoxy-ethyl)-ammonium napadisylate,
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium mesylate,
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium bromide,
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium napadisylate,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium bromide,
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium napadisylate,
and
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide,
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium napadisylate, and
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium mesylate.
In an embodiment of the invention, the muscarinic receptor antagonist is in the form of a bromide or napadisylate salt.

In an embodiment of the invention, the muscarinic receptor antagonist is in the form of a napadisylate salt. When the muscarinic antagonist is a napadisylate salt the cation/anion ratio may vary, and for example may be 1:1 or 2:1, or a value between 1:1 and 2:1.

In an embodiment of the invention the muscarinic antagonist is in the form of a napadisylate salt wherein the napadisylate salt cation/anion ratio is 2:1, i.e. a hemi-napadisylate. Examples of muscarinic antagonists according to this embodiment include:

- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium hemi-naphthalene-1,5-disulfonate,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium hemi-naphthalene-1,5-disulfonate,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate, and

In an embodiment of the invention, the muscarinic receptor antagonist is in the form of a bromide salt.

The second active ingredient of the present invention is selected from:

i) a phosphodiesterase inhibitor,

ii) a modulator of chemokine receptor function,

iii) an inhibitor of kinase function,

iv) a protease inhibitor,
v) a steroidal glucocorticoid receptor agonist,
vi) a non-steroidal glucocorticoid receptor agonist, and
vii) a purinoceptor antagonist.

In an embodiment of the invention the second active ingredient is a phosphodiesterase inhibitor. Examples of a phosphodiesterase inhibitor that may be used according to this embodiment include a PDE4 inhibitor such as an inhibitor of the isoform PDE4D, a PDE3 inhibitor and a PDE5 inhibitor. Examples include the compounds

(Z)-3-(3,5-dichloro-4-pyridyl)-2-[4-(2-indanyloxy-5-methoxy-2-pyridyl)propenenitrile,
N-[9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][l,4]benzodiazepin-3(R)-yl]pyridine-3-carboxamide (CI-1044),
3-(benzyloxy)-1-(4-fluorobenzyl)-N-[3-(methylsulphonyl)phenyl]-1H-indole-2-carboxamide,
(IS-exo)-5-[3-(bicyclo[2.2.1]hept-2-yloxy)-2-yl]-4-methoxyphenyl]tetrahydro-2(1H)-pyrimidinone (Atizoram),
N-(3,5,dichloro-4-pyridinyl)-2-[l-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (AWD-12-281),
β-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,3-dihydro-1,3-dioxo-2H-isooindole-2-propanamide (CDC-801),
N-[9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][l,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide (CI-1018),
cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid (Cilomilast),
8-amino-1,3-bis(cyclopropylmethyl)xanthine (Cipamfylline),
N-(2,5-dichloro-3-pyridinyl)-8-methoxy-5-quinolinecarboxamide (D-44 18),
5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-iminothiazolidin-4-one (Darbufelone), 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-1-propanone (Ibidilast),
2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzofuran-6-yl methanesulphonate (Lirimilast),
(-)-(R)-5-(4-methoxy-3-propoxyphenyl)-5-methyloxazolidin-2-one (Mesopram),
(-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6-(4-diisopropylaminocarbonylphenyl)benzo[c][1,6]naphthyridine (Pumafentrine),
3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide (Roflumilast),
the N-oxide of Roflumilast, 5,6-diethoxybenzo[b]thiophene-2-carboxylic acid (Tibenelast),
2,3,6,7-tetrahydro-2-(mesitylimino)-9, 10-dimethoxy-3-methyl-4H-pyrimido[6, 1-
aljisoquinolin-4-one (trequinsin) and
3-[[3-(cyclopentyloxy)-4-methoxyphenyl]-methyl]-N-ethyl-8-(l-methylethyl)-3H-purine-
6-amine (V-1 1294A).

In an embodiment of the invention the second active ingredient is a modulator of chemokine receptor function. Examples of a modulator of chemokine receptor function that may be used in this embodiment include a CCR3 receptor antagonist, a CCR4 receptor antagonist, a CCR5 receptor antagonist and a CCR8 receptor antagonist.

In an embodiment of the invention the second active ingredient is a CCR1 receptor antagonist.

In an embodiment of the invention, the second active ingredient is a CCR1 receptor antagonist which is a compound of general formula

\[
\text{R}^1_{m} \text{X}^{1} \text{N} \text{H}_{(\text{CH})_{p}} \text{A} \text{R}^{5}_{n} \text{R}^{2}_{p} \text{R}^{3}_{q} \text{OH} \text{I}
\]

wherein
m is 0, 1 or 2;
R¹ is halogen, Cl-C₃ haloalkyl or cyano;
X¹ is -CH₂⁻ or -C(O)-;
n is 0, 1 or 2;
p is 0, 1 or 2;
R² is Ci-C₆cycloalkyl; or
R² forms a bicyclic ring together with the ring it is attached to;
R^3 is hydrogen, C_i-C_4 alkyl;

R^4 is hydrogen, halogen, hydroxyl, C_i-C_6 hydroxyalkyl, optionally substituted by one substituent independently selected from halogen, cyano, amino (-NH_2), amido (-CONH_2), hydroxyl, oxo (=0), C_i-C_6 haloalkyl, carboxyl, C_i-C_6 alkoxy, C_i-C_6 alkoxy carbonyl, C_p C_6 alkyl carbonylamino and a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=0), C_i-C_6 alkyl, C_i-C_6 hydroxyalkyl and C_i-C_6 haloalkyl;

A is a bond or C_pQhaloalkyl;

R^5 is hydrogen, hydroxyl, -NHC(O)R^6, -NHS(O)_2R^6, -C(O)NR^7R^8, -COOR^9 or SO_3R^9;

R^6 is hydrogen, C_pQalkyl, a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, C-C_6 alkyl, C_pC_6 hydroxyalkyl and C_i-C_6 haloalkyl, oxo (=0) and -OR^9;

R^7 and R^8 each independently represent (i) hydrogen atom,

(ii) a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=0), C_pC_6 alkyl, C_i-C_6 hydroxyalkyl and C_pC_6 haloalkyl,

(iii) a C_i-C_6 alkyl group, optionally substituted by one or more substituent independently selected from halogen, amino (-NH_2), hydroxyl, oxo (=0), C_pC_6 haloalkyl, carboxyl, C_pC_6 alkoxy, C_pC_6 alkoxy carbonyl, C_pC_6 alkyl carbonylamino and a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=0), C_pC_6 alkyl, C_pC_6 hydroxyalkyl and C_pC_6 haloalkyl, or

(iv) C_pC_6 alkyl sulphonyl, or
(v) $R^7$ and $R^8$ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, amido (-CONH$_2$), Ci-C$_6$ alkyl, CpC$_6$ hydroxyalkyl, C$_1$-C$_6$ alkoxy, Ci-C$_6$ alkoxy carbonyl, Ci-C$_6$ haloalkyl, Ci-C$_6$ alkylamino, di-C$_1$-C$_6$ alkylamino, Ci-C$_6$ alkylcarbonyl, C$_1$-C$_6$ alkylcarbonylamino, C$_1$-C$_6$ alkylaminocarbonyl, di-C$_1$-C$_6$ alkylaminocarbonyl, phenyl, halophenyl, phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

$R^9$ is hydrogen or Ci-C$_6$ alkyl;

$q$ is 0, 1 or 2;

$R^{10}$ is halogen, hydroxyl, cyano, Ci-C$_3$ haloalkyl or Ci-C$_6$ alkoxy;

or a pharmaceutically acceptable salt thereof;

or,

a compound of general formula

\[
\begin{align*}
&\text{(II)} \\
&R^{11} \text{ is hydrogen, OH or NH}_2; \\
&R^3 \text{ is hydrogen or CpQalkyl;} \\
&A \text{ is a bond or Ci-C}_3 \text{ alkyl;} \\
\end{align*}
\]

wherein

$m$ is 0, 1 or 2;

$R^1$ is halogen, cyano, Ci-C$_6$ haloalkyl;

$X$, $Y$ and $Z$ is a bond, -O-, -NH-, CH$_2$- or -C(O)-, provided that only one of $X$, $Y$ and $Z$ is a bond, and provided that $X$ and $Y$ are not simultaneously -O- or -C(O)-;

$n$ is 0, 1 or 2;

$R^2$ is Ci-C$_6$(cyclo)alkyl;

$p$ is 0 or 1;

$R^{11}$ is hydrogen, OH or NH$_2$;
R^5 is hydrogen, hydroxyl, -NHC(O)R^6, -NHS(O)R^6, -C(O)NR^7R^8, -COOR^9 or SO_3R^9;
R^4 is hydrogen, halogen, hydroxyl, OC(CH_3)_2COOH, Crhydroxyalkyl optionally substituted by one or more substituent independently selected from halogen, cyano, amino (-NH_2), amido (-CONH_2), hydroxyl, oxo (=0), C_1-C_6 haloalkyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy carbonyl, Ci-C_6 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom independently selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=0), Ci-C_6 alkyl, Ci-C_6 hydroxyalkyl and Ci-C_6 haloalkyl;
t is 0, 1 or 2;
R^6 is hydrogen, C_1-C_3 alkyl, NR^7R^8, or OR^9;
R^7 and R^8 are independently selected from hydrogen or Ci-C_6 alkyl and C_3-C_7 cycloalkyl; or
R^7 and R^8 together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclic ring, which is optionally substituted with on or more hydroxyl groups;
R^9 is a hydrogen or C_1-C_3 alkyl; and
R^{10} is halogen, cyano, C_1-C_3 alkoxy or Ci-C_3 haloalkyl, or a pharmaceutically acceptable salt thereof.

In the definitions of compounds of formula (I) and formula (II), an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Moreover, it will be appreciated that the number and nature of substituents on rings in the compounds of formula (I) and formula (II), will be selected so as to avoid sterically undesirable combinations.

In one embodiment of the invention where the second active ingredient is a compound of formula (I) or (H), m is 1 and R^1 is a halogen atom, particularly a chlorine or fluorine atom.
In a further embodiment, where the second active ingredient is a compound of formula (I) or (II), m is 1 and R\textsuperscript{1} is chlorine in the 4-position of the benzene ring relative to the carbon atom to which the CH\textsubscript{2} linking group is attached.

In another embodiment, where the second active ingredient is a compound of formula (I), X\textsuperscript{1} is a -CH\textsubscript{2} or a -C(O)-. In one embodiment X\textsuperscript{1} is -CH\textsubscript{2}. In a further embodiment, X\textsuperscript{1} is -C(O)-.

In a further embodiment, where the second active ingredient is a compound of formula (I) or (II), the integer n is 0, 1 or 2. In one embodiment n is 0. In another embodiment n is 1 or 2.

In another embodiment, where the second active ingredient is a compound of formula (I), R\textsuperscript{2} is C\textsubscript{1}-C\textsubscript{6} alkyl. In one embodiment of the present invention, where the second active ingredient is a compound of formula (I), n is 2 and R\textsuperscript{2} is methyl. In yet another embodiment, where the second active ingredient is a compound of formula (I), R\textsuperscript{3} is the group C1-C4 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl). In one embodiment R\textsuperscript{3} is methyl or ethyl.

In yet another embodiment, where the second active ingredient is a compound of formula (II), R\textsuperscript{11} is hydrogen, hydroxyl or amino group. In one embodiment R\textsuperscript{11} is hydrogen. In yet another embodiment, R\textsuperscript{12} is a hydroxyl or aminogroup, particularly a hydroxyl group.

In another embodiment, where the second active ingredient is a compound of formula (II), X, Y and Z are a bond, -O-, -NH-, CH\textsubscript{2} or -C(O)-, provided that only one of X, Y and Z is a bond, and provided that X and Y are not simultaneously -O- or -C(O)-.

In one embodiment X is -O-, Y is a bond and Z is CH\textsubscript{2}. In yet another embodiment X is a bond, Y is -NH-, and Z is -C(O). In yet another embodiment, X is -CH\textsubscript{2}, Y is -O- and Z is a bond.
In one embodiment, where the second active ingredient is a compound of formula (I) or (II), R4 is hydrogen, halogen, hydroxyl or Ci-C6 hydroxyalkyl, optionally substituted with halogen, cyano, hydroxyl, carboxyl or amido. In one embodiment R4 is hydrogen. In another embodiment R4 is halogen such as fluorine. In another embodiment R4 is hydroxyl.

In yet another embodiment R4 is -OCH2COOH or -OC(CH3)2COOH.

In another embodiment of the present invention, where the second active ingredient is a compound of formula (II), R4 is selected from -OCH3CF3, -OCH2CH2CF3, -OCH2CHF2 or -OCH2CN.

In yet another embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II), the integer q is Oor 1. In one embodiment, q is 0. In yet another embodiment q is 1.

In a further embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II). In one embodiment, R10 is a halogen, such as chlorine and fluorine. In one embodiment q is 1 and R10 is chlorine.

In yet a further embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II), R3 is hydrogen or Ci-C6 alkyl. In one embodiment, R3 is hydrogen. In another embodiment R3 is hydrogen or methyl. In one embodiment, R3 is methyl.

In one embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II), A is a bond or Ci-C3 alkyl. In one embodiment A is a bond. In another embodiment, A is Ci-C3 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl), in particular methyl or ethyl.

In a further embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II), R5 is hydrogen, hydroxyl, -NHC(O)R6, -NHS(O)2R6, -C(O)NR7R8, -COOR9 or SO3R9.
Where $R^5$ is $\text{NH}(O)R^6$, $\text{NHS}(O)R^6$, $-\text{C}(O)NR^7R^8$, and suitable $R^6$, $R^7$ and $R^8$ are independently selected from hydrogen or $\text{C}_1\text{C}_6$ alkyl, such as methyl.

In one embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II) $R^6$ is $\text{NR}^7R^8$, and $R^7$ and $R^8$ are independently selected from hydrogen or $\text{C}_1\text{C}_6$ alkyl, such as methyl. In another embodiment $A$ is a bond, $R^6$ is $\text{NR}^7R^8$, $R^7$ is hydrogen and $R^8$ is $\text{C}_1\text{C}_6$ alkyl, such as methyl. In one embodiment $A$ is a bond, $R^6$ is $\text{NR}^7R^8$ and $R^7$ and $R^8$ are both $\text{C}_1\text{C}_6$ alkyl, such as methyl.

In a further embodiment of the present invention, where the second active ingredient is a compound of formula (I) or (II) $A$ is a bond, $R^5$ is $\text{NH}(O)R^6$ and $R^6$ is $\text{C}_1\text{C}_6$ alkyl, such as methyl. In another embodiment $A$ is a bond $R^5$ is $\text{C}(O)NR^7R^8$ and $R^7$ and $R^8$ are both $\text{C}_1\text{C}_6$ alkyl, such as methyl. In yet another embodiment $A$ is a bond $R^5$ is $\text{C}(O)NR^7R^8$ and $R^7$ is a hydrogen and $R^8$ is $\text{C}_1\text{C}_6$ alkyl such as methyl.

In yet another embodiment of the present invention, where the second active ingredient is a compound of formula (I) $A$ is a bond, $R^5$ is $\text{NH}(O)R^6$, $R^6$ is $\text{NR}^7R^8$, and $R^7$ and $R^8$ together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more hydroxyl groups.

In a further embodiment of the present invention, where the second active ingredient is a compound of formula (II) $A$ is a bond, $R^5$ is $\text{C}(O)NR^7R^8$ and $R^7$ and $R^8$ together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more hydroxyl groups. In one embodiment heterocyclic groups for $R^7$ and $R^8$ and the nitrogen atom to which they are attached include azetininyl, pyrrolidinyl, piperadiny1 and pyrrolidinyl.

In a further embodiment of the present invention, where the second active ingredient is a compound of formula (II) $A$ is methyl or ethyl and $R^5$ is OH. In another embodiment of the present invention $A$ is methyl or ethyl and $R^5$ is a group $\text{COOR}^9$ or $\text{SO}_3R^9$, where suitable $R^9$ substituents are independently selected from hydrogen or $\text{C}_3$ alkyl, such as methyl and ethyl.
For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C\textsubscript{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl or i-hexyl. The term C\textsubscript{1-4} alkyl having 1 to 4 carbon atoms and may be but are not limited to methyl, ethyl, n-propyl, i-propyl or tert-butyl.

The term "alkoxy", unless stated otherwise, refers to radicals of the general formula -O-R, wherein R is selected from a hydrocarbon radical. The term "alkoxy" may include, but is not limited to methoxy, ethoxy, propoxy, isoproxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy or propargyloxy.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, partially or completely saturated monocyclic, bicyclic or bridged hydrocarbon ring system. The term "C\textsubscript{3-6}cycloalkyl" may be, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In this specification, unless stated otherwise, the term "3 to 8-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, or the term "4 to 7-membered heterocyclic ring" refers to a ringsystem having, in addition to carbon atoms, zero to three heteroatoms, including the oxidized form of nitrogen and sulfur and any quaternized form of a basic nitrogen, including, but not limited to cyclopropane, oxirane, cyclobutane, azetidine, cyclopentane,
cyclohexane, benzyl, furane, thiophene, pyrrolidine, morpholine, piperidine, piperazine, pyrazine, azepane.

In this specification, unless stated otherwise, the term "bicyclic ring" refers to a ringsystem in which one (carbo)cycle is fused to another (carbo)cycle. The term "a 8 to 11-membered ring system" refers to a hydrocarbon moiety comprising one to three fused rings, optionally having 6, 10 or 14 π atoms shared in a cyclic array and having, in addition to carbon atoms, zero to five heteroatoms. Fused ringsystems may include, but are not limited to, 8-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 2-azabicyclo[2.2.2]octane, indole, indoline, benzofuran, benzothiophene, naphtalene, chroman, quinazoline, phenoxazine, azulene, adamantane, anthracene or phenoxazine.

In this specification, unless stated otherwise, the terms "halo" and "halogen" may be fluorine, iodine, chlorine or bromine.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halogen as defined above. The term "Q-C₄haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C₁₋₃haloalkyLO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy. The term "halophenyl" may include, but is not limited to fluorophenyl, difluorophenyl, trfluorophenyl, chlorophenyl, dichlorophenyl or trichlorophenyl.

In this specification, unless stated otherwise, the term "alkylcarbonyl" or "alkoxycarbonyl" may include, but is not limited to an alkyl or alkoxy group as defined above, which is substituted with COOH.

In this specification, unless stated otherwise, the term "alkylcarbonylamino" may include, but is not limited to an alkyl group as defined above, which is substituted with NHCOOH.

In this specification, unless stated otherwise, the term "hydroxyalkyl" may include, but is not limited to an alkyl group as defined above, which is substituted with one or more hydroxyl groups.
In this specification, unless stated otherwise, the term "alkylsulphonyl" may include, but is not limited to an alkyl group as defined above, which is substituted with SO₂.

In another embodiment of the present invention, the second active ingredient is selected from

N-(2-{(2S)-3-[(3R)-1-[(4-chlorophenyldimethyl]-3-pyrrolidinyl]amino]-2-hydroxypropoxy}-4-fluorophenyl)acetamide;
N-(2-{(2S)-3-[(3S)-1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl]amino}-2-hydroxypropoxy}-4-fluorophenyl)acetamide;
N-(2-{(2S)-3-[1-[(4-chlorobenzoyl)-4-piperidinyl]amino]-2-hydroxypropoxy}-4-fluorophenyl)acetamide;
(2-{{(2S)-3-[(2R.5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
(2-{[(2S)-3-{{(3S,4R)-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
(2-{[(2S)-3-[(3R.4R)-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
(2-{[(2S)-3-[(3R.4R)-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
(2-{[(2S)-3-[(3R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
(2-{[(2S)-3-[(2R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropoxyl}oxy}-4-fluorophenyl)acetic acid;
Methyl (2-{[(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropoxy}oxy}-4-fluorophenyl)propanoate;
N-[2-{(2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy}-4-chlorophenyl]acetamide;
N-[2-{(2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy}-4-hydroxyphenyl]acetamide;
N-[2-({2S}-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino)-2-hydroxy-2-methylpropoxy)-4-fluorophenyl] acetamide;
N-[5-chloro-2-{(2S)-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-4-hydroxyphenyl] acetamide;
N-[5-chloro-2-{(2S)-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino}-2-hydroxy-2-methylpropoxy)-4-hydroxyphenyl] propanamide;
(2-{(2S)-3-[1-[4-chlorobenzyl]piperidin-4-yl]amino}-2-hydroxy-2-methylpropoxy)-4-fluorophenyl)methanesulfonic acid;
Urea, N-5-chloro-(2-{(2S)-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino}-2-hydroxypropoxy)-4-hydroxyphenyl)-N’-cyclopropyl-
Urea, N-(2-{(2S)-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino}-2-hydroxypropoxy)-phenyl)-N’-ethyl-
(2S)-1-(2-ethylphenoxy)-3-[1-[4-chlorobenzyl]4-piperidinyl]amino]propan-2-ol;
(2S)-1-[2-(-hydroxyethyl)phenoxy]-2-methyl-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino]propan-2-ol;
2-({2S}-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino)-2-hydroxy-2-methylpropoxy)benzaldehyde;
2-({2S}-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino)-2-hydroxy-4-hydroxy-N-methylbenzamide trifluoroacetate (salt);
Methyl 2-(2S)-3-[1-[4-chlorobenzyl]-4-piperidinyl]amino]-2-hydroxypropoxy)-4-fluorobenzoate;
or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the second active ingredient is selected from
N-(2-{(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4′-piperidin]-1′-yl)-2-hydroxypropyl]oxy]-4-hydroxyphenyl)acetamide;
N-(2-{(2S)-3-(5-chloro-1H-spiro[1,3-benzodioxole-2,4′-piperidin]-1′-yl)-2-hydroxypropyl]oxy]-4-hydroxyphenyl)acetamide trifluoroacetate (salt);
2-[{(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4′-piperidin]-1′-yl)-2-hydroxypropyl]oxy]-4-hydroxy-N-methylbenzamide trifluoroacetate (salt);
2 - {[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid trifluoroacetate (salt);
N-(2-[(2S)-3-(5-chloro-1H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate (salt);
2 - {[(2S)-3-(5-chloro-1H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-N-methylbenzamide;
N-(2-[(2S)-3-(5-fluoro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide;
2-[(2S)-3-(5-fluoro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxy-N-methylbenzamide;
N-[2-([(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)urea trifluoroacetate (salt);
4-fluoro-2 - {[(2S)-3-(5-fluoro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-benzoic acid hydrochloride;
N-(2-[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-fluorophenyl)urea trifluoroacetate (salt);
N-(2-[(2S)-2-amino-3-(5-fluoro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy)-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt);
Benzaldehyde, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidine]-1'-yl)-2-hydroxypropoxy];
Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[2-(2-hydroxyethyl)phenoxy]methyl]-, (αS)-;
Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[2-(hydroxymethyl)phenoxy]methyl]-, (αS)-;
N-(2-[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-5-chloro-4-hydroxyphenyl)acetamide;
2-Chloro-5-[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-(4- {acetylamino} phenoxy)acetic acid;
5- \{[(25)-3-(5-Chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-(4-\{acetylamino\}phenoxy)acetic acid;  
2-Chloro-5- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-(4-\{(methylamino)carbonyl\}phenoxy)acetic acid;  
2-Chloro-5- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(phenyl)propanoic acid;  
2-Chloro-5- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(3,3,3-trifluoropropoxy)benzoic acid trifluoroacetate (salt);  
5-Chloro-2- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(cyanomethoxy)benzoic acid trifluoroacetate (salt);  
5-Chloro-2- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(2,2-difluoroethoxy)benzoic acid trifluoroacetate (salt);  
2-Chloro-5- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(2,2-difluoroethoxy)benzoic acid trifluoroacetate (salt);  
5-Chloro-2- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-(2,2-difluoroethoxy)benzoic acid trifluoroacetate (salt);  
N-(2- \{3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy \}phenyl)acetamide trifluoroacetate (salt);  
Methyl 3-(2- \{[(2S)-3-(5-chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-r-yl)-2-hydroxypropyl]oxy \}-4-fluorophenyl)propanoic acid trifluoroacetic acid salt;  
N-(2- \{[(2S)-3-(spiro[indole-2,4'-piperidin]-3(1H)-one]-1'-yl)-2-hydroxypropyl]oxy \}A-acetamide; and  
(2- \{[(2S)-3-(5-Chloro-1'H,3'H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy \}-4-fluorophenyl)methanesulfonic acid,  
or a pharmaceutically acceptable salt, solvate or solvated salt thereof.

Compounds of formula (I) and (II) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and (II) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Preferred optical isomers are the (S)-enantiomers (i.e. compounds with the S configuration at the stereocentre with R¹ and R³ or OH attached). It will be appreciated that the compounds of formula (I) and (II) and salts thereof may exist as zwitterions. Thus, whilst the compounds are drawn and referred to in the neutral form, they may exist also in internal salt
(zwitterionic) form. The representation of formula (I) and (II) and the examples of the present invention covers both neutral and zwitterionic forms and mixtures thereof in all proportions. The compounds of formula (I) and (II) may be used in the form of a pharmaceutically acceptable salt thereof, conceivably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, sulphate, acetate, ascorbate, benzoate, 2-fluorobenzoate, 2,6-difluorobenzoate, (hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate or toluenesulphonate. Pharmaceutically acceptable salts may also be formed together with metals such as calcium, magnesium, sodium, potassium or zinc or bases such as piperazine, 2-aminoethanol, choline, diethylamine or diethanol amine. Furthermore, the compounds of formula (I) and (II) may be used in the form of a pharmaceutically acceptable salt thereof, like an amino acid addition salt such as L-lysine, glycine, L-glutamine, L-asparagine or L-arginine. A pharmaceutically acceptable salt also includes internal salt (zwitterionic) forms. Any reference to compounds of formula (I) and (II) or salts thereof also encompasses solvates of such compounds and solvates of such salts (e.g. hydrates).

In another embodiment of the present invention, the second active ingredient is a salt of N-\(\{2-[(2S)-3-\{\text{l-(4-chlorobenzyl)piperidin-4-y]amino\}-2-hydroxy-2-methylpropyl]oxy\}-4-hydroxyphenyl\} acetamide or N-{5-Chloro-2-\{(2S)-3-\{\text{l-(4-chlorobenzyl)piperidin-4-y]amino\}-2-hydroxy-2-methylpropyl]oxy\}-4-hydroxyphenyl \}acetamide, for example hydrochloride, hydrobromide, phosphate, sulphate, acetate, ascorbate, benzoate, fumarate, hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate or p-toluenesulphonate salt.

In another embodiment of the present invention, the second active ingredient is a benzoate, furoate or hemifumarate salt of \(\{2-\{(2S)-3-\{\text{l-(4-chlorobenzyl)piperidin-4-y]amino\}-2-hydroxy-2-methylpropyl]oxy\}-4-hydroxyphenyl\} acetamide, as described in PCT/SE2006/000920, PCT/SE2006/000921 and PCT/SE2006/000922 (WO2007/0 15666, WO2007/0 15667 and WO2007/0 15668).

In another embodiment of the present invention, the second active ingredient is the hemifumarate, furoate, benzoate, 2-fluorobenzoate or 2,6-difluorobenzoate salt of N-\(\{5-
In one embodiment of the invention, the second active ingredient is a hemifumarate salt of 

\[ N-2-\{(2S)-3-\{1-(4-chlorobenzyl)piperidin-4-yl\}amino\}-2-hydroxy-2-methylpropyl\}oxy]-4-hydroxyphenyl \] acetamide, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\( \Theta \)):

1. 6.3, 11.0 and 12.7, or
2. 6.3, 10.7 and 12.7, or
3. 6.3, 11.0, 12.7 and 15.9, or
4. 6.3, 10.7, 11.0, 12.7, 13.9, 14.2 and 15.9, or
5. 6.3, 10.7, 11.0, 12.7, 15.9, 17.7, 19.1, 19.7 and 25.5, or

In another embodiment of the invention, the second active ingredient is a furoate salt of 

\[ N-2-\{(2S)-3-\{1-(4-chlorobenzyl)piperidin-4-yl\}amino\}-2-hydroxy-2-methylpropyl\}oxy]-4-hydroxyphenyl \] acetamide, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\( \Theta \)):

1. 6.1, 10.7 and 19.3, or
2. 6.1, 12.2 and 14.1, or
3. 6.1, 10.7, 12.2, 14.1, 18.1 and 19.3, or
4. 6.1, 10.7, 12.2, 14.1, 15.7, 18.1 and 19.3, or
5. 6.1, 10.7, 12.2, 14.1, 15.1 and 19.3, or
6. 6.1, 10.7, 12.2, 14.1, 15.1, 15.7, 18.1 and 19.3, or

In yet another embodiment of the invention, the second active ingredient is a benzoate salt of 

\[ N-2-\{(2S)-3-\{1-(4-chlorobenzyl)piperidin-4-yl\}amino\}-2-hydroxy-2-methylpropyl\}oxy]-4-hydroxyphenyl \] acetamide, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\( \Theta \)):

1. 6.5, 9.3 and 10.5, or
2. 6.5, 9.3, 17.6 and 17.8, or
(3) 6.5, 9.3, 10.5, 12.0 and 12.4, or
(4) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6 and 17.8, or
(5) 6.5, 13.0 and 20.2, or
(6) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8 and 19.2, or
(7) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8 and 26.0, or
(8) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8, 24.2, 26.0 and 30.7.

In a further embodiment of the invention, the second active ingredient is a hemifumarate salt of \( \text{IV}-[5\text{-chloro-2-}\{(2S)-3\{-[1\text{-}(4\text{-chlorobenzyl)piperidin-4-yl}]\text{amino}\}-2\text{-hydroxy-2-methylpropyl]oxy}\}-4\text{-hydroxyphenyl}]\text{acetamide} \) which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\( \Theta \)):

(1) 6.2, 14.7 and 20.5, or
(2) 8.0, 10.1 and 14.7, or
(3) 10.1, 12.4, 14.7 and 19.5, or
(4) 6.2, 10.1, 12.4, 13.4, 19.5 and 20.1, or
(5) 8.0, 10.1, 12.4, 14.7, 19.5, 20.1, 21.2 and 23.8, or
(6) 6.2, 8.0, 10.1, 11.5, 12.4, 13.4, 19.5, 20.1 and 21.2, or
(7) 6.2, 8.0, 11.5, 12.4, 13.4, 14.7, 20.1, 20.5, 21.2 and 23.8, or
(8) 6.2, 8.0, 10.1, 11.5, 12.4, 13.4, 14.7, 16.1, 20.5, 21.2 and 23.8

In another embodiment of the invention, the second active ingredient is a furoate salt of \( \text{N}-[5\text{-chloro-2-}\{(2S)-3\{-[1\text{-}(4\text{-chlorobenzyl)piperidin-4-yl}]\text{amino}\}]\text{-2-hydroxy-2-methylpropyl]oxy}\}-4\text{-hydroxyphenyl}]\text{acetamide} \) which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\( \Theta \)):

(1) 6.7, 17.9 and 20.9 or
(2) 12.2, 13.3, 17.9 and 18.6 or
(3) 6.7, 12.2, 16.0, 17.3 and 27.0 or
(4) 6.7, 8.7, 12.2, 13.3, 16.0, 17.9 and 18.6 or
(5) 6.7, 12.2, 13.3, 16.0, 17.3, 17.9, 18.6, 20.9 and 27.0 or
(6) 6.7, 12.2, 13.3, 13.6, 15.5, 16.0, 17.3, 17.9, 18.6, 19.4, 20.9 and 27.3 or
(7) 6.7, 12.2, 13.3, 13.6, 15.5, 16.0, 17.3, 17.9, 18.6, 19.4, 20.9, 23.4 and 23.6 or
In one embodiment of the invention, the second active ingredient is a benzoate salt of $N$-{5-chloro-2-[[[(25)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees $2\Theta$):

1. 5.6, 10.4 and 14.3
2. 9.2, 12.9, 16.9, and 25.4
3. 5.6, 9.2, 11.3, 14.3, 16.9, and 23.0
4. 5.6, 11.3, 12.9, 18.0, 19.5, and 20.0, 23.0, 25.4
5. 5.6, 9.2, 10.4, 12.9, 14.3, 16.9, 18.0, 19.5, 20.0, and 25.4
6. 5.6, 9.2, 10.4, 11.3, 12.9, 14.3, 16.9, 18.0, 19.5, 23.0, and 25.4
7. 5.6, 9.2, 10.4, 11.3, 14.3, 16.9, 18.0, 19.5, 20.0, 23.0, and 25.4
8. 5.6, 9.2, 10.4, 11.3, 12.9, 14.3, 16.9, 18.0, 19.5, 20.0, 23.0, and 25.4

In yet another embodiment of the invention, the second active ingredient is a 2-fluorobenzoate salt of $N$-{5-chloro-2-[[[(25)$_-$3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees $2\Theta$):

1. 5.6, 9.2, and 11.2
2. 5.6, 10.4, and 12.4
3. 9.2, 10.4, 11.2, 12.4, 14.2, and 15.0
4. 5.6, 10.4, 12.7, 13.6, 14.2, 15.0, 17.5, and 18.8
5. 5.6, 9.2, 11.2, 12.4, 12.7, 13.6, 14.2, 15.0, 16.8, 17.7, and 19.1
6. 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 18.8, 19.1, and 19.5
7. 5.6, 9.2, 10.4, 12.4, 13.6, 14.2, 15.0, 16.8, 17.5, 18.8, 19.5, and 20.6
8. 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 17.5, 17.7, 19.1, 19.5, 21.0, 22.6, and 25.2
9. 5.6, 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 16.6, 16.8, 17.5, 18.8, 19.1, 19.5, 20.5, 21.0, and 22.6
In a further embodiment of the invention, the second active ingredient is a 2,6-difluorobenzoate salt of N-[5-chloro-2-{[(25)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl]acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

1. 5.6, 9.1 and 12.2, or
2. 5.6, 10.3 and 12.6, or
3. 9.1, 10.3, 11.2, 12.3, 14.9 and 16.7 or
4. 5.6, 10.3, 12.6, 13.5, 14.2, 14.9, 17.4 and 19.0 or
5. 5.6, 9.1, 11.2, 12.6, 13.5, 14.2, 16.7, 18.4, 18.7, 19.0 and 20.8 or
6. 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.7 and 19.0 or
7. 5.6, 9.1, 10.3, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 19.5 and 20.3 or
8. 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 18.7, 19.0, 20.3, 21.0 and 22.6 or

In another embodiment of the invention, the second active ingredient is a sulphate salt of N-[5-chloro-2-{[(25)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl]acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

1. 3.3, 9.9 and 19.8, or
2. 8.4, 16.5 and 19.8, or
3. 3.3, 9.9, 16.5, 17.9, 20.2 and 23.5, or
4. 9.9, 16.5, 17.1, 17.9, 19.8, 20.2 and 23.5, or
5. 3.3, 8.4, 9.9, 14.8, 17.1, 19.4, 19.8 and 20.2, or
6. 9.0, 9.9, 11.8, 14.0, 14.8, 16.5, 19.8, 20.2 and 23.5, or
7. 3.3, 8.4, 9.0, 9.9, 11.8, 12.7, 14.0, 17.1, 17.9, 19.4, 19.8 and 20.2, or
8. 3.3, 8.4, 9.9, 11.8, 12.7, 14.0, 14.8, 16.5, 17.1, 17.9, 19.4, 19.8, 20.2 and 23.5

The compounds of formula (I) may be synthesised using the procedures set out in WO01/98273, WO03/05 1839 and WO 2005/0378 14. The compounds of formula (II) may be synthesised using the procedures set out in WO2004/005295, US 60/831,776 and WO 2004/005295.
The compounds of formula (I) and (II) or a pharmaceutically acceptable or a pharmaceutically acceptable salt, solvate or solvated salt thereof, as defined above may also be prepared according to the preparation routes described in schemes 1 to 4 below.

**Scheme 1:** Process described in WO2004005295

**Scheme 2:** Starting phenol described in WO00/12468; R₁⁴ and R₁⁵ are hydrogen, C₁-₃ alkyl or together with the carbon atom to which they are attached form a 3-6 membered aliphatic ring.

**Scheme 3:** Starting material commercially available; R is C₁₋₂ alkyl
Scheme 4: $R^{14}$ and $R^{15}$ are hydrogen, $C_i$ alkyl or together with the carbon atom to which they are attached form a 3-6 membered aliphatic ring.

In an embodiment of the present invention the second active ingredient is 2-{2-chloro-5-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy}-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. 2-{2-Chloro-5-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy}-2-methylpropanoic acid may be prepared by methods according or analogous to those described in PCT/SE2007/000694 (WO2008/010765).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, and the second active ingredient is yV-2-{2-[[25]-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyljacetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-
In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium salt, and the second active ingredient is $N\cdot\{2\cdot[(25)-3\cdot\{1-(4-chlorobenzyl)piperidin-4-yl]amino\}-2-hydroxy-2-methylpropoxy\}-4-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium salt and the second active ingredient is $N\cdot\{2\cdot[(25)-3\cdot\{1-(4-chlorobenzyl)piperidin-4-yl]amino\}-2-hydroxy-2-methylpropoxy\}-4-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyl oxy)-ethyl]-dimethyl-ammonium salt and the second active ingredient is $N\cdot\{2\cdot[(25)-3\cdot\{1-(4-
chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-
hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-
dichloro-benzyloxy)-ethyl]-dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]-dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium salt and the second active ingredient is N-{2-[(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, and the second active ingredient is yV-{5-chloro-2-[(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide.
In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyty-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium salt, and the second active ingredient is Λ-[5-chloro-2-[[((2S)-3-[[1-(4-chlorobenzyl)piperidin-4-yl] amino ]-2-hydroxy-2-methylpropyloxy]-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium salt and the second active ingredient is Λ-[5-chloro-2-[[((2S)-3-[[1-(4-chlorobenzyl)piperidin-4-yl] amino ]-2-hydroxy-2-methylpropyloxy]-4-hydroxyphenyl]acetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]-dimethyl-ammonium salt and the second active ingredient is Λ-[5-chloro-2-[[((2S)-3-]]
3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyloxy]-4-hydroxyphenylacetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt and the second active ingredient is N-{5-chloro-2-[(25)-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyloxy]-4-hydroxyphenylacetamide or a pharmaceutically acceptable salt thereof (e.g. benzoate, hemifumarate or furoate). In one aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, and the second active ingredient is 2-2-Chloro-5-{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyloxy]-[methylamino]carbonyl]phenoxy]-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide.
In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl-oxazol-5-ylmethyl] dimethyl-(2-phenethyloxy-ethyl)-ammonium salt and the second active ingredient is 2-{2-Chloro-5-{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy}-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-(2-phenethyloxy-ethyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-(2-phenethyloxy-ethyl)-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium salt and the second active ingredient is 2-{2-Chloro-5-{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-A-[(methylamino)carbonyl]phenoxy]-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the muscarinic receptor antagonist is [[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt and the second active ingredient is 2-{2-Chloro-5-[(2S)-
3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4’-piperidin]-1’-yl)-2-hydroxypropyl]oxy]-4-[(methylamino)carbonyl]phenoxy]-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]-dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]-dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium salt and the second active ingredient is 2-[2-Chloro-5-{{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4’-piperidin]-1’-yl]-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy]-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention the second active ingredient is an inhibitor of kinase function. Examples of an inhibitor of kinase function that may be used in this embodiment include a p38 kinase inhibitor and an IKK inhibitor.

In an embodiment of the invention the second active ingredient is a protease inhibitor. Examples of a protease inhibitor that may be used in this embodiment include an inhibitor of neutrophil elastase or an inhibitor of MMP-12.

In an embodiment of the invention the second active ingredient is a steroidal glucocorticoid receptor agonist. Examples of a steroidal glucocorticoid receptor agonist
that may be used in this embodiment include budesonide, fluticasone (e.g. as propionate ester), mometasone (e.g. as furoate ester), beclomethasone (e.g. as 17-propionate or 17,21-dipropionate esters), ciclesonide, loteprednol (as e.g. etabonate), etiprednol (as e.g. dicloacetate), triamcinolone (e.g. as acetonide), flunisolide, zoticasone, flumoxonide, rolleponide, butixocort (e.g. as propionate ester), prednisolone, prednisone, tipredane, steroid esters e.g. 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester and 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazone-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, steroid esters according to DE 4129535, steroids according to WO 2002/00679, WO 2005/041980, or steroids GSK 870086, GSK 685698 and GSK 799943.

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, and the second active ingredient is budesonide. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium salt, and the second active ingredient is budesonide. In one aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).
In an embodiment of the invention, the muscarinic receptor antagonist is a \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl]\) dimethyl-ammonium salt and the second active ingredient is budesonide. In one aspect of this embodiment, the muscarinic receptor antagonist is \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl]\) dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichloro-phenoxy)-propyl]\) dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]\) dimethyl-ammonium salt and the second active ingredient is budesonide. In one aspect of this embodiment, the muscarinic receptor antagonist is \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]\) dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]\) dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).

In an embodiment of the invention, the muscarinic receptor antagonist is a \([2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]\) dimethyl-ammonium salt and the second active ingredient is budesonide. In one aspect of this embodiment, the muscarinic receptor antagonist is \([2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]\) dimethyl-ammonium bromide. In another aspect of this embodiment, the muscarinic receptor antagonist is \([2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]\) dimethyl-ammonium napadisylate (e.g. hemi-naphthalene-1,5-disulfonate).
In an embodiment of the invention the second active ingredient is a non-steroidal glucocorticoid receptor agonist. Examples of a modulator of a non-steroidal glucocorticoid receptor agonist that may be used in this embodiment include selective non-steroidal glucocorticoid receptor agonists. Non-steroidal glucocorticoid receptor agonists are described for example in WO2006/046916 and US6323199.

In an embodiment of the invention the second active ingredient is a purinoceptor antagonist, for example a P2X7 receptor antagonist. Examples of P2X7 receptor antagonists are described in WO00/61569, WO01/44170, WO01/94338, WO03/041707, WO03/080579, WO04/106305, WO05/009968, WO06/025784 and WO06/059945.

The combination of the present invention may provide a beneficial therapeutic effect in the treatment of respiratory diseases. Examples of such possible effects include improvements in one or more of the following parameters: reducing inflammatory cell influx into the lung, mild and severe exacerbations, FEVi (forced expiratory volume in one second), vital capacity (VC), peak expiratory flow (PEF), symptom scores and Quality of Life.

The muscarinic antagonist (first active ingredient) and second active ingredient of the present invention may be administered simultaneously, sequentially or separately to treat respiratory diseases. By sequential it is meant that the active ingredients are administered, in any order, one immediately after the other. They may still have the desired effect if they are administered separately, but when administered in this manner they will generally be administered less than 4 hours apart, more conveniently less than two hours apart, more conveniently less than 30 minutes apart and most conveniently less than 10 minutes apart.

The active ingredients of the present invention may be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. The active ingredients may also be administered topically (to the lung and/or
airways) in the form of solutions, suspensions, aerosols and dry powder. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

In one embodiment of the present invention the active ingredients are administered via separate pharmaceutical preparations. Therefore, in one aspect, the present invention provides a kit comprising a preparation of a first active ingredient which is a muscarinic antagonist according to the present invention, and a preparation of a second active ingredient, and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

In another embodiment the active ingredients may be administered via a single pharmaceutical composition. Therefore, the present invention further provides a pharmaceutical composition comprising, in admixture, a first active ingredient, which is a muscarinic antagonist according to the present invention, and a second active ingredient, as defined above.

The pharmaceutical compositions of the present invention may be prepared by mixing the muscarinic antagonist (first active ingredient) with the second active ingredient and a pharmaceutically acceptable adjuvant, diluent or carrier. Therefore, in a further aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition, which comprises mixing a muscarinic antagonist according to the present invention with a second active ingredient according to the present invention and a pharmaceutically acceptable adjuvant, diluent or carrier.
It will be understood that the therapeutic dose of each active ingredient administered in accordance with the present invention will vary depending upon the particular active ingredient employed, the mode by which the active ingredient is to be administered, and the condition or disorder to be treated.

In one embodiment of the present invention, the muscarinic antagonist (first active ingredient) according to the present invention is administered via inhalation. When administered via inhalation the dose of the muscarinic antagonist according to the present invention will generally be in the range of from 0.1 microgram (µg) to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 100 µg, 0.1 to 50 µg, 5 to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 100 µg, 5 to 50 µg, 5 to 10 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In one embodiment of the present invention the second active ingredient of the present invention may conveniently be administered by inhalation. When administered via inhalation the dose of the second active ingredient will generally be in the range of from 0.1 to 50 µg, 0.1 to 40 µg, 0.1 to 30 µg, 0.1 to 20 µg, 0.1 to 10 µg, 5 to 50 µg, 5 to 40 µg, 5 to 30 µg, 5 to 20 µg, 5 to 10 µg, 10 to 50 µg, 10 to 40 µg, 10 to 30 µg, or 10 to 20 µg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In another embodiment of the present invention, the second active ingredient is administered orally. Oral administration of the second active ingredient may for example be used in a pharmaceutical product or kit wherein the other active ingredient(s) are administered by inhalation. When administered orally, satisfactory results will generally be obtained when the dose of the second active ingredient is in the range of from 5 to 1000 milligram (mg), 5 to 800mg, 5 to 600mg, 5 to 500mg, 5 to 400mg, 5 to 300mg, 5 to
200mg, 5 to 100mg, 5 to 50mg, 20 to 1000 mg, 20 to 800mg, 20 to 600mg, 20 to 500mg, 20 to 400mg, 20 to 300mg, 20 to 200mg, 20 to 100mg, 50 to 1000 mg, 50 to 800mg, 50 to 600mg, 50 to 500mg, 50 to 400mg, 50 to 300mg, 50 to 200mg, 50 to 100mg, 100 to 1000 mg, 100 to 800mg, 100 to 600mg, 100 to 500mg, 100 to 400mg, 100 to 300mg, or 100 to 200mg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a muscarinic antagonist, and a second active ingredient, as defined herein above, wherein each active ingredient is formulated for inhaled administration.

In another embodiment of the present invention, the first active ingredient, which is a muscarinic antagonist, may be formulated for oral administration and the second active ingredient(s), as defined herein above, may be formulated for inhaled administration.

In yet another embodiment of the present invention, the first active ingredient, which is a muscarinic antagonist, may be formulated for inhaled administration and the second active ingredient(s), as defined herein above, may be formulated for oral administration.

In yet a further embodiment of the present invention, the first active ingredient, which is a muscarinic antagonist, and the second active ingredient(s), as defined herein above, wherein each active ingredient is formulated for oral administration.

In an embodiment the pharmaceutical preparations of active ingredients may be administered simultaneously.

In an embodiment the different pharmaceutical preparations of active ingredients may be administered sequentially.
In an embodiment the different pharmaceutical preparations of active ingredients may be administered separately.

The active ingredients of the present invention are conveniently administered via inhalation (e.g. topically to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations. For example metered dose inhaler devices may be used to administer the active ingredients, dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents. Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Preferred propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactant and/or other excipients. Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose.

Dry powders and pressurized HFA aerosols of the active ingredients may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 µm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_{8-20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.
Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

The combination of the present invention is useful in the treatment or prevention of respiratory-tract disorders such 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 or pneumoconiosis (for example aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis).

Dry powder inhalers may be used to administer the active ingredients, alone or in combination with a pharmaceutically acceptable carrier, in the later case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

The present invention further provides a pharmaceutical product, kit or pharmaceutical composition according to the invention for simultaneous, sequential or separate use in therapy.

The present invention further provides the use of a pharmaceutical product, kit or pharmaceutical composition according to the invention in the manufacture of a
medicament for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease or asthma.

The present invention further provides a pharmaceutical product, kit or pharmaceutical composition according to the invention for use in the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease or asthma.

The present invention still further provides a method of treating a respiratory disease which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a muscarinic antagonist according to the present invention; and
(b) a (therapeutically effective) dose of a second active according to the present invention; to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly. Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The term "disease, unless stated otherwise, has the same meaning as the terms "condition" and "disorder" and are used interchangeably throughout the description and claims. The term "agent" and "active ingredient" means the compounds comprised in the combination of the present invention, e.g. a muscarine antagonist or a CCR1 antagonist.
The pharmaceutical product, kit or composition of the present invention may optionally comprise a third active ingredient which third active ingredient is a substance suitable for use in the treatment of respiratory diseases.

Examples of third active ingredients that may be incorporated into the present invention include those listed herein above as second active ingredients (i.e. a phosphodiesterase inhibitor, a modulator of chemokine receptor function, an inhibitor of kinase function, a protease inhibitor, a steroidal glucocorticoid receptor agonist, a non-steroidal glucocorticoid receptor agonist or a purinoceptor antagonist) it being recognised that they may be utilised as third active ingredients in embodiments where they have not been utilised as the second active ingredient.

In one embodiment of the invention, the third active ingredient is a β2-adrenoceptor agonist. The β2-adrenoceptor agonist may be any compound or substance capable of stimulating the β2-receptors and acting as a bronchodilator. Examples of β2-adrenoceptor agonists that may be employed in the present invention include formoterol. The chemical name for formoterol is \(\Lambda\)-f-[2-hydroxy-5-][(l)-l-hydroxy-2-[[[(l)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]phenyl]-formamide. The preparation of formoterol is described, for example, in WO 92/05 147. In one aspect of this embodiment, the β2-adrenoceptor agonist is formoterol fumarate. It will be understood that the invention encompasses the use of all optical isomers of formoterol and mixtures thereof including racemates. Thus for example, the term formoterol encompasses \(N\)-[2-hydroxy-5-][(lR)-l-hydroxy-2-[[[(lR)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]phenyl]-formamide, \(N\)-[2-hydroxy-5-][(lS)-l-hydroxy-2-[[[(lS)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]phenyl]-formamide and a mixture of such enantiomers, including a racemate.

In an alternative embodiment of the present invention, the pharmaceutical product, kit or pharmaceutical composition does not contain a β2-adrenoceptor agonist.
The invention is illustrated by the following non-limiting Examples. In the Examples the following Figures are presented:

Figure 1: X-ray powder diffraction pattern of Muscarinic Antagonist 2 (MA2) \[2-((R)\text{-cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)}\text{-ammonium bromide: Crystalline Form A.}

Figure 2: X-ray powder diffraction pattern of Muscarinic Antagonist 7 (MA7) \[2-((R)\text{-cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)}\text{-ammonium hemi-naphthalene-1,5-disulfonate: Crystalline Form 1.}

Figure 3: X-ray powder diffraction pattern of Muscarinic Antagonist 7 (MA7): Crystalline Form 2.

Figure 4: X-ray powder diffraction pattern of Muscarinic Antagonist 7 (MA7): Crystalline Form 3.

Figure 5: X-ray powder diffraction pattern of Muscarinic Antagonist 11 (MA11) \[2-(4\text{-chloro-benzyloxy})\text{-ethyl}]\text{-[2-((R)\text{-cyclohexyl-hydroxy-phenyl-methyl})\text{-oxazol-5-ylmethyl}]\text{-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate: Crystalline Form A.}

Figure 6: X-ray powder diffraction pattern of the hemifumarate salt of \(N\{-5\text{-chloro-2-[(25)-3-[(1-(4-chlorobenzyl)piperidin-4-yl]amino]}\text{-2-hydroxy-2-methylpropyl)}\text{oxy}]}\text{-4-hydroxyphenyl }\text{acetamide}

Figure 7: X-ray powder diffraction pattern of the sulphate salt of \(N\{-5\text{-chloro-2-[(25)-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]}\text{-2-hydroxy-2-methylpropyl)}\text{oxy]}\text{-4-hydroxyphenyl }\text{acetamide (CCRI antagonist)}

**Preparation of Muscarinic Antagonists**

Muscarinic antagonists according to the present invention may be prepared as follows. Alternative salts to those described herein may be prepared by conventional chemistry using methods analogous to those described.
Unless otherwise stated the following general conditions were used in the preparation of the Muscarinic Antagonists:

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

NMR spectra were obtained on a Varian Unity Inova 400 spectrometer with a 5 mm inverse detection triple resonance probe operating at 400 MHz or on a Bruker Avance DRX 400 spectrometer with a 5 mm inverse detection triple resonance TXI probe operating at 400 MHz or on a Bruker Avance DPX 300 spectrometer with a standard 5 mm dual frequency probe operating at 300 MHz. Shifts are given in ppm relative to tetramethylsilane.

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:
C18-reverse-phase column (100 x 22.5 mm i.d. Genesis column with 7 µm particle size).
UV detection at 230 nm.

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

LC-MS method 1
Waters 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:

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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector at 254 nm)
MS ionisation method - Electrospray (positive ion)

LC-MS method 2
Waters Platform LC 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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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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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 (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:

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<th>Gradient - Time</th>
<th>flow mL/min</th>
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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector at 254 nm)
MS ionisation method - Electrospray (positive ion)
X-Ray Powder Diffraction (XRPD) patterns were collected, on a high resolution Philips X-Pert MPD machine in reflection mode and θ - 2θ configuration, over the scan range 2° to 40° 2θ with 100-second exposure per 0.03° increment. The X-rays were generated by a copper tube operated at 45kV and 40mA. The wavelengths of the direct beam X-rays was 1.5406Å (K$_{\text{Cu}}$) as a monochromator was used. The data was collected on zero background holders on which ~ 2mg of the compound was placed. The holder (provided by PANalytical) was made from a single crystal of silicon, which had been cut along a non-diffracting plane in the 2° to 40° 2θ range and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction. Raw data were stored electronically and evaluation was performed on raw or smoothed diffraction patterns. XRPD were recorded at ambient temperature and relative humidity.

Differential scanning calorimetry (DSC) thermograms were measured using a TA Q1000 Differential Scanning Calorimeter, with aluminium pans and pierced lids. The sample weights varied between 0.5 to 5mg. The procedure was carried out under a flow of nitrogen gas (50ml/min) and the temperature studied from 25 to 300°C at a constant rate of temperature increase of 10°C per minute.

Thermogravimetric analysis (TGA) thermograms were measured using a TA Q500 Thermogravimetric Analyser, with platinum pans. The sample weights varied between 1 and 5mg. The procedure was carried out under a flow of nitrogen gas (60ml/min) and the temperature studied from 25 to 200°C at a constant rate of temperature increase of 10°C per minute.

Gravimetric vapour sorption (GVS) profiles were measured using a Dynamic Vapour Sorption DVS-I instrument. The solid sample ca. 1-5mg was placed into a glass vessel and the weight of the sample was recorded during a dual cycle step method (40 to 90 to 0 to 90 to 0% relative humidity (RH), in steps of 10% RH). GVS profiles were recorded at ambient temperature.

Abbreviations used in the experimental section:

Aq = aqueous
DCM = dichloromethane
DMF = dimethylformamide
EtOAc = ethyl acetate
EtOH = ethanol
TBME (or tBME) = tert-butyl methyl ether
MeOH = methanol
RT = room or ambient temperature, i.e. a temperature of from 16 to 25 °C,
Rt = retention time
THF = tetrahydrofuran
Satd = saturated
NMS = N-methyl scopolamine

Muscarinic antagonists, and the intermediates used in their preparation, described herein have been given IUPAC names generated by the Autonom 2000 plug in for IsisDraw version 2.5, as supplied by MDL Information Systems. Inc.

Intermediates used in Preparation of Muscarinic Antagonists

The following intermediates 1 - 16 used in the preparation of muscarinic antagonists were prepared as follows:

**Intermediate 1**: Z-Oxo-Z-phenyl-N-prop⁻-vnyl-acetamide

Oxalyl chloride (6.1 g, 48 mmol) was added to a solution of phenylglyoxylic acid (6.0 g, 40 mmol) and 3 drops of DMF in dry DCM (50 mL). The reaction mixture was stirred at RT for 3 h then the solvent was removed. The residue was taken up in dry DCM (50 mL) and the solution was cooled to 0 °C. A mixture of propargyl amine (2.2 g, 40 mmol) and triethylamine (4.05 g, 40 mmol) was added cautiously over a period of 10 min then the mixture was allowed to warm to RT. Stirring was continued for 2.5 h then water (10 mL) was added. The mixture was washed with 1 M HCl, sat. sodium hydrogencarbonate (aq.),
then brine. The organic phase was then dried (Na$_2$SO$_4$) and the solvent was removed. The residue was crystallized from cyclohexane to afford the product as a light brown solid. Yield: 5.75 g, 76%. LC-MS (Method 3): Rt 2.47 min, m/z 188 [MH$^+$.]

**Intermediate 2: (5-Methyl-oxazol-2-vI)-phenyl-methanone.**

\[
\begin{align*}
\text{Methane sulfonic acid (10 g, 104 mmol)} & \text{ was added drop wise to a solution of 2-oxo-2-phenyl-\text{/V-prop-2-ynyl-acetamide (Intermediate 1) (2.4 g, 12.83 mmol) in 1,4-dioxane (20 mL). The resultant solution was heated at 90 }^\circ\text{C for 66 h. The reaction mixture was cooled and the solvent was removed. The dark residue was partitioned between DCM and water.}\n
\text{The DCM fraction was washed with 1 M HCl (2x), satd. sodium hydrogen carbonate solution (aq., 2x), then brine. The solution was dried (Na$_2$SO$_4$) and the solvent was removed to give the crude product. Purification was achieved via column chromatography, eluting with cyclohexane/EtOAc (4:1). This afforded the product as an off-white solid.}

\text{Yield: 1.0 g, 41%. LC-MS (Method 3): Rt 2.94 min, m/z 188 [MH$^+$.].}
\end{align*}
\]

**Intermediate 3: (5-Bromomethyl-oxazoI-2-vl)-phenyl-methanone.**

\[
\begin{align*}
\text{A mixture of (5-methyl-oxazol-2-vl)-phenyl-methanone (Intermediate T) (0.8 g, 4.28 mmol), }\text{Af-bromo-succinimide (0.9 g, 5.06 mmol) and 2,2'-azobis(2-methylpropionitrile) (56 mg, 0.34 mmol) in carbon tetrachloride (8 mL) was heated at reflux for 1.5 h. The reaction mixture was cooled to RT and filtered. The filtrate was diluted with DCM and washed with water, satd. sodium hydrogen carbonate solution (aq.) and brine. It was dried (Na$_2$SO$_4$) and the solvent was removed. Purification was achieved via column chromatography eluting with cyclohexane/EtOAc (4:1). This afforded the product as a yellow solid.}

\text{Yield: 0.9 g, 79%. LC-MS (Method 3): Rt 3.26 min, m/z 266, 268 [MH$^+$.].}
\end{align*}
\]
Intermediate 4: (5-Dimethylaminoinethyl-oxazol-2-yl)-phenyl-methanone.

(5-Bromomethyl-oxazol-2-yl)-phenyl-methanone (Intermediate 3) (0.18 g, 0.68 mmol) was dissolved in a 2 M solution of dimethylamine in THF (3 mL, 6 mmol). The mixture was stirred at RT for 1 h with a precipitate forming almost instantly. The solvent was removed and the residue was partitioned between DCM and satd. sodium hydrogencarbonate solution (aq.). The aqueous phase was extracted with DCM and the combined organic phase was dried (Na₂SO₄) and the solvent removed to give the product as an orange oil that crystallized on standing. Yield: 0.16 g, 99%. LC-MS (Method 2): Rt 1.22 min, m/z 231 [MH⁺].

Intermediate 5: Cyclohexyl-(5-methyl-oxazol-2-yl)-phenyl-methanol

A solution of (5-methyl-oxazol-2-yl)-phenyl-methanone (intermediate 2) (3.0 g, 16 mmol) in 32 mL dry THF at 0 °C under nitrogen was treated dropwise over 10 min with a 2 M solution of cyclohexylmagnesium chloride in diethyl ether (10 mL, 20 mmol). The resulting deep yellow solution was stirred at 0°C for about 30 min during which time a precipitate was formed, and then at RT for 1.5 h. The reaction mixture was cooled to 0 °C again and treated cautiously with satd. ammonium chloride solution (aq.). The mixture was stirred at RT for 10 min then diluted with water (10 mL). The phases were separated and the organic phase was washed with brine. The combined aqueous phase was extracted with DCM and the combined organic phase was dried (MgSO₄) and concentrated in vacuo to give the crude product, which was triturated with ether, filtered off and dried. Yield: 3.65 g, 84%. LCMS (Method 3): Rt 3.78 min, m/z 272 [MH⁺].

Intermediate 6: (S-Bromomethyl-oxazol-1-yl-cyclohexyl-phenyl-methanol.
A solution of cyclohexyl-(5-methyl-oxazol-2-yl)-phenyl-methanol (Intermediate 5) (3.0 g, 11.1 mmol) in 1,2-dichloroethane (22 mL) was treated with iV-bromo-succinimide (2.16 g, 12.2 mmol) followed by 2,2'-azobis(2-methylpropionitrile) (0.18 g, 2.1 mmol). The mixture was heated to 80 °C for 2.5 h and then allowed to cool to RT. Satd. sodium hydrogen carbonate solution (aq.) was added and the phases were separated. The organic layer was washed with brine and the combined aqueous layers were extracted with DCM. The combined organic phase was dried (MgSO₄) and concentrated in vacuo to give the crude product as a brown oil. Purification was achieved via column chromatography eluting with 33-100% DCM/cyclohexane, followed by 25% EtOAc/DCM. Yield: 1.85 g, 48%. LCMS (Method 3): Rt 4.27 min, m/z 350, 352 [MH⁺].

**Intermediate 7; 2-Phenethyloxy-ethanol**


**Intermediate 8: 2-(2-Bromo-ethoxy)-ethyl-benzene**

Triphenyl phosphine (1.65 g, 6.3 mmol) was added to a solution of 2-phenethyloxy-ethanol (Intermediate 7) (950 mg, 5.7 mmol) and carbon tetrabromide (2.09 g, 6.3 mmol) in DCM (25 mL) and stirred at RT for 6 h. Then a further equivalent of triphenyl phosphine and carbon tetrabromide was added and stirred overnight. The reaction mixture was concentrated and the residue was purified by column chromatography over silica using cyclohexane as eluent. Concentration of the pure fractions afforded the product as a clear oil.
Yield: 1.25 g, 96%.

$^1$H NMR (CDCl$_3$): £2.91 (t, 2H), 3.44 (t, 2H), 3.71 (t, 2H), 3.76 (t, 2H), 7.19-7.24 (m, 3H), 7.27-7.31 (m, 2H) ppm.

**Intermediate 9: 2-(4-Methyl-benzyloxy)-ethanol**

A mixture of potassium hydroxide (1.19 g, 21.3 mmol) in ethylene glycol (12 mL, 213 mmol) was heated at 130 °C for 3 h, then cooled to 35 °C, and 4-methylbenzyl bromide (3.94 g, 21.3 mmol) was added. The reaction mixture was heated at 35 °C for 20 h, cooled to RT, and partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated to dryness to afford a brown oil. This was purified by column chromatography over silica using a gradient of 0-100% diethyl ether/cyclohexane. The pure fractions were combined and concentrated to afford a yellow liquid.

Yield: 2.97 g, 84%.

$^1$H NMR (CDCl$_3$): £2.04 (t, 1H), 2.35 (s, 3H), 3.58 (t, 2H), 3.75 (m, 2H), 4.52 (s, 2H), 7.16 (d, 2H), 7.23 (d, 2H) ppm.

**Intermediate 10: 1-(2-Bromo-ethoxymethyl)-4-methyl-benzene**

Prepared analogous to the method used for Intermediate 8, but using 1-(2-bromo-ethoxymethyl)-4-methyl-benzene (Intermediate 9) instead of 2-phenethyloxy-ethanol (Intermediate 9) was:

Yield: 85%.

$^1$H NMR (CDCl$_3$): £2.35 (s, 3H), 3.47 (t, 2H), 3.76 (t, 2H), 4.55 (s, 2H), 7.16 (d, 2H), 7.24 (d, 2H) ppm.

**Intermediate 11: 4-(3-Bromo-propoxy)-1,2-dichloro-benzene**
A mixture of 3,4-dichlorophenol (1.98 g, 12.14 mmol), 1,3-dibromopropane (6.0 mL, 59 mmol, and potassium carbonate (2.5 g, 18 mmol) in acetonitrile was heated at 80 °C overnight. The reaction mixture was cooled to RT, filtered, and the filtrate partitioned between water and diethyl ether. The organic layer was dried (MgSO₄), concentrated, and purified by column chromatography over silica using 0-10% diethyl ether/cyclohexane as eluent to afford the product.

Yield: 2.96 g, 86%.

\[ ^1H \text{NMR (CDCl}_3\): } \delta 2.32 \text{ (m, 2H), 3.59 (t, 2H), 4.08 (t, 2H), 6.77 (dd, IH), 7.00 (d, IH), 7.32 (d, IH) ppm.} \]

**Intermediate 12: 2-(3,4-Dichloro-benzyloxy)-ethanol**

Prepared analogous to the method used for Intermediate 9, but using 3,4-dichlorobenzyl chloride instead of 4-methylbenzyl bromide was:

\[ \text{Yield: 72\%.} \]

\[ ^1H \text{NMR (CDCl}_3\): } \delta 1.83 \text{ (br.s, IH), 3.61 (t, 2H), 3.79 (t, 2H), 4.52 (s, 2H), 7.17 (dd, IH), 7.42 (d, IH), 7.45 (d, IH) ppm.} \]

**Intermediate 13: 4-(2-Bromo-ethoxymethyl)-1,2-dichloro-benzene**

Prepared analogous to the method used for Intermediate 8, but using 2-(3,4-dichloro-benzyloxy)-ethanol (Intermediate 12) instead of 2-phenethyloxy-ethanol (Intermediate 7) was:

\[ \text{Yield: quantitative.} \]

\[ ^1H \text{NMR (CDCl}_3\): } \delta 3.50 \text{ (t, 2H), 3.80 (t, 2H), 4.53 (s, 2H), 7.19 (dd, IH), 7.42 (d, IH), 7.46 (d, IH) ppm.} \]
**Intermediate 14: Methanesulfonic acid 2-(4-chloro-benzyloxy)-ethyl ester**

![Chemical structure of Intermediate 14](image)

A solution of methanesulfonyl chloride (980 µL, 12.6 mmol) in dry DCM (10 mL) was slowly added to a cooled (0 °C) solution of 2-(4-chloro-benzyloxy)-ethanol (2.14 g, 11.46 mmol) and diisopropylethylamine (2.0 mL, 23 mmol) in dry DCM (10 mL). The reaction mixture was allowed to warm to RT overnight. Water was added and the organic layer was dried (MgSO₄) and concentrated. The residue was purified by column chromatography over silica using a gradient of 0-20% diethyl ether/cyclohexane to afford the pure product.

**Yield:** 1.87 g, 67%.

**1H NMR (CDCl₃):** δ3.03 (s, 3H), 3.74 (m, 2H), 4.39 (m, 2H), 4.54 (s, 2H), 7.27 (d, 2H), 7.33 (d, 2H) ppm.

**Intermediate 15: l-(2-Bromo-ethoxymethyl)-4-chloro-benzene**

![Chemical structure of Intermediate 15](image)

A mixture of methanesulfonic acid 2-(4-chloro-benzyloxy)-ethyl ester (Intermediate 14) (1.37 g, 5.18 mmol) and lithium bromide (1.80 g, 20.7 mmol) in acetone (15 mL) was heated at reflux overnight. The reaction mixture was concentrated to dryness and the residue partitioned between DCM and water. The organic layer was dried (MgSO₄), and concentrated, and purified by column chromatography over silica using DCM/cyclohexane (1:3) as eluent to afford the product as a colourless oil.

**Yield:** 0.67 g, 78%.

**1H NMR (CDCl₃):** δ3.49 (t, 2H), 3.79 (t, 2H), 4.55 (s, 2H), 7.30 (d, 2H), 7.32 (d, 2H) ppm.

**Intermediate 16: CvcIohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol**

![Chemical structure of Intermediate 16](image)
A solution of (5-bromomethyl-oxazol-2-yl)-cyclohexyl-phenyl-methanol (Intermediate 6) (3.2 g, 9.2 mmol) in THF (40 mL) was treated with a 2 M solution of dimethylamine in THF (40 mL, 80 mmol). A suspension formed after stirring for a few minutes. The reaction mixture was left at RT overnight and then the solid was filtered off and discarded. The filtrate was concentrated under reduced pressure and the residue was partitioned between DCM and satd. sodium hydrogen carbonate solution (aq.). The organic layer was dried (Na$_2$SO$_4$) and evaporated to afford the title compound as a solid. Yield: 2.74 g, 95%.

LC-MS (Method 1): Rt 6.57 min, m/z 315 [MH$^+$].

$^1$H NMR (DMSO-d$_6$): $\delta$ 0.92-1.29 (m, 6H), 1.42-1.74 (m, 4H), 2.10 (s, 6H), 2.22 (m, IH), 3.45 (s, 2H), 5.90 (s, IH), 6.98 (s, IH), 7.18-7.22 (m, IH), 7.27-7.34 (m, 2H), 7.40-7.46 (m, 2H) ppm.

The two enantiomers of cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (Intermediate 16) (2.74 g) were separated by preparative chiral HPLC using a 250x20 mm Chiralpak® IA column packed with amylose tris(3,5-dimethylphenyl-carbamate) immobilized on 5 µm silica gel. The column was eluted with 5% EtOH in heptane buffered with 0.1% diethylamine at 15 mL/min. The first eluting enantiomer (Rt 8.5 min) afforded (S)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (Intermediate 16a) as a white solid.

**Intermediate 16a:** (SVcyclohexyHS-dimethylaminomethyl-oxazoI-l-vP-phenyl-methanol

![Structure](image)

Yield: 0.73 g, 27%.

LC-MS (Method 1): Rt 6.50 min, m/z 315 [MH$^+$].
1H NMR (CDCl₃): £1.12-1.39 (m, 7H), 1.62-1.76 (m, 3H), 2.25 (s, 6H), 2.29-2.32 (m, IH), 3.54 (dd_{AB}, 2H), 3.70 (br.s, IH), 6.84 (s, IH), 7.24 (t, IH), 7.33 (t, 2H), 7.64 (d, 2H) ppm.

The second eluting enantiomer (Rt 10.3 min) afforded (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (Intermediate 16b) as a white solid.

**Intermediate 16b: (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol**

Yield: 1.04 g, 38%.

LC-MS (Method 1): Rt 6.48 min, m/z 315 [MH⁺].

1H NMR (CDCl₃): £1.10-1.39 (m, 7H), 1.62-1.76 (m, 3H), 2.25 (s, 6H), 2.29-2.35 (m, IH), 3.54 (dd_{AB}, 2H), 3.70 (br.s, IH), 6.84 (s, IH), 7.24 (t, IH), 7.33 (t, 2H), 7.64 (d, 2H) ppm.

**Muscarinic Antagonist 1 (MAI): [2-((S)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-dimethyl-(3-phenoxy-propyl)-ammonium bromide**

A solution of (S)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (Intermediate 16a) (0.060 g, 0.19 mmol) and 3-phenoxypropyl bromide (0.215 g, 1 mmol) in acetonitrile (1.33 mL) and chloroform (2 mL) was allowed to stand at RT for 5 days.

The solvent was removed to afford the crude product. Purification was achieved by column
chromatography eluting sequentially with DCM, 2.5%, 5%, 10% then 20% MeOH in DCM.
Yield: 50 mg, 43%.

LC-MS (Method 1): Rt 8.32 min, m/z 449 [M+].

$^1$H NMR (CDCl$_3$): <Jl.06-1.17 (m, 3H), 1.23-1.36 (m, 4H), 1.52-1.85 (m, 3H), 2.28-2.35 (m, 3H), 3.32 (s, 3H), 3.33 (s, 3H), 3.63 (dd, 2H), 4.04 (t, 2H), 5.23 (dd, 2H), 6.85 (d, 2H), 6.98 (t, 1H), 7.20 (t, 1H), 7.26-7.30 (m, 4H), 7.55-7.58 (m, 3H) ppm.

Muscarinic Antagonist 2 (MA2): r2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-dimethyl-(3-phenoxy-propyl)-ammonium bromide

A solution of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (Intermediate 16b) (98 mg, 0.31 mg) and 3-phenoxypropyl bromide (740 mg, 3.44 mmol) in chloroform (1.5 mL) and acetonitrile (1.5 mL) was heated at 50 °C for 22 h. The RM was concentrated to dryness to afford a colourless viscous oil, which was triturated with diethyl ether to furnish a white gum. This was purified by column chromatography eluting with 2.5-25% MeOH/DCM to afford the product as a turbid viscous oil. Drying under vacuum at 45 °C for 1-2 days afforded a white solid.

Yield: 142 mg, 86%.

LC-MS (Method 1): Rt 8.41 min, m/z 449 [M+].

$^1$H NMR (CDCl$_3$): £1.06-1.16 (m, 3H), 1.21-1.37 (m, 4H), 1.59-1.74 (m, 3H), 2.32 (m, 3H), 3.32 (s, 3H), 3.33 (s, 3H), 3.61 (dd, 2H), 4.03 (t, 2H), 4.14 (br.s, 1H), 5.20 (dd, 2H), 6.85 (d, 2H), 6.98 (t, 1H), 7.19 (t, 1H), 7.26-7.30 (m, 4H), 7.55-7.58 (m, 3H) ppm.

Muscarinic Antagonist 2 (MA2): r2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-dimethyl-(3-phenoxy-propyl)-ammonium bromide - Crystalline Form A
General Experimental conditions for the preparation of MA2 Crystalline Form A are the same as those described herein below in Preparation [2] of MA 11.

(R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol

(5-Dimethylaminomethyl-oxazo-2-yl)-phenyl-methanone

was dissolved in THF (8.4 L/kg) and cooled to a temperature of 0 ±5°C, to which cyclohexyl magnesium chloride (1.3 eq., as a 20 w/w% solution in Toluene/THF) was dosed over at least 1 h. The reaction mixture was heated to 20°C over 40 min and stirred at 20°C for at least 1 h, at which point conversion to product was > 96% by HPLC. The reaction mixture was dosed to a mixture of 23.1 w/w% NH₄Cl (3.97 L/kg) and water (3.97 L/kg). The phases were separated and the aqueous layer extracted with ethyl acetate (7 L/kg). The combined organic layers were washed with water (5.25 L/kg), and 70% of the volume removed by distillation (p ≥ 130 mbar, 50°C). To the distillation residue acetonitrile (7.82 L/kg) was added and the suspension heated until complete dissolution was attained (70°C). The reaction was then cooled to 0°C over 7 h and stirred at 0°C for at least 1 h. The reaction product (±)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol was then collected by filtration and washed three times with cold acetonitrile (1.65 L/kg). Yields achieved with this procedure ranged between 60-70% and the purities achieved were > 97% peak area (HPLC) and > 97% w/w (NMR). R)-Cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol was separated from this racemic mixture by chiral SMB chromatography on a Chiralpak AD column using acetonitrile : isopropanol : diethylmethylamine (90:10:0.1) as eluent.

1 An alternative preparation of (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol is described in WO 2007/017669 (example 6).

2 A preparation of (5-dimethylaminomethyl-oxazo-2-yl)-phenyl-methanone is described in WO 2007/017669 (intermediate 4).

**Procedure for Preparing Seed Crystals of (MA2) Crystalline Form A - Procedure 1**

(R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (leq) and 3-phenoxypropyl bromide (1.1 eq) were suspended in iso-propanol (4.3 L/kg). The resulting
suspension was heated at reflux for at least 20h, or until the conversion to product was > 98\% by HPLC. The resulting solution was diluted with iso-propanol (2 L/kg) and cooled to 50\(^0\)C. At 50\(^0\)C, tert-butyl methyl ether (TBME) (9.5 L/kg) was added and the solution stirred at 50\(^0\)C for a further 2h during which time spontaneous crystallization occurred. The mixture was gradually cooled to 0\(^0\)C over a 3h period and stirred at 0\(^0\)C for at least 1h. The crystalline product was collected by filtration and washed four times with cold TBME (0.16 L/kg). Product yields with this procedure were > 80\% and the purity was > 98\% peak area (HPLC) and > 97\% w/w (NMR).

**Procedure for Preparing Seed Crystals of (MA2) Crystalline Form A - Procedure 2**

(R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (leq) and 3-phenoxypropyl bromide (1.1 eq) were slurried in iso-propanol (3.14 L/kg). The resulting suspension was heated to reflux (100 \(^0\)C), at which complete dissolution was achieved. After heating at reflux for 8 h the reaction mixture was cooled to ambient temperature over night. Analysis by HPLC showed complete conversion to product. A sample of the reaction mixture (0.043 L/kg) was withdrawn and TBME (0.14 L/kg) added dropwise whereupon precipitation occurred. This suspension was charged to the reaction mixture at ambient temperature whereupon crystallization occurred. The resulting suspension was cooled to 0\(^0\)C and stirred for 3 h at this temperature. The product was collected by filtration, using iso-propanol (2.14 L/kg) to aid transfer from vessel to filter. The filter cake was washed with iso-propanol (1 L/kg) and dried on a rotary evaporator over night. The crude product was obtained as a white solid in 86\% yield.

The crude product was charged in TBME (10.4 L/kg with respect to crude product) and stirred at ambient temperature for 2 h. The product was collected by filtration, and the filter cake washed with TBME (20 ml), and dried on a rotary evaporator overnight. Yield was 94\% from crude product, and purity 98.3\% peak area by HPLC.

**Preparation of (MA2) Crystalline Form A**

To (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (1 eq) in iso-propanol (4.44 L/kg) at ambient temperature was added 3-phenoxypropyl bromide (1.leq).
The mixture was heated to reflux temperature (83°C) over 90 min. and stirred at reflux for 20h. After that time the mixture was cooled to 57°C over 13 min. A sample was taken and then the reaction mixture was heated again to reflux. Reaction conversion was determined to be 98.4% by HPLC.

The reaction mixture was diluted with iso-propanol (5.55 L/kg) and cooled to 57°C. The solution was filtered through a heated in line filter into a stirring vessel. The reactor and the filter lines were rinsed with warm (55°C) iso-propanol (1.1 L/kg). The content of the stirring vessel was transferred back into the reactor and rinsed with iso-propanol (1.1 L/kg). Iso-propanol (5.517kg) was distilled off at a temperature of 47°C-50°C and a pressure of 200 mbar. The residue was cooled to 52°C. At this temperature TBME (10 L/kg) was added over 35 min. The resulting solution was stirred for 2 h at 50°C. Seed crystals (1.18 %w/w (with respect to input (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol)) were added and the mixture was stirred for additional 2 h at 50°C. The suspension formed was cooled to 0°C over 3 h and stirred at that temperature for 13 h. After filtration the filter cake was rinsed four times with 1°C-8°C cold TBME (1.48 L/kg, 1.67 L/kg, 2.04 L/kg and 2.04 L/kg). The filter cake was pre-dried for 4.5hr in a stream of nitrogen and afterwards it was further dried on a rotary evaporator at 45°C and >12mmbar to yield the product as a crystalline white solid. Yield obtained by this process on a 2.7kg scale was 90.5% and the purity 98.3% peak area (HPLC) and 98.9% w/w (NMR). Loss on drying was 0.23% w/w (gravimetric).

**Analysis of Muscarinic Antagonist 2 (MA2) Crystalline Form A**

A sample of crystalline Form A obtained by the 'Procedure for Preparing Seed Crystals of Crystalline Form A - Procedure 2’ was analysed by XRPD, DSC and TGA.

The melting temperature of Form A as determined by DSC was found to be 150°C (onset) (±2.0°C). Weight loss observed prior to melting by TGA was negligible, near 0.0%. GVS determination gave a 0.8% weight increase (%w/w) at 80% RH (±0.2%).
An XRPD spectrum of Muscarinic Antagonist 2 (MA2) Crystalline Form A is presented in Figure 1.

Prepared according to the method used in preparing MA2, but using [2-(2-bromo-ethoxy)-ethyl]-benzene (Intermediate 10) instead of 3-phenoxypropyl bromide.

Yield: 94%.

LC-MS (Method 1): Rt 8.50 min, m/z 463 [M+].

$^1$H NMR (CD$_3$OD): $\delta$51.06-1.39 (m, 6H), 1.55 (m, 1H), 1.65-1.79 (m, 3H), 2.40 (m, 1H), 2.90 (t, 2H), 2.94 (s, 6H), 3.47 (m, 2H), 3.78 (t, 2H), 3.86 (m, 2H), 4.56 (s, 2H), 7.12 (m, IH), 7.19-7.28 (m, 5H), 7.32-7.37 (m, 3H), 7.55 (m, 2H) ppm

Muscarinic Antagonist 4 (MA4): 2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethy1H3-(3,4-dichloro-phenoxy)-propyl-dimethyl-ammonium bromide
Prepared according to the method used in MA2, but using 4-(3-bromo-propoxy)-1,2-dichloro-benzene (Intermediate 11) instead of 3-phenoxypropyl bromide.

Yield: 59%.

LC-MS (Method 4): Rt 8.85 min, m/z 517 [M+].

$^1$H NMR (CDCl$_3$): $\delta$ 1.08-1.40 (m, 7H), 1.60-1.76 (m, 3H), 2.34 (m, 3H), 3.34 (s, 6H), 3.65 (m, 2H), 3.99 (m, 3H), 5.25 (dd $\Delta$AB, 2H), 6.73 (dd, IH), 6.96 (d, IH), 7.22 (t, IH), 7.26-7.34 (m, 3H), 7.56 (m, 3H) ppm
Muscarinic Antagonist 5 (MA5): \( r_2-((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyn-r}_2-(3,4-\text{dichIoro-benz \gamma Ioxyl})-\text{ethyl-dimethyl-ammonium bromide} \)

Prepared according to the method used in MA2, but using 4-(2-bromo-ethoxymethyl)-1,2-dichloro-benzene (Intermediate 13) instead of 3-phenoxypropyl bromide.

Yield: 86%.

LC-MS (Method 1): Rt 9.07 min, m/z 517 [M+].

\( ^1\text{H NMR (CDCl}_3\text{): }\delta 1.09-1.37 \text{ (m, 7H), } 1.60-1.77 \text{ (m, 3H), } 2.31 \text{ (m, IH), } 3.33 \text{ (s, 6H), } 3.91 \text{ (m, 2H), } 3.98 \text{ (m, 3H), } 4.55 \text{ (s, 2H), } 5.20 \text{ (dd}_{AB}, 2H), 7.17 \text{ (dd, IH), } 7.24 \text{ (m, IH), } 7.31 \text{ (t, 2H), } 7.40 \text{ (d, IH), } 7.44 \text{, (d, IH), } 7.48 \text{, (s, IH), } 7.56 \text{ (d, 2H) ppm.} \)

Muscarinic Antagonist 6 (MA6): \( r_2-(4-\text{chIoro-benzvIoxyl})-\text{ethylI1-[2-((R)-\text{cyclohexyl-hydroxy-phenyl-methyI})-oxazol-5-vImethyll-dimethyl-ammonium bromide} \)

Prepared according to the method used in MA2, but using 1-(2-bromo-ethoxymethyl)-4-chloro-benzene (Intermediate 15) instead of 3-phenoxypropyl bromide.

A solution of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (0.40g, 1.27mmol) and 1-(2-bromo-ethoxymethyl)-4-chloro-benzene (Intermediate 15) (0.67g, 2.68mmol) in chloroform (4mL) and acetonitrile (4mL) was heated at 50°C for 3 days. The reaction mixture was concentrated to dryness to afford a yellow oil, which was purified by column chromatography eluting with 2.5-25% MeOH/DCM to afford the product as a white foam. Yield, 0.68g, 92%

Yield: 92%.
LC-MS (Method 1): Rt 8.72 min, m/z 483 [M+].

\[ ^1\text{H} \text{NMR (CDCl}_3\text{): } \delta \ 1.08-1.40 \text{ (m, } 7\text{H}), \ 1.61-1.76 \text{ (m, } 3\text{H}), \ 2.31 \text{ (m, } 1\text{H}), \ 3.32 \text{ (s, } 6\text{H}), \ 3.88 \text{ (m, } 2\text{H}), \ 3.94 \text{ (m, } 2\text{H}), \ 4.03 \text{ (br. s, } 2\text{H}), \ 4.54 \text{ (s, } 2\text{H}), \ 5.17 \text{ (dd } _{AB}, 2\text{H}), \ 7.21-7.26 \text{ (m, } 3\text{H}), \ 7.28-7.34 \text{ (m, } 4\text{H}), \ 7.46 \text{ (s, } 1\text{H}), \ 7.56 \text{ (d, } 2\text{H) ppm.}

**Muscarinic Antagonist 7 (MA7):** \( \text{r}^2(-((R)-CvcIohexyl-hydroxy-phenyl-methyl)-oxazoI-5-ylmethyl[}-\text{dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-}

\text{disulfonate}}

A mixture of \([2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide (MA2) (201 mg, 0.372 mmol), naphthalene-1,5-disulfonate disodium salt (68 mg, 0.21 mmol), DCM (2.8 mL), and water (2.8 mL) was stirred vigorously at RT overnight. The solids were collected by filtration, washed with DCM/water mixture, and dried under vacuum at 40°C. The sample of MA7 obtained is hereinafter referred to as the MA7 Amorphous Form.

\[ ^1\text{H} \text{NMR showed a spectrum corresponding to the hemi-salt (2:1 ratio of cation/anion).}

Yield: 208 mg, 94%.

LC-MS (Method 1): Rt 8.35 min, m/z 449 [M+].

\[ ^1\text{H} \text{NMR (CD}_3\text{OD): } \delta \ 1.04-1.37 \text{ (m, } 12\text{H}), \ 1.55-1.75 \text{ (m, } 8\text{H}), \ 2.22 \text{ (m, } 4\text{H}), \ 2.40 \text{ (m, } 2\text{H}), \ 3.01 \text{ (s, } 6\text{H}), \ 3.02 \text{ (s, } 6\text{H}), \ 3.37 \text{ (m, } 2\text{H}), \ 3.97 \text{ (m, } 4\text{H}), \ 4.67 \text{ (s, } 4\text{H}), \ 6.89 \text{ (d, } 4\text{H), } 6.95 \text{ (t, } 2\text{H), } 7.21 \text{ (t, } 2\text{H), } 7.28 \text{ (m, } 8\text{H), } 7.51 \text{ (m, } 8\text{H), } 8.19 \text{ (d, } 2\text{H), } 9.02 \text{ (d, } 2\text{H) ppm.}
Salt Form 1
MA7 Amorphous form (as prepared herein above) was heated in toluene with stirring at 60° for 48 hours and allowed to cool to RT while stirring to afford the product as small platelets. The product was collected by filtration and dried under vacuum at 50 °C for 3 h. The melting temperature of Form 1 was determined by DSC, during which testing Form 1 underwent dehydration and subsequently the dehydrated Form 1, totally or partially converted into an anhydrous form, melted at 225 °C ±2°C (onset). Water content as determined by TGA was 0.7 % (±0.2%). GVS determination gave a 3.1 % weight increase (%w/w) at 80 % RH (±0.5%).

An XRPD spectrum of Form 1 is presented in Figure 2.

Further quantities of Form 1 were prepared as follows: MA7 Amorphous form was crystallised from refluxing acetonitrile using a hot filtration of the solution and allowed to cool to RT while stirring to afford the product as small platelets. The product was collected by filtration and stirred in toluene at 60 °C for 19 h. The solids were collected by decanting the solvent and dried under vacuum at 50 °C for 3h. XRPD and DSC analysis were consistent with Form 1.

Salt Form 2
MA7 Amorphous form was heated in anisole at 154 °C for 3hrs then left to stand at RT for 48hrs. The solids were collected by decanting the solvent and dried under vacuum at 45 °C. The melting temperature of Form 2 as determined by DSC was found to be 227 °C ±2°C (onset). Water content as determined by TGA was 0.0 %. GVS determination gave a 0.7 % weight increase (%w/w) at 80 % RH (±0.2%).

An XRPD spectrum of Form 2 is presented in Figure 3.

Further quantities of Form 2 were prepared as follows: MA7 Amorphous form was crystallised from refluxing chlorobenzene and allowed to slowly cool to RT to afford the product as fine needles. The product was collected by filtration and dried under vacuum at RT overnight. XRPD and DSC analysis were consistent with Form 2.
Further quantities of Form 2 were prepared as follows: MA7 Amorphous form was stirred in toluene at 80 °C over for at least 60 hours. The solids were collected by decanting the solvent and dried under vacuum at 45 °C. XRPD and DSC analysis were consistent with Form 2.

Salt Form 3
MA7 Amorphous form was crystallised from refluxing acetone/water mixture using a hot filtration of the solution and allowed to cool to RT while stirring to afford the product as a white powder. The product was collected by filtration and dried under vacuum at RT overnight.

The melting temperature of Form 3 was determined by DSC, during which testing Form 3 underwent dehydration and subsequently the dehydrated Form 3, totally or partially converted into an anhydrous form, melted at 224 °C ±2°C (onset). Water content as determined by TGA was 2.1 % (±0.2%). GVS determination gave a 3.0 % weight increase (%w/w) at 80 % RH (±0.2%).

An XRPD spectrum of Form 3 is presented in Figure 4.

Muscarinic Antagonist 8 (MA8): [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium hemi-naphthalene-1,5-disulfonate
Yield: 98%.

LC-MS (Method 1): Rt 8.64 min, m/z 463 [M⁺].

\(^1\)H NMR (CD\(_3\)OD): \(\delta\) 1.05-1.39 (m, 12H), 1.53 (m, 2H), 1.68 (m, 4H), 1.77 (m, 2H), 2.39 (m, 2H), 2.85 (s, 12H), 2.87 (t, 4H), 3.36 (m, 4H), 3.72 (t, 4H), 3.76 (m, 4H), 4.46 (s, 4H), 7.11 (m, 2H), 7.20 (m, 8H), 7.22-7.27 (m, 2H), 7.33 (t, 6H), 7.54 (m, 6H), 8.20 (dd, 2H), 9.02 (d, 2H) ppm.

Crystallised from refluxing acetonitrile and allowed to slowly cool to RT to afford the product as fine needles. Melting point: 215-216 (10 °C/min).

**Muscarinic Antagonist 9 (MA9):** r2-((R)-Cyclohexyl-hydroxy-phenyl-inethyl)-oxazol-S-ylmethvn-rB-O^-dichloro-phenoxyl-propyll-diniethyl-ammonium hemi-naphthalene-1,5-disulfonate


Yield: 56%.

LC-MS (Method 1): Rt 9.13 min, m/z 517 [M⁺].

\(^1\)H NMR (CD\(_3\)OD): \(\delta\) 1.05-1.37 (m, 12H), 1.56-1.75 (m, 8H), 2.23 (m, 4H), 2.40 (m, 2H), 3.03 (s, 6H), 3.04 (s, 6H), 3.34 (m, 4H), 3.96 (m, 4H), 4.68 (s, 4H), 6.85 (dd, 2H), 7.09 (d, 2H), 7.21 (m, 2H), 7.30 (t, 4H), 7.42 (d, 2H), 7.52 (m, 8H), 8.20 (dd, 2H), 9.02 (dd, 2H) ppm.

Crystallised from hot MeOH. Melting point: 225-227 °C (10 °C/min).
Muscarinic Antagonist 10 (MA10): 2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-r2-(3,4-dichloro-benzoxy)-ethyl-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate


Yield: 76%. LC-MS (Method 1): Rt 9.06 min, m/z 517 [M+].

1H NMR (CD3OD): δ 1.05-1.37 (m, 12H), 1.54 (m, 2H), 1.63-1.76 (m, 6H), 2.38 (m, 2H), 3.03 (s, 12H), 3.47 (m, 4H), 3.86 (m, 4H), 4.51 (s, 4H), 4.71 (s, 4H), 7.22-7.33 (m, 8H), 7.46 (s, 2H), 7.52 (m, 10H), 8.20 (dd, 2H), 9.02 (d, 2H) ppm.

Muscarinic Antagonist 11 (MA11): f2-(4-chloro-benzoxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate

Preparation [11]

MA11 may be prepared according to the method used in MA7, but using [2-(4-chloro-benzoxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide (MA6) instead of [2-((R)-cyclohexyl-hydroxy-phenyl-
methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. An example preparation is described below.

A mixture of [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide (0.20 g, 0.36 mmol), naphthalene-1,5-disulfonate disodium salt (0.059 g, 0.18 mmol), DCM (2.8 mL), and water (2.8 mL) was stirred vigorously at RT overnight. N-heptane (1.0 mL) was added and the mixture was stirred vigorously. On standing two clear layers and a yellow oil were obtained. DCM (1.0 mL) was added (causing the oil to dissolve) and the mixture was stirred at RT overnight resulting in precipitation of a white solid. The solid was collected by filtration, washed with DCM/water mixture, and dried under vacuum at 50 °C.

^1H NMR showed a spectrum corresponding to the hemi-salt (2:1 ratio of cation/anion). Yield: 0.17 g, 77%.

LC-MS (Method 1): Rt 8.62 min, m/z 483 [M+].
^1H NMR (CD$_3$OD): O 1.04-1.37 (m, 12H), 1.53 (m, 2H), 1.64-1.76 (m, 6H), 2.38 (m, 2H), 3.03 (s, 12H), 3.46 (m, 4H), 3.85 (m, 4H), 4.52 (s, 4H), 4.70 (s, 4H), 7.24 (m, 2H), 7.34 (m, 12H), 7.43 (s, 2H), 7.52 (m, 6H), 8.20 (d, 2H), 9.02 (d, 2H) ppm.
'Salt Form A' of r2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate

[2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate (as prepared herein above) (107mg, 0.17mmol) was dissolved in the minimum quantity of MeCN at RT. The solution was heated and then allowed to cool back to RT. The resulting crystalline solid was filtered off and dried under vacuum. Yield: 83 mg, 78%. Analysis of product prepared by this route was by XRPD identified the product as 'Salt Form A'.

Preparation [21]

General Experimental Conditions for Preparation [21]
All reactions were carried out under an atmosphere of inert gas unless specified otherwise.

NMR spectra were obtained on a Bruker AVANCE400 spectrometer: Frequency: 400 MHz; 2-Channel; z-Gradient. Temp Range: 0-120°C.

HPLC conditions:
Phenomenex Luna C18(2) column (50 x 4.6 mm), 3 μm particle size. UV detection at 210 nm. Elution with A: water + 0.05% Trifluoroacetic acid; B: acetonitrile + 0.05 % Trifluoroacetic 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>90</td>
<td>10</td>
</tr>
<tr>
<td>8.00</td>
<td>1.0</td>
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<td>90</td>
</tr>
<tr>
<td>9.00</td>
<td>1.0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>9.50</td>
<td>1.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>12.00</td>
<td>1.0</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>
LC-MS Method: LC-Method as given above. MS: HP-1 100 MSD. Detection - API-ES, positive mode.

Preparation [21]

A mixture of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (1 eq.) and 1-(2-bromo-ethoxymethyl)-4-chloro-benzene (2 eq) in 2-propanol (5 Vol.) was heated at 52°C for 164 h. HPLC showed a conversion of 98%. The reaction mixture was evaporated to dryness to yield [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide. The crude sample of [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium bromide was dissolved in dichloromethane (4.98 Vol.) and a solution of 1,5-naphthalene disulfonic acid di-sodium salt (1 eq.) in water (10 Vol.) added at room temperature over a period of 10 min. The mixture was diluted with dichloromethane (4.98 Vol.) and stirred for 1 hour at room temperature. The stirrer was turned off and the emulsion settled before separation. To the organic layer was added a mixture of tert-Butyl Methyl Ether (tBME) (10 Vol.) and 2-propanol (1.6 Vol.) at room temperature over a period of 72 min. The resulting suspension was filtered and the cake rinsed with tBME (2.15 Vol.). Drying (rotary evaporator at a bath temperature of 40-50°C at 5-10 mbar) gave [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate. The yield obtained by this preparation using 130 g of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol was 216g, 83%. ¹H NMR showed a spectrum corresponding to the hemi-salt (2:1 ratio of cation/anion).

Conversion to 'Salt Form A' was achieved by suspending a crude batch of [2-(4-chloro-benzyloxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate as prepared above in acetonitrile (13.8 Vol.). The suspension was heated to reflux and stirred at reflux for 1 hour. Then the suspension was cooled to 70°C and stirred at this temperature over night. The suspension was cooled to room temperature and the solid filtered and washed with acetonitrile (1.4 Vol.) and dried (rotary evaporator at a bath temperature of 40-50°C at 5-10 mbar) to yield
'Salt Form A'. The yield obtained by this conversion using 216 g of crude [2-(4-chloro-benzyleoxy)-ethyl]-[2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium hemi-naphthalene-1,5-disulfonate as starting material was 203.5 g, 94%.

**Preparation [3]**

General Experimental Conditions for Preparation [3] are the same as for Preparation [2].

A mixture of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (1 eq.) and 1-(2-bromo-ethoxymethyl)-4-chloro-benzene (2 eq.) in 2-propanol (5 Vol.) was submitted to the following temperature program:

- Heat to 70°C (internal temperature) over 1 hour, stir at 70°C for 26 hours and then cool to 20°C over 30 minutes. The conversion is checked by HPLC.
- The reaction mixture was evaporated to dryness (rotary evaporator at a bath temperature of 40-50°C at 10-15 mbar) and the residue dissolved in dichloromethane (8.9 Vol.). To the solution was added a solution of 1,5-naphthalene disulfonic acid di-sodium salt (1 eq.) in water (17.7 Vol.) over at least 10 minutes. The resulting mixture was diluted with dichloromethane (8.9 Vol.) and stirring continued at room temperature for 1 hour. The stirrer was turned off and the emulsion settled before separation. To the organic layer was added, over a period of at least 60 minutes at room temperature, a mixture of tBME (17.7 Vol.) and 2-propanol (2.86 Vol.). The suspension formed was stirred at room temperature for 10 to 60 minutes and then filtered. The filter cake is washed with tBME (2 x 3.46 Vol.) and dried (rotary evaporator at a bath temperature of 40-50°C at 5-10 mbar) until a Loss On Drying (LOD) ≤ 2 w/w% is obtained. The material was suspended in (22.9 Vol.) of acetonitrile and the suspension submitted to the following temperature program:

- Heat to reflux over a period of at least 30 minutes. Stir at reflux for 60 to 70 minutes, then cool to 70°C (internal temperature) and stir at 70°C for 16 to 24 hours and finally cool to 20°C over 1 hour. The suspension was filtered and the filter cake washed with acetonitrile (4.61 Vol.). The material was dried (rotary evaporator at a bath temperature of 40-50°C at 5-10 mbar) until a LOD ≤ 1 w/w% is obtained.
The yield obtained by this preparation using 25.0 g of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol was 38.7 g, 78%.

The yield obtained by this preparation using 129.9 g of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol was 203.6 g, 79%.

HPLC and NMR showed a spectrum corresponding to the hemi-salt (2:1 ratio of cation/anion).

**Solid State Analysis of MA 11 Salt Form A of r2-(4-chloro-benzzyloxy)-ethyl1-[2-((R)-cyclohexyl-hydroxy-phenyl-methyD-oxazol-S-ylmethyli-dimethyl-ammonium hemi-naphthalene- 1,5-disulfonate**

The melting temperature of Form A as determined by DSC was found to be 233 °C (onset) (±3 °C). Weight loss observed prior to melting by TGA was very low (0.0% - 0.5 %) GVS determination gave weight increase of less than 0.5(%w/w) at 80% RH (±0.3%).

An XRPD spectrum of 'MA11 Salt Form A' is presented in Figure 5.

'Salt Form A' was Micronised in a 50 mm jet mill, with ejector pressure 5 bar and milling pressure 1.5-2 bar, giving (90% yield). Particle size of the micronised material as determined by Malvern Laser Diffraction with dry powder feeder was d(0,l) 0,77µm: d(0,5), 1,45 µ: d(0,9): 2,65 µm. An investigational evaluation of the deaggregation properties of micronised 'Salt Form A' showed excellent Fine Particle Fraction (FPF >60%) across a range of relative humidity (0-75% RH).

**Biological Activity of Muscarinic Antagonists**

The inhibitory effects of compounds of the muscarinic antagonists were determined by a Muscarinic Receptor Radioligand Binding Assay.

Radioligand binding studies utilising [3H]-N-methyl scopolamine ([3H]-NMS) and commercially available cell membranes expressing the human muscarinic receptors (M2 or 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 [3H]-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 [³H]-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 [³H]-QNB ligand, with membranes expressing the human muscarinic receptors. At the end of this time, [³H]-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.

The following compounds were tested in the receptor binding assay:

<table>
<thead>
<tr>
<th>Muscarinic Antagonist</th>
<th>M3 binding Ki, nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA 1</td>
<td>9.4</td>
</tr>
<tr>
<td>MA 2</td>
<td>0.2</td>
</tr>
<tr>
<td>MA 3</td>
<td>0.6</td>
</tr>
<tr>
<td>MA 4</td>
<td>0.9</td>
</tr>
<tr>
<td>MA 5</td>
<td>2.1</td>
</tr>
<tr>
<td>MA 6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Preparation of CCRI Antagonists
General Methods in Preparation of CCR1 Antagonists

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian Inova 400 MHz or a Varian Mercury-VX 300 MHz instrument. The central peaks of chloroform-$^\wedge$ ( $^1$H 7.27 ppm), dimethylsulfoxide- $^d$ ( $^1$H 2.50 ppm), acetonitrile-$^d$ ( $^1$H 1.95 ppm) or methanol-$^\wedge$ ( $^1$H 3.31 ppm) were used as internal references. Flash chromatography was carried out using silica gel (0.040-0.063 mm, Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

The following method was used for LC/MS analysis:
Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 ml/min; Wavelength 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA; Gradient 15-95%/B 2.7 min, 95% B 0.3 min.

The following method was used for LC analysis:
Method A. Instrument Agilent 1100; Column: Kromasil C18 100 x 3 mm, 5µ particle size, Solvent A: 0.1%TFA/water, Solvent B: 0.08%TFA/acetonitrile Flow: 1 ml/min, Gradient 10-100% B 20 min, 100% B 1 min. Absorption was measured at 220, 254 and 280 nm.
Method B. Instrument Agilent 1100; Column: XTerra C8, 100 x 3 mm, 5 µ particle size, Solvent A: 15 mM NH$_4$H$_2$O/water, Solvent B: acetonitrile Flow: 1 ml/min, Gradient 10-100% B 20 min, 100% B 1 min. Absorption was measured at 220, 254 and 280 nm.


X-ray powder diffraction patterns of the Forms A salt described in Examples 1 and 2 (in anhydrous form) were obtained as described below:
A Bragg-Brentano parafocusing powder X-ray diffractometer using monochromatic CuKa radiation (45 kV and 40 mA) was used for the analyses. The primary optics contained soller slits and an automatic divergence slit. Flat samples were prepared on zero background plates that were rotated during the measurements. The secondary optics contained soller slits, an automatic anti scatter slit, a receiving slit and a monochromator. The diffracted signal was detected with a proportional xenon-filled detector. Diffraction patterns were collected between $2^\circ \leq 2\Theta(\text{theta}) \leq 40^\circ$ in a continous scan mode with a step size of $0.016^\circ 2\Theta$ at a rate of $4^\circ 2\Theta$ per minute. Raw data were stored electronically. Evaluation was performed on raw or smoothed diffraction patterns.

A Panalytical X’pert PRO MPD 0-0 diffractometer in reflection mode was used for the above-mentioned measurements. A person skilled in the art can set up instrumental parameters for a powder X-ray diffractometer so that diffraction data comparable to the data presented can be collected.

The following abbreviations are used in the following preparations of CCRI Antagonists.

- **APCI-MS** Atmospheric Pressure Chemical Ionisation Mass Spectroscopy;
- **DCM** Dichloromethane
- **DIEA** $N,N$-Diisopropylethylamine;
- **DMF** $N,N$-Dimethylformamide
- **DMSO** Dimethylsulfoxide;
- **HPLC** High Performance Liquid Chromatography;
- **LC/MS** Liquid Column Chromatography / Mass Spectroscopy;
- **TFA** Trifluoroacetic acid;
- **THF** Tetrahydrofuran

**CCRI Antagonist 1**

iV-{5-chloro-2-[(2S)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl]acetamide hemifumarate salt

A 40 °C warm solution of $N$-{5-chloro-2-[(2S)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl]acetamide (2.62 g) in methanol (15 mL) is added to a 40°C warm solution of fumaric acid (675 mg) in methanol (10 mL). The solution was allowed to cool to room temperature and the precipitate was
collected after 72 h, washed with cold methanol and vacuum-dried, to provide 1.33 g of the
titled compound.

\[ ^1\text{H NMR (300 MHz, DMSOD)} \delta 7.62 (m, 2H), 7.47 (m, 2H), 7.27 (s, IH), 7.1 1 (s, IH), 6.98 (s), 6.71 (s), 4.44 (s, 2H), 4.1 1-4.05 (m, 2H), 3.71-3.55 (m, 4H), 3.39-2.41 (m, 7H), 2.07 (m, 3H), 1.35 (s, 3H); APCI-MS: m/z 496 [MH+]; X-ray powder diffraction peaks

(expressed in degrees 2Θ):

(1) 6.2, 14.7 and 20.5, or 8.0, 10.1 and 14.7, or
(3) 10.1, 12.4, 14.7 and 19.5, or
(4) 6.2, 10.1, 12.4, 13.4, 19.5 and 20.1, or
(5) 8.0, 10.1, 12.4, 14.7, 19.5, 20.1, 21.2 and 23.8, or
(6) 6.2, 8.0, 10.1, 11.5, 12.4, 13.4, 19.5, 20.1 and 21.2, or
(7) 6.2, 8.0, 11.5, 12.4, 13.4, 14.7, 20.1, 20.5, 21.2 and 23.8, or
(8) 6.2, 8.0, 10.1, 11.5, 12.4, 13.4, 14.7, 16.1, 20.5, 21.2 and 23.8

**CCRI Antagonist 2**

\[N\{5-chloro-2-[(2S)-3-{{1-(4-chlorobenzyl)piperidin-4-yl}amino}-2-hydroxy-2-
-methylpropyloxy]-4-hydroxyphenyl}acetamide \] **sulphate salt**

\[N\{5-chloro-2-[(2S)-3- {{1-(4-chlorobenzyl)piperidin-4-yl}amino}]-2-hydroxy-2-
-methylpropyloxy]-4-hydroxyphenyl}acetamide \] (55 mg) is dissolved in 2-butanol (4 mL)

and, under stirring, heated to 55 0C. To this a 1M H₂SO₄ in 2-butanol solution (0.1 l mL),

that is kept at room temperature, is added in one portion. The mixture is warmed to 700C,

additional 2-butanol is added (16 mL) and the suspension stirred for 12h. The precipitate is

filtered off, dried and redissolved in methanol (4 mL). The solution is stirred at room

temperature and the solvent allowed to evaporate slowly to the open air, providing the

sulphate salt of \[N\{5-chloro-2-[(2S)-3-{{1-(4-chlorobenzyl)piperidin-4-yl}amino}-2-
-hydroxy-2-methylpropyloxy]-4-hydroxyphenyl}acetamide \].

\[ ^1\text{H NMR (300 MHz, DMSO-4)} \delta 10.08 (broad), 9.08 (s, IH), 7.78 (s, IH), 7.49-7.38 (m, 4H), 6.69 (s, IH), 3.91 (m, 2H), 3.56 (s, 2H), 3.23-2.81 (m, 5H), 2.13 (s, 3H), 2.09-2.00

(m, 4H), 1.69-1.63 (m, 2H), 1.38 (s, 3H); APCI-MS: m/z 496 [MH+]; X-ray powder
diffraction peaks (expressed in degrees 2Θ):

(1) 3.3, 9.9 and 19.8, or
(2) 8.4, 16.5 and 19.8, or
(3) 3.3, 9.9, 16.5, 17.9, 20.2 and 23.5, or
(4) 9.9, 16.5, 17.1, 17.9, 19.8, 20.2 and 23.5, or
(5) 3.3, 8.4, 9.9, 14.8, 17.1, 19.4, 19.8 and 20.2, or
(6) 9.0, 9.9, 11.8, 14.0, 14.8, 16.5, 19.8, 20.2 and 23.5, or
(7) 3.3, 8.4, 9.9, 11.8, 12.7, 14.0, 17.1, 17.9, 19.4, 19.8 and 20.2, or
(8) 3.3, 8.4, 9.9, 11.8, 12.7, 14.0, 14.8, 16.5, 17.1, 17.9, 19.4, 19.8, 20.2 and 23.5

**CCRI Antagonist 2**

Methyl 3-{2-[(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl)amino]-2-hydroxypropyl]oxy}-4-fluorophenylpropanoate

**Step I:** Methyl 3-(4-fluoro-2-((2S')-oxiran-2-ylmethoxy)phenyl)propanoate

A mixture of (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (130 mg), methyl 3-(4-fluoro-2-hydroxyphenyl)propanoate (99 mg) and Cs₂CO₃ (196 mg) in DMF (3 ml) was stirred at room temperature for 18h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0.20% ethyl acetate in petroleum ether 40-60 °C) to give the subtitled compound (105 mg).

**1H-NMR** (CDCl₃, 400 MHz): δ 7.10 (t, J = 7.5 Hz, 1H); 6.64-6.55 (m, 2H); 4.26 (dd, J = 2.8, 11.1 Hz, 1H); 3.93 (dd, 7 = 5.6, 11.1 Hz, 1H); 3.69 (s, 3H); 3.39 (m, 1H); 2.96-2.90 (m, 3H); 2.78 (dd, J = 2.7, 4.9 Hz, 1H); 2.60 (t, J = 7.7 Hz, 2H).

**Step II:**

Methyl 3-{4-fluoro-2-[(25)-oxiran-2-ylmethoxy]phenyl}propanoate (100 mg) and 1-(4-chlorobenzyl)piperidin-4-amine (88 mg) were taken into methanol (3 ml) and the solution stirred at 80°C for 18h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (0-2.5% methanol in dichloromethane containing 0.2% NH₄OH) to give the titled compound (100 mg).

**1H-NMR** (DMSO-(I₆, 400 MHz): δ 7.35 (m, 2H); 7.29 (m, 2H); 7.13 (t, J = 7.6 Hz, 1H); 6.84 (dd, J = 2.3, 11.4 Hz, 1H); 6.68-6.60 (m, IH); 4.99 (br.s, IH); 3.99-3.80 (m, 3H); 3.57 (s, 3H); 3.41 (s, 2H); 2.77 (t, J = 7.7 Hz, 2H); 2.74-2.51 (m, 6H); 2.38 (m, IH); 1.95 (t, J = 10.5 Hz, 2H); 1.73 (m, 2H); 1.20 (m, 2H).
APCI-MS: m/z 479 (MH⁺).

**CCR1 Antagonist 4**

(2-\{[(2S)-3-\{[l-(4-chlorobenzyl)piperidin-4-yl]amino\}-2-hydroxy-2-methylpropyl\}oxy\}-4-fluorophenyl) methanesulfonic acid

**Step I:** (4-Fluoro-2-{ r(2S)-2-methyloxiran-2-yllmethoxy}phenyl)methanol

A mixture of 5-fluoro-2-(hydroxymethyl)phenol (284 mg), [(2S)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (546 mg), and Cs₂CO₃ (986 mg) in DMF (5 ml) was stirred at room temperature for 18h. The mixture then was diluted with ethyl acetate (100 ml), and washed with water (2 x 50 ml). The organic layer was dried with sodium sulphate. The solvent was removed *in vacuo* to afford subtitle compound, 452 mg, which was used in the next step without further purification.

**\(^1\)H-NMR (CDCl₃, 400 MHz):** δ 7.26 (s, 1H), 6.67 (td, J = 8.3, 2.5 Hz, 1H), 6.61 (dd, J = 10.4, 2.3 Hz, 1H), 4.67 (dd, 7 = 33.3, 12.7 Hz, 2H), 4.11 (d, J = 10.4 Hz, 1H), 4.00 (d, J = 10.4 Hz, 1H), 2.94 (d, J = 4.6 Hz, 1H), 2.77 (d, J = 4.6 Hz, 1H), 1.50 (s, 3H).

**Step II:** tert-Butyl ri-(4-chlorobenzyl)piperidin-4-yl[(25)-3-r5-fluoro-2-(hydroxymethyl)phenoxyl-2-hydroxy-2-methylpropyl] carbamate

A mixture of 1-(4-chlorobenzyl)piperidin-4-amine (449 mg) and (4-fluoro-2-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl)methanol (424 mg) in dry ethanol (15 ml) was heated at 80 °C for 7 h. Then the solution was allowed to cool to room temperature, and di-tert-butyl carbonate (436 mg) was added. The mixture was stirred at room temperature for 18h, afterwhich the solvent was removed *in vacuo*. The residue was redissolved in ethyl acetate (50 ml), and washed with water (3 x 30 ml). The organic layer was dried with sodium sulphate, and after filtration removed *in vacuo* to afford the subtitle compound as yellowish oil, 1.02 g (95%).

APCI-MS: m/z 537 (MH⁺).

**Step III:** rerf-Butyl ri-(4-chlorobenzyl)piperidin-4-yl[(25)-3-r2-(chloromethyl)-5-fluorophenoxyl-2-hydroxy-2-methylpropyl carbamate

Polymer-bound triphenylphosphine (3 mmol/g; 83 mg) was stirred in dichloromethane (10 ml) for 30 min. rerf-Butyl [l-(4-chlorobenzyl)piperidin-4-yl][(25)-3-[5-fluoro-2-
(hydroxymethyl)phenoxy]-2-hydroxy-2-methylpropyl} carbamate (134 nig) was added, followed by tetrachloromethane (100 µl), and the mixture was stirred at room temperature for 18h. Additional portions of tetrachloromethane (2 ml) and polymer-bound triphenylphosphine (3 mmol/g; 166 mg) were added, and stirring was continued for 7 h. Then the insoluble material was removed by filtration, and the solvent removed in vacuo to afford a brownish oil, which was used without purification in the next step.

APCI-MS: m/z 555 (MH+).

Step IV: (2-f[2S]-3-\{4-chlorobenzyl\}piperidin-4-yllamino)-2-hydroxy-2-methylpropyl\}oxy \}4-fluorophenyl)methanesulfonic acid

Sodium sulphite (1.0 g) was suspended in water (2 ml). A solution of tert-butyl [l-(4-chlorobenzyl)piperidin-4-yl][[(2S)-3-[2-(chloromethyl)-5-fluorophenoxy]-2-hydroxy-2-methylpropyl \}carbamate (0.25 mmol) in ethanol (4 ml) was added. The mixture was stirred overnight at 80 °C. The intermediate (2-\{[(2S)-3-\{(tert-butoxycarbonyl)[l-(4-chlorobenzyl)piperidin-4-yl]amino \}]-2-hydroxy-2-methylpropyl\}oxy \}4-fluorophenyl)methanesulfonic acid was purified by HPLC (water/acetonitrile), and the solvent was removed by freeze-drying. The residue was redissolved in dichloromethane (10 ml), and TFA (95 % in water, 5 ml) was added. After stirring at room temperature for 3 h the solvent was removed in vacuo, and the residue purified by HPLC to afford title compound, 17 mg (9 %).

1H-NMR (CD$_3$OD, 400 MHz): δ 7.52 (s, 4H), 7.35 (dd, J = 8.2, 7.0 Hz, IH), 6.84 (d, J = 10.6 Hz, IH), 6.73 (td, J = 8.4, 2.2 Hz, IH), 4.34 (s, 2H), 4.24 (d, J = 13.6 Hz, IH), 4.10 (d, J = 13.3 Hz, IH), 4.07 (s, 2H), 3.93 (d, J = 9.7 Hz, IH), 3.61 (d, J = 12.4 Hz, 2H), 3.47 (m, IH), 3.1 1 (br.s, IH), 3.04 (d, J = 12.7 Hz, IH), 2.38 (brs, 2H), 2.15 (br.s, IH), 1.40 (s, 3H).

CCRI Antagonist 5

Urea, N-5-chloro-\{2-(2S)-3-\{[(4-chlorobenzyl)-4-piperidiny]lamino]-2-hydroxypropoxy\}4-hydroxyphenyl)-N'-cyclopropyl-

Step 1: 5-Chloro-2,4-dihydroxybenzoic acid

To a solution of 4-chlororesorcinol (43.3 g) in water (250 mL), sodium bicarbonate (180 g) was added in portions. The reaction was refluxed for 2h, cooled to room temperature and
concentrated hydrochloric acid (150 mL) was added dropwise (pH <1). The mixture was cooled on ice and the precipitate collected. The brown solid was washed with water (5 x 50 mL) and dried to air yielding 11.4 g of the subtitle compound as a brown solid.

\[^1\text{H-NMR}\ (\text{dms}-d_6, 400 \text{ MHz}): \delta 11.21 \text{ (s, IH)}, 7.67 \text{ (s, IH)}, 6.50 \text{ (s, IH)}.\]

**Step II: Ethyl 5-chloro-2,4-dihydroxybenzoate**

To a solution of 5-chloro-2,4-dihydroxybenzoic acid (20.9 g) thionyl chloride (50 mL) was added dropwise. The reaction was stirred at 80°C for 18 h, after which the solvent was removed *in vacuo*. The residue was redissolved in EtOAc (300 mL) and washed with an aqueous solution of NaHCO	extsubscript{3} (10%; 100 mL). The organic phase was washed with water (3 x 100 mL), dried and removed *in vacuo*. The residue was purified by suspending in EtOAc (150 mL) and heptane (150 mL) and filtrating over silica (230-400 mesh). The filtrate was concentrated *in vacuo* and resuspended in EtOAc (35 mL) and heptane (250 mL). This suspension was filtrated over silica (230-400 mesh) and the filtrate collected and concentrated in vacuo, giving 14.0 g of the subtitle compound as a white solid.

\[^1\text{H-NMR}\ (\text{acetone}-d_6, 300 \text{ MHz}): \delta 10.87 \text{ (broad), 7.78 \text{ (s, I)}, 6.58 \text{ (s, IH)}; 4.40 \text{ (m, 2H)}, 1.39 \text{ (m, 3H)}.\]

**Step III: Ethyl 5-chloro-4-hydroxy-4-([4-methoxybenzyl]oxy)benzoate**

To a solution of ethyl 5-chloro-2,4-dihydroxybenzoate (1.96 g) in aceton (50 mL) were added 4-methoxybenzylchloride (1.42 g) and K	extsubscript{2}CO	extsubscript{3} (1.25 g). The reaction was heated to reflux for 18 h, after which the solvent was removed *in vacuo*. The residue was redissolved in EtOAc and washed with water. The organic solvent was removed *in vacuo* and the residue recrystallized from methanol and subsequently from ethanol, yielding 1.38 g of the subtitle compound as a white solid.

\[^1\text{H-NMR}\ (\text{acetone}-d_6, 400 \text{ MHz}): \delta 11.01 \text{ (broad), 7.81 \text{ (s, IH)}, 7.46 \text{ (m, 2H)}, 6.98 \text{ (m, 2H)}, 6.76 \text{ (s, IH)}, 4.40 \text{ (m, 2H)}, 3.82 \text{ (s, 3H)}, 1.39 \text{ (m, 3H)}.\]

**Step IV: 5-Chloro-2-hydroxy-4-(4-methoxybenzyl)oxybenzoi acid**

To solution of ethyl 5-chloro-2-hydroxy-4-([4-methoxybenzyl]oxy)benzoate (1.38 g) in ethanol (15 mL) 1 M NaOH aq (15 mL) was added. The reaction was heated to reflux for 1 h, diluted with water (100 mL) and the pH adjusted with 1 M HCl aq (15 mL) to acidic.
The precipitate was filtered, washed with water and dried in a vacuum oven yielding 1.09 g of the subtitled compound as a white solid.

\[ ^1H-NMR \text{ (dmso-}d_6, 400 \text{ MHz): } \delta 7.73 \text{ (s, IH), 7.39 (m, 2H), 6.97 (m, 2H), 6.82 (s, IH), 3.77 (s, 3H).} \]

**Step V:** 5-Chloro-2-hydroxy-4-r(4-methoxybenzyl)oxy1benzoyl azide

To a solution of 5-chloro-2-hydroxy-4-[4-methoxybenzyl]oxy]benzoic acid (154 mg) and triethylamine (1 eq) in DCM (3 mL) DPPA (3 eq) was added. The reaction was stirred for 48 h, after which the solvent was removed in vacuo. The residue was suspended in acetonitrile and the precipitate collected (96 mg of the subtitled compound). The filtrate was purified over HPLC (water/acetonitrile) yielding 30 mg of the subtitled compound as a white solid.

\[ ^1H-NMR \text{ (CDCl}_3, 400 \text{ MHz): } \delta 10.97 \text{ (broad), 7.76 (s, IH), 7.38 (m, 2H), 6.94 (m, 2H), 6.57 (s, IH), 3.83 (s, 3H).} \]

**Step VA:** 5-Chloro-6-r(4-methoxybenzyl)oxy-1,3-benzoxazol-2(3H)-one

A solution of 5-chloro-2-hydroxy-4-[4-methoxybenzyl]oxy]benzoyl azide (30 mg) in toluene (2 mL) was stirred at 100 °C for 18 h. The precipitate was collected, yielding 19 mg of the subtitled compound.

\[ ^1H-NMR \text{ (dmso-}d_6, 400 \text{ MHz): } \delta 7.40-7.38 \text{ (m, 3H), 7.16 (s, IH), 6.95 (m, 2H), 3.76 (s, 3H).} \]

**Step VI:** N-15-Chloro-4-f(4-methoxybenzyl)oxy1-2-r(2S)-oxiran-2-ylmethoxylphenyl- N’-cyclopropyl urea

A solution of 5-chloro-6-[4-methoxybenzyl]oxy]-1,3-benzoxazol-2(3H)-one (1.62 g) in cyclopentylamine (10 mL) was stirred at room temperature for 2 h and at 50 °C for 2 h. The solvent was removed in vacuo and the residue redissolved in DMF (25 mL) to which (+)-glycidynosylate (1.4 g) and cesium carbonate (2.6 g) were added. The reaction was stirred at room temperature for 18 h. EtOAc (300 mL) was added and the organic phase was extracted with water (3 x 100 mL). The organic phase was dried and the solvent removed in vacuo. The residue was washed with EtOAc (5 x 5 mL) and dried in a vacuum oven, yielding 1.60 g of the subtitled compound as a light brown solid.
1H-NMR (CD$_3$OD, 400 MHz): δ 8.25 (s, IH), 7.51 (broad), 7.36 (m, 2H), 6.90 (m, 2H), 6.55 (s, IH), 4.31-4.27 (m, IH), 3.83-3.97 (m, IH), 3.82 (s, 3H), 3.32 (m, IH), 2.92 (m, IH), 2.75-2.72 (m, IH), 2.59 (m, IH), 0.86 (m, 2H), 0.68 (m, 2H).

Step VII:
A solution of N-\([5\text{-Chloro-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-y]methoxy}phenyl-7\text{-cyclopropyl urea (126 mg) and l-(4-chlorobenzyl)piperidin-4-amine (68 mg) in ethanol (3 mL) was heated to 80 °C for 18 h. The solvent was removed in vacuo and the residue purified over HPLC (water/acetonitrile with 0.1% TFA), yielding 38 mg of the titled compound as a white solid.

1H-NMR (acetone-d$_6$, 400 MHz): δ 8.31 (s, IH), 7.61-7.46 (m, 4H), 6.87 (broad, IH), 6.62 (s, IH), 4.38-4.35 (m, 3H), 4.10-4.06 (m, IH), 3.94-3.90 (m, IH), 3.69-3.66 (m, 4H), 3.40-3.35 (m, IH), 3.18 (m, 2H), 2.56-2.47 (m, 3H) 2.34-2.21 (m, 2H), 0.64-0.60 (m, 2H), 0.47-0.41 (m, 2H); APCI-MS: m/z 523 (MH$^+$).

CCRI Antagonist 6
Urea, N-(2-\([2S]-3-[1-(4-chlorobenzyl)-4-piperidinyl]amino\)-2-hydroxypropoxy\)-phenyl)-N'-ethyl-

Step I: N-ethyl-N-\([2S]-2\text{-[(2S)-oxiran-2-y]methoxy}phenylurea
Two stock solutions of 0.2 M N-ethyl-W-(2-hydroxyphenyl)urea in DMF and 0.2 M [(2S)-2methylxiran-2-y] methyl 3-nitrobenzenesulfonate in DMF were combined (total volume 100 µL). To this mixture cesium carbonate (0.03 mmol) was added and the reaction was stirred at room temperature for 18 h. The mixture was partitioned between water and DCM and the organic layer washed with water. The organic solvent was removed and the compound used without further purification in step II, example 6
APCI-MS: m/z 251 (MH$^+$).

Step II:
Two stock solutions of 0.1 M N-ethyl-N'-\([2S]-2\text{-[(2S)-oxiran-2-y]methoxy}phenylurea in EtOH and 0.1 M l-(4-chlorobenzyl)piperidin-4-amine in EtOH were combined (total volume 400 µL). The mixture was heated to 80 °C for 12 h, after which the solvent was removed yielding the titled compound.
APCI-MS: m/z 476 (MH$^+$).

**CCR1 Antagonist 7**

(2S)-l-(2-ethyIphenoxy)-3[(l-[4-chlorobenzyl]4-piperidinyl)amino]propan-2-ol

Prepared following procedure as described for CCR1 Antagonist 6. APCI-MS: m/z 403 (MH$^+$).

**CCR1 Antagonist 8**

(2S)-l-[2-(hydroxyethyl)phenoxy]-2-methyl-3[(l-[4-chlorobenzyl]-4-piperidinyl)amino]propan-2-ol **trifluoroacetate salt**

Prepared following procedure as described for CCR1 Antagonist 6. APCI-MS: m/z 434 (MH$^+$).

**CCR1 Antagonist 9**

2-({2S}-3-[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy)benzaldehyde

Prepared following procedure as described for CCR1 Antagonist 6. APCI-MS: m/z 417 (MH$^+$).

**CCR1 Antagonist 10**

2-({2S}-3-[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)-N-cyclopropylbenzamide

**Step I: N-cyclopropyl-2-fluoro-6-hydroxy benzamide**

To a suspension of PS-carbodiimid (1.09 mmol/g; 6g) in chloroform (40 mL) and DMF (10 mL) first cyclopropylamine (315 mg) and consequently 2-fluoro-6-hydroxy benzoic acid (780 mg) were added. The reaction was stirred at room temperature for 48 h. The mixture was filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (DCM/EtOH) yielding 243 mg of the subtitled compound. APCI-MS: m/z 196 (MH$^+$).

**Step II. N-cyclopropyl-2-fluoro-6-r(2S)-oxiran-2ylmethoxy1benzamide**
To a solution of 3-cyclopropyl-2-fluoro-6-hydroxy benzamide (100 mg) and (S)-glycidyl nosylate (110 mg) in DMF (3 mL) cesium carbonate (250 mg) was added. The suspension was stirred at room temperature for 18 h. The mixture was partitioned between EtOAc and water and the organic layer washed four times with water, dried over sodium sulphate and removed in vacuo yielding 89 mg of the subtitled compound. The material was used without further purification in step III of example 10.

APCI-MS: m/z 252 (MH⁺).

**Step πi**

Prepared following procedure as described for CCR1 Antagonist 6, step II.

1H-NMR (acetone-d₆, 400 MHz): δ 7.62 (m, 2H), 7.47 (m, 2H), 7.39-7.36 (m, 1H), 6.91 (m, IH), 6.79 (m, IH), 4.48 (s, 2H), 4.41-4.14 (m, 7H), 2.97-2.92 (m, IH), 2.60-2.51 (m, 4H), 0.77-0.72 (m, 2H), 0.63-0.59 (m, 2H); APCI-MS: m/z 476 (MH⁺).

**CCR1 Antagonist 11**

Methyl 2-([(2S)-3-[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)-4-fluorobenzoate trifluoroacetic acid salt

Prepared following procedure as described for CCR1 Antagonist 6. APCI-MS: m/z 451 (MH⁺).

**CCR1 Antagonist 12**

N-[2-((2S)-3-[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)-4-chlorophenyl acetamide

**Step I**

N-[4-chloro-2r(2S)-oxiran-2ylmethoxyphenyl] acetamide

To a solution of N-(4-chloro-2-hydroxyphenyl)acetamide (1.27 g) and (2S)-glycidyl nosylate (0.93 g) in DMF (7.5 mL) cesium carbonate (2.6 g) is added and the reaction is stirred at room temperature for 24 h. The mixture is partitioned between EtOAc (50 mL) and water (50 mL) and the organic phase is washed several times with water, dried over sodium sulphate and removed in vacuo. The residue is purified using flash chromatography (DCM/EtOH) to provide 317 mg of the subtitled compound.
**Protocols for Combination Experiments**

1. **Evaluation of compound activity on isolated tracheal rings from guinea-pig preconstricted with methacholine.**

The following protocol may be used to evaluate the effects of muscarinic M3 receptor antagonists according to the present invention in combination with budesonide.

Male albino Dunkin Hartley guinea-pigs (300-350 g) are killed by cervical dislocation and the trachea excised. Adherent connective tissue is removed and the trachea cut into ring segments (2-3 mm wide). These are suspended in 10ml organ baths containing a modified Krebs solution composition (mM): NaCl 117.56, KCl 5.36, NaH₂PO₄ 1.15, MgSO₄ 1.18, glucose 11.10, NaHCO₃ 25.00 and CaCl₂ 2.55. This is maintained at 37°C and continually gassed with 5% CO₂ in O₂. Indomethacin (2.8 µM), corticosterone (10 µM), ascorbate (1 mM), CGP20712A (1 µM) and phentolamine (3 µM) are added to the Krebs solution: indomethacin to prevent development of smooth muscle tone due to the synthesis of cyclooxygenase products, corticosterone to inhibit the uptake 2 process, ascorbate to prevent catecholamine oxidation and CGP20712A and phentolamine to avoid any
complicating effects of β1- and α-adrenoceptor activation respectively. The tracheal rings
are suspended between two stainless steel hooks, one attached to an isometric force
transducer and the other to a stationary support in the organ bath. Changes in isometric
force are recorded.

Acetyl-β-methylcholine chloride (Methacholine), Indomethacin, Corticosterone-21-acetate,
Phentolamine hydrochloride, Ascorbic acid, and CGP20712A methanesulphate may be obtained from the Sigma chemical company. Indomethacin may be dissolved in 10% w/v Na₂CO₃, corticosterone 21-acetate in ethanol and other compounds in DMSO. Muscarinic antagonists and Budesonide may be diluted in Krebs prior to adding to tissues and the level of DMSO in the bath < 0.1%.

At the beginning of each experiment a force of 1.0 g.wt. is applied to the tissues and this is reinstated over a 30min equilibration period until it remained steady. Tissues are then exposed to 1µM of the muscarinic agonist, methacholine, to assess tissue viability. Tissues are washed by exchanging the bathing Krebs solution three times. After 30 minutes the tissues are precontracted with 1µM methacholine. When the contraction reaches a plateau, 100nM Budesonide, 10nM Muscarinic antagonist or a combination of the two is added to the bathing media and left for 60 minutes.

Data may be collected using the ADInstruments Chart5 for windows software, the tension generated may be measured before addition of methacholine and after its response reaches a plateau. The response to the muscarinic antagonist and/or Budesonide may be measured at 10 minute intervals following their addition. All responses may be expressed as percentage inhibition of the methacholine-induced contraction.

2. Inflammatory Cell influx experiment in LPS-Challenged Rats

The following protocol may be used to evaluate the effects of muscarinic M3 receptor antagonists according to the present invention, in combination with CCR1 antagonists.
The effect of a CCR1 receptor antagonist and a muscarinic antagonist according to the invention, and their combination, on inflammatory cell influx can be assayed by monitoring the effect on total cell number in broncholalveolar lavage (BAL) fluid of rats challenged intra-tracheally (i.t.) with Lipopolyaccharide (LPS) [N = 10 rats per treatment group].

Methodology

**LPS instillation:** Rats are anaesthetized with Efrane and put in a supine position, head up, on a board tilted at 30°. LPS (Lipopolysaccharide B.E.coli 026:B6) (2.5 µg/ml) is dissolved in saline (0.9% NaCl), or saline alone (negative control) in a volume of 200 µl and administered i.t. using a modified metal cannula. Rats remain in this position until regaining consciousness.

**Preparation of solutions:** CCR1 antagonists are dissolved in 0.9% NaCl solution to a final concentration of 0.001 to 0.100 mg. Muscarinic antagonists are dissolved in 0.9% NaCl solution to an appropriate final concentration of 0.001 to 1.0 mg/ml. CCR1 antagonist, Muscarinic antagonist or mixed s are made by dissolving CCR1 antagonist in Muscarinic antagonist suspensions, giving a final concentration of 001 to 0.100 CCR1 antagonist /ml and 001 to 1.0 mg Muscarinic antagonist /ml.

**Treatments:** Animals were intratracheally instilled with solutions (1 ml/kg) of Muscarinic antagonist / CCR1 antagonist (0.002/ 001 to 0.100 mg/kg), or of Muscarinic antagonist (001 to 1.0 mg/kg) alone, or CCR1 antagonist (001 to 0.100 mg/kg) alone, or with saline (negative and positive control animals). The treatments were carried out under light anaesthesia (Efrane) to secure that the solution reached the lungs. The drugs were administrated 30 min before the LPS instillation.

**Termination:** 4 hours after the LPS challenge, rats are intraperitoneally injected with the mixture (0.3 ml) of pentobarbital (60 mg/ml, Apoteksbolaget, Sweden) and PBS (1:1) for 1 - 2 min.
Bronchoalveolar lavage: After termination, BAL is performed twice with PBS. The BAL fluid is centrifuged and the cell pellet was resuspended in PBS. The total numbers of BAL cells is counted in a SYSMEX cell counter.
CLAIMS

1. A pharmaceutical product comprising, in combination, a first active ingredient which is a muscarinic antagonist selected from:

- [2-((S)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(2-phenethyloxy-ethyl)-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[3-(3,4-dichlorophenoxy)-propyl] dimethyl-ammonium salt,
- [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichlorobenzyloxy)-ethyl]-dimethyl-ammonium salt, and
- [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium salt,

and a second active ingredient which selected from

- i) a phosphodiesterase inhibitor,
- ii) a modulator of chemokine receptor function
- iii) an inhibitor of kinase function,
- iv) a protease inhibitor,
- v) a steroidal glucocorticoid receptor agonist,
- vi) a non-steroidal glucocorticoid receptor agonist, and
- vii) a purinoceptor antagonist.

2. A product according to claim 1 wherein the first active ingredient is a muscarinic antagonist, which is a bromide or a napadisylate salt.
3. A product according to claim 1 wherein the first active ingredient is a muscarinic antagonist which is a napadisylate salt.

4. A product according to any one of claims 1 to 3, wherein the second active ingredient is a CCRI antagonist.

5. A product according to claim 4 wherein the second active ingredient is a CCRI antagonist, which is a compound of general formula

\[
(R^1)_m \text{N}^{(CH_2)_n}(\text{CH}_2)p \text{N}^{(CH_2)}\text{OH} A - R^5
\]

wherein

- \(m\) is 0, 1 or 2;
- \(R^1\) is halogen, \(C_1-C_3\) haloalkyl or cyano;
- \(X^1\) is -CH\(_2\) or -C(O)-;
- \(n\) is 0, 1 or 2;
- \(p\) is 0, 1 or 2;
- \(R^2\) is \(C_1-C_6\) cycloalkyl; or
- \(R^2\) forms a bicyclic ring together with the ring it is attached to;
- \(R^3\) is hydrogen, \(CpC_4\) alkyl;
- \(R^4\) is hydrogen, halogen, hydroxyl, \(CpC_6\) hydroxyalkyl, optionally substituted by one substituent independently selected from halogen, cyano, amino (-NH\(_2\)), amido (-CONH\(_2\)), hydroxyl, oxo (=O), \(C_1-C_6\) haloalkyl, carboxyl, \(C_1-C_6\) alkoxy, \(C_1-C_6\) alkoxy carbonyl, \(C_1-C_6\) alky carbonylamino and a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=O), \(C_1-C_6\) alkyl, \(C_1-C_6\) hydroxyalkyl and \(C_1-C_6\) haloalkyl;
- \(A\) is a bond or d-Qhaloalkyl;
R^5 is hydrogen, hydroxyl, -NHC(O)R^6, -NHS(O)_2R^6, -C(O)NR^7R^8, -COOR^9 or SO_3R^9.

R^6 is hydrogen, Ci-C_6 alkyl, a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, Ci-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl, oxo (=0) and -OR^9;

R^7 and R^8 each independently represent (i) hydrogen atom,
(ii) a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=O), Ci-C_6 alkyl, Ci-C_6 hydroxyalkyl and Ci-C_6 haloalkyl,
(iii) a Ci-C_6 alkyl group, optionally substituted by one or more substituent independently selected from halogen, amino (-NH_2), hydroxyl, oxo (=O), Ci-C_6 haloalkyl, carboxyl, Ci-C_6 alkoxy, Q-C_6 alkoxy carbonyl, Ci-C_6 alkyl carbonylamino and a 3- to 6-membered saturated or unsaturated ring, optionally comprising one or more heteroatom selected from nitrogen, oxygen and sulphur, and optionally further comprising a bridging group, the ring being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, oxo (=O), Ci-C_6 alkyl, C_1-C_6 hydroxyalkyl and Ci-C_6 haloalkyl, or
(iv) Ci-C_6 alkyl sulphonyl, or
(v) R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with one or more substituent independently selected from halogen, hydroxyl, amidoo (-CONH_2), Ci-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy carbonyl, C_1-C_6 haloalkyl, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_1-C_6 alkyl carbonyl, C_1-C_6 alkyl carboxylamino, C_1-C_6 alkylaminocarbonyl, di-C_1-C_6 alkylaminocarbonyl, phenyl, halophenyl, phenyl carbonyl, phenyl carboxyloxy and hydroxy diphenylmethyl;

R^9 is hydrogen or C_1-C_6 alkyl;

q is 0, 1 or 2;
R\textsuperscript{10} is halogen, hydroxyl, cyano, \textit{C}_{3}-\textit{C}_{6} haloalkyl or \textit{C}_{6} alkoxy; or a pharmaceutically acceptable salt thereof; or,
a compound of general formula

\begin{equation}
\text{(II)}
\end{equation}

wherein

m is 0, 1 or 2;

R\textsuperscript{1} is halogen, cyano, \textit{C}_{6} haloalkyl;

X, Y and Z is a bond, -O-, -NH-, \textit{CH}_{2} or -C(O)-, provided that only one of X, Y and Z is a bond, and provided that X and Y are not simultaneously -O- or -C(O)-;

n is 0, 1 or 2;

R\textsuperscript{2} is \textit{C}_{1}-\textit{C}_{6}(\textit{cyclo})alkyl;

p is 0 or 1;

R\textsuperscript{3} is hydrogen or \textit{C}_{6} alkyl;

A is a bond or \textit{C}_{3} alkyl;

R\textsuperscript{4} is hydrogen, halogen, hydroxyl, -NH\textsubscript{2}(O)R\textsubscript{6}, -NHS(O)\textsubscript{2}R\textsubscript{6}, -C(O)NR\textsubscript{7}R\textsubscript{8}, -COOR\textsubscript{9} or SO\textsubscript{3}R\textsubscript{9};

R\textsuperscript{5} is hydrogen, hydroxyl, -NHC(O)R\textsubscript{6}, -NHS(O)\textsubscript{2}R\textsubscript{6}, -C(O)NR\textsubscript{7}R\textsubscript{8}, -COOR\textsubscript{9} or SO\textsubscript{3}R\textsubscript{9};

R\textsuperscript{6} is hydrogen, C-C\textsubscript{3} alkyl,NR\textsubscript{7}R\textsubscript{8}, or OR\textsubscript{9};
R\(^7\) and R\(^8\) are independently selected from hydrogen or CpC\(_6\) alkyl and \(C_3\)-\(C_7\) cycloalkyl; or
R\(^7\) and R\(^8\) together with the nitrogen atom to which they are attached form a 4-7 membered heterocyclic ring, which is optionally substituted with one or more hydroxyl groups;
R\(^9\) is a hydrogen or C\(_1\)-C\(_3\) alkyl; and
R\(^{10}\) is halogen, cyano, C\(_1\)-C\(_3\) alkoxy or Q-Qhaloalkyl, or a pharmaceutically acceptable salt thereof.

6. A product according to claim 5, wherein the second active ingredient is \(N\!\!-(2\!\!-(2S)-3-[/((2S)-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl)oxy]-A-hydroxyphenyljacetamide or a pharmaceutically acceptable salt thereof.

7. A product according to claim 5, wherein the second active ingredient is \(N\!\!-(5-chloro-2-[(2S)-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyljacetamide or a pharmaceutically acceptable salt thereof.

8. A product according to claim 5, wherein the second active ingredient is 2-\{2-chloro-5\!\!-[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(methylamino)carbonyl]phenoxy\}-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof.

9. A product according to any one of claims 1 to 3, wherein the second active ingredient is a steroidal glucocorticoid receptor agonist.

10. Use of a product according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a respiratory disease.

11. Use according to claim 10, wherein the respiratory disease is chronic obstructive pulmonary disease.
12. A method of treating a respiratory disease, which method comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a muscarinic receptor antagonist as defined in any one of claims 1 to 3; and

(b) a (therapeutically effective) dose of a second active ingredient as defined in claim 1; to a patient in need thereof.

13. A kit comprising a preparation of a first active ingredient which is a muscarinic receptor antagonist as defined in any one of claims 1 to 3, and a preparation of a second active ingredient as defined in claim 1 and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

14. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a muscarinic receptor antagonist as defined in any one of claims 1 to 3 and a second active ingredient as defined in claim 1.
Figure 3

Counts

40000
10000

Position [°2Theta]

Figure 4

Counts

6400
3600
1600
400

Position [°2Theta]
Figure 6

Counts

2Theta

5 10 15 20 25 30 35

5 10 15 20 25 30 35
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/421 A61K31/4468 A61P11/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/112778 A (ASTRAZENECA AB [SE]; BAILEY ANDREW [GB]; DONALD DAVID [GB]) 26 October 2006 (2006-10-26) pages 28-31</td>
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X Further documents are listed in the continuation of Box C. X See patent family annex.

'A' special category of cited documents

'A' earlier document but published on or after the international filing date

'F' document which may throw doubts on priority claims

'O' document refering to an oral disclosure, use, exhibition or other means

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

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

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

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

'S' document member of the same patent family

Date of the actual completion of the international search: 13 June 2008

Date of mailing of the international search report: 24/06/2008

Name and mailing address of the ISA:
European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016

Authorized officer: Steendijk, Martin
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