

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 January 2010 (21.01.2010)

PCT

(10) International Publication Number
WO 2010/008341 A1

(51) International Patent Classification:

A61K 31/416 (2006.01) *A61P 11/00* (2006.01)
A61K 31/421 (2006.01) *A61P 11/06* (2006.01)
A61K 31/46 (2006.01)

(21) International Application Number:

PCT/SE2009/050900

(22) International Filing Date:

15 July 2009 (15.07.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/081,059 16 July 2008 (16.07.2008) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: A COMBINATION OF (A) GLUCOCORTICOID RECEPTOR MODULATOR AND (B) A MUSCARINIC ANTAGONIST

(57) Abstract: The present invention relates to a combination of (a) a glucocorticoid receptor modulator and (b) a muscarinic antagonist. The invention further relates to pharmaceutical compositions comprising said combination and to methods of treatment of airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma in mammals by administering said combination. The invention further relates to a kit comprising the combination and use of said kit in treatment of airway diseases.



WO 2010/008341 A1

A combination of (a) glucocorticoid receptor modulator and (b) a muscarinic antagonist.

THE FIELD OF THE INVENTION

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The present invention relates to a combination of (a) glucocorticoid receptor modulator and (b) a muscarinic antagonist. The invention further relates to pharmaceutical compositions comprising said combination and to methods of treatment of airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma in mammals by administering
10 said combination. The invention further relates to a kit comprising the combination and use of said kit in treatment of airway diseases.

BACKGROUND OF THE INVENTION

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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
20 diseases of the respiratory system (or airway diseases). A number of these diseases are of great public health importance. Airway 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.

25

Among the most common airway 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
30 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.

5 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
10 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.

15 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
20 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
25 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.

Sulphonamide derivatives are disclosed as anti-inflammatories in WO 2004/019935 and WO 2004/050631. Pharmaceutically active sulphonamides are also disclosed in Arch.

30 Pharm. (1980) 313 166-173, J. Med. Chem. (2003) 46 64-73, J. Med. Chem (1997) 40 996-

1004, EP 0031954, EP 1190710 (WO 200124786), US 5861401, US 4948809, US3992441 and WO 99/33786.

It is known that certain non-steroidal compounds interact with the glucocorticoid receptor (GR) and, as a result of this interaction, produce a suppression of inflammation (see, for
5 example, US6323199). Such compounds can show a clear dissociation between anti-inflammatory and metabolic actions making them superior to earlier reported steroidal and non-steroidal glucocorticoids.

The muscarinic receptors M1, M2 and M3 are expressed in human lungs, M2 and M3
10 dominating in the airways and M1 found only in smaller peripheral airways. Most cell types in airways and lung including inflammatory cells express muscarinic receptors. Acetylcholine (ACh) being the classical neurotransmitter of the parasympathetic nervous system is the main endogenous ligand binding to the muscarinic receptors. M3 receptors are expressed on airway smooth muscle cells and mediate bronchoconstriction leading to
15 airway narrowing. M1 receptors facilitate cholinergic neurotransmission and enhance airway bronchoconstriction. The M2 receptor acts as a feedback autoreceptor inhibiting the release of ACh at the nerve endings. In airway smooth muscle cells activation of M2 receptors augment ACh-triggered smooth muscle contraction initiated by activation of M3 receptors, leading to bronchoconstriction and an overall reduced lung functional capacity
20 being a hallmark of COPD.

M3 signalling mediates smooth muscle cell proliferation and accordingly contributes to the remodelling process in chronic inflammatory airways. M3 signalling enhances mucus production from airway goblet cells, contributing to plugging of small airways, leading to cough (bronchitis) and reduced lung function in COPD patients. Muscarinic agonists, such
25 as ACh, act on airway tracheal epithelial cells and increase cell proliferation, release of inflammatory mediators from epithelial and inflammatory cells, which results in increased chemotactic activity of neutrophils and macrophages.

Treatment of COPD patients with inhaled M1 and M3 selective muscarinic antagonists targets cholinergic bronchoconstriction by opening narrowed airways resulting in sustained
30 improvement in lung function, reduced mucus production, reduced exacerbation frequency,

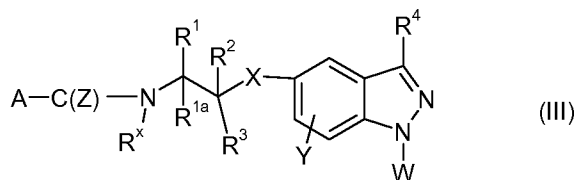
less activity-induced breathlessness, improved exercise endurance and an overall quality of life (QOL) improvement for these patients.

The present invention relates to a combination of a glucocorticoid receptor modulator with
 5 a muscarinic antagonist.

It is contemplated that the combination of the present invention has a beneficial therapeutic effect in the treatment of airway diseases. For example, the combination according to the invention is considered to be particularly effective in reducing inflammatory cell influx into the lung. The beneficial effect may be observed when the two active substances are
 10 administered simultaneously (either in a single pharmaceutical composition or in separate compositions), or sequentially or separately.

DETAILED DESCRIPTION OF THE INVENTION

Thus, according to the present invention, there is provided a pharmaceutical product for
 15 treating an airway disease comprising, in combination,
 (a) a first active ingredient, which is glucocorticoid receptor modulator of formula (III)



20 wherein:

A is C₁₋₃hydroxyalkyl, C₃₋₅cycloalkyl, C₁₋₃haloalkyl or NR⁵R⁶C(O);

R¹ and R^{1a} are independently selected from hydrogen and C₁₋₃alkyl;

R² is hydrogen;

R³ is C₅₋₁₀aryl C₅₋₁₀arylOC₁₋₂alkyl or C₅₋₁₀heteroaryl, which may be optionally substituted
 25 by one or more substituents independently selected from B;

B is C₁₋₃alkoxy or C₁₋₃alkylS(O)_n;

n is 2;

R⁴ is hydrogen;

W is phenyl which is optionally substituted by one or more halo;

X is O;

Y is hydrogen;

5 Z is O;

R⁵ and R⁶ are independently selected from hydrogen and C₁₋₃alkyl; and

R^x is hydrogen;

or a pharmaceutically acceptable salt thereof.

and

- 10 (b) a second active ingredient, which is a muscarinic antagonist selected from a
[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,
15 [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-dichloro-
phenoxy)-propyl] dimethyl-ammonium salt,
[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-
20 benzyloxy)-ethyl]- dimethyl-ammonium salt;
[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-
ylmethyl]- dimethyl-ammonium salt,
(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-
azonia-bicyclo[2.2.2]octane salt, and
25 (R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-
bicyclo[2.2.2]octane salt.

For the avoidance of doubt, the present invention relates to a pharmaceutical product
whereby the muscarinic antagonist is combined with any compound falling within the
30 scope of compounds of formula (III) as defined above.

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 'C₁₋₆' 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 C₁₋₄ 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, isopropoxy, 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 "C₁₋₆cycloalkyl" may be, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

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 "C₁₋

C₆haloalkyl” 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, trifluorophenyl, 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.

It will be appreciated that throughout the specification, the number and nature of substituents on rings in the compounds of the invention will be selected so as to avoid sterically undesirable combinations.

In one embodiment the first active compound, which is a glucocorticoid receptor modulator is selected from:

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]cyclopropanecarboxamide,

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]propanamide, methyl N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]carbamate,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-2-methyl-propanamide,

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide,

5 N-[(1R,2S)-1-(4-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]-2,2-dimethyl-propanamide,

10 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(4-methylsulfonylphenyl)propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide,

15 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide,

N-[(1R,2S)-1-(2,5-dioxabicyclo[4.4.0]deca-7,9,11-trien-8-yl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2,2,2-trifluoro-acetamide,

20 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-naphthalen-2-yl-propan-2-yl]acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-naphthalen-2-yl-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-(3-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2,2,2-trifluoro-acetamide,

25 N-[(1R,2S)-1-(3-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2-hydroxy-acetamide, and

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methylphenyl)propan-2-yl]acetamide,

or a pharmaceutically acceptable salt thereof.

The glucocorticoid receptor modulator of the present invention have been named with the aid of computer software (ACDLabs 8.0/Name(IUPAC)).

The compound of formula (III) 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 (III) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. In one embodiment the optical isomers are the (S)-enantiomers.

It will be appreciated that the compounds of formula (III) 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 (III) and the compounds of the examples of the present invention covers both neutral and zwitterionic forms and mixtures thereof in all proportions.

The compounds of formula (III) 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, (hemi)fumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate,

methanesulphonate, trifluoroacetate or *p*-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 (III) 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 (III) or salts thereof also encompasses solvates of such compounds and solvates of such salts (e.g. hydrates) as well as cocrystals.

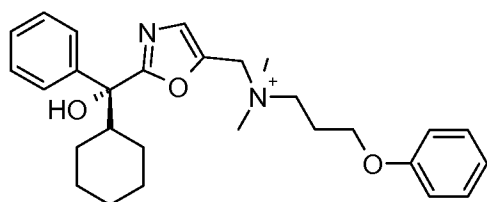
The glucocorticoid receptor modulators mentioned above may be prepared according to the process described in patent application PCT/SE2007/001136.

The second active ingredient in the combination of the present invention is a muscarinic antagonist. One embodiment of the invention relates to long acting muscarinic antagonists. Another embodiment relates to short acting muscarinic antagonists.

One embodiment relates to a pharmaceutical product whereby the first active ingredient is 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide or a pharmaceutically acceptable salt thereof, and the second active ingredient is 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-dichloro-phenoxy)-propyl] dimethyl-ammonium salt, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt, and [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt.

In another embodiment of the present invention, the first active ingredient is 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide or a pharmaceutically acceptable salt thereof, and the second active ingredient is a [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt (e.g. bromide or hemi-naphthalene-1,5-disulfonate).

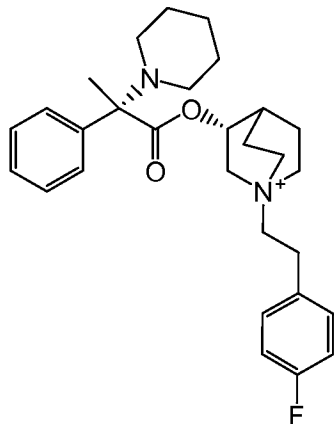
The muscarinic antagonists of this embodiment are selected members of a novel class of compound described in WO2007/017669 which display high potency to the M3 receptor. The names of the muscarinic antagonists according to this embodiment are IUPAC names generated by the Autonom 2000 plug in for IsisDraw 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, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt has the structure



The muscarinic receptor antagonists of this embodiment 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, toluenesulfonate (tosylate), edisylate (ethane-1,2-disulfonate), isethionate (2-hydroxyethylsulfonate), nitrate or phosphate; or an anion of a suitable organic acid, for example acetate, maleate, fumarate, citrate, lactate, oxalate, oleic, succinate, tartrate, methanesulphonate (mesylate), p-toluenesulphonate, benzenesulphonate, napadisylate (naphthalene-1,5-disulphonate) (e.g. a heminapadisylate), maleate ((Z)-3-carboxy-acrylate), succinate (3-carboxy-propionate), malate ((S)-3-carboxy-2-hydroxy-propionate), p-acetamidobenzoate, 2,5-dichlorobenzenesulphonate, 1-hydroxy-2-naphthoate (xinafoate) or 1-hydroxynaphthalene-2-sulphonate.

In another embodiment the muscarinic antagonist is (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane X; wherein X represents a pharmaceutically acceptable anion of a mono or polyvalent acid. The muscarinic antagonist (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-

propionyloxy)-1-azonia-bicyclo[2.2.2]octane X is described in WO2008/075005, and has the structure



The anion X may be any pharmaceutically acceptable anion of a mono or polyvalent (e.g. bivalent) acid. In an embodiment of the invention X may be an anion of a mineral acid, for example chloride, bromide, iodide, sulfate, toluenesulfonate (tosylate), edisylate (ethane-1,2-disulfonate), isethionate (2-hydroxyethylsulfonate), nitrate or phosphate; or an anion of a suitable organic acid, for example acetate, maleate, fumarate, citrate, lactate, oxalate, oleic, succinate, tartrate, methanesulphonate (mesylate), p-toluenesulphonate, benzenesulphonate, napadisylate (naphthalene-1,5-disulphonate) (e.g. a heminapadisylate), maleate ((Z)-3-carboxy-acrylate), succinate (3-carboxy-propionate), malate ((S)-3-carboxy-2-hydroxy-propionate), p-acetamidobenzoate, 2,5-dichlorobenzenesulphonate, 1-hydroxy-2-naphthoate (xinafoate) or 1-hydroxynaphthalene-2-sulphonate.

In another embodiment of the present invention, the first active ingredient is 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide or a pharmaceutically acceptable salt thereof, and the second active ingredient is a (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt (e.g. bromide, chloride or benzenesulphonate).

In another embodiment the muscarinic antagonist is (R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane

X; wherein X represents a pharmaceutically acceptable anion of a mono or polyvalent acid. The muscarinic antagonist (*R*)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane belongs to a novel class of muscarinic antagonist described in WO 2008/059245 and in PCT/GB2008/001647. The anion X may be any pharmaceutically acceptable anion of a mono or polyvalent (e.g. bivalent) acid. In an embodiment of the invention X may be an anion of a mineral acid, for example chloride, bromide, iodide, sulfate, toluenesulfonate (tosylate), edisylate (ethane-1,2-disulfonate), isethionate (2-hydroxyethylsulfonate), nitrate or phosphate; or an anion of a suitable organic acid, for example acetate, maleate, fumarate, citrate, lactate, oxalate, oleic, succinate, tartrate, methanesulphonate (mesylate), p-toluenesulphonate, benzenesulphonate, napadisylate (naphthalene-1,5-disulphonate) (e.g. a heminapadisylate), maleate ((*Z*)-3-carboxy-acrylate), succinate (3-carboxy-propionate), malate ((*S*)-3-carboxy-2-hydroxy-propionate), p-acetamidobenzoate, 2,5-dichlorobenzenesulphonate, 1-hydroxy-2-naphthoate (xinafoate) or 1-hydroxynaphthalene-2-sulphonate.

In another embodiment of the present invention, the first active ingredient is 2,2,2-trifluoro-N-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide or a pharmaceutically acceptable salt thereof, and the second active ingredient is a (*R*)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt (e.g. bromide).

In another embodiment, the muscarinic antagonist is selected from [2-((*S*)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide, [2-((*R*)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide, [2-((*R*)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-(2-phenethyloxy-ethyl)-ammonium bromide, [2-((*R*)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium bromide,

[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium bromide,
 [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium bromide,
 5 (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane bromide,
 [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-
 10 phenethyloxy-ethyl)-ammonium hemi-naphthalene-1,5-disulfonate,
 [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium hemi-naphthalene-1,5-disulfonate,
 [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium hemi-naphthalene-1,5-disulfonate,
 15 [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium hemi-naphthalene-1,5-disulfonate, and
 (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane hemi-naphthalene-1,5-disulfonate.

20 For the avoidance of doubt, the present invention relates to a pharmaceutical product whereby any one of the compounds of formula (III) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), is combined with any one of the specific the muscarinic antagonist mentioned above.

Pharmaceutical compositions

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
 30 oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or

suspensions. The active ingredients may also be administered topically (e.g. to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder compositions. 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.

- One embodiment relates to a pharmaceutical composition comprising, in admixture, a first active ingredient which is a compound of formula (III) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above) or a pharmaceutically acceptable salt thereof, and a second active ingredient which is a muscarinic antagonist mentioned above, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

In one embodiment of the present invention the active ingredients are administered via separate pharmaceutical compositions.

- Therefore, in one aspect, the present invention provides a kit comprising a composition of a first active ingredient, which is a compound of formula (III) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above) and a composition of a second active ingredient, which is a muscarinic antagonist mentioned above, and optionally instructions for the simultaneous, sequential or separate administration of the compositions to a patient in need thereof.

- The pharmaceutical compositions of the present invention may be prepared by mixing the first active ingredient and the second active ingredient with 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 compound of formula (III) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), with a second active ingredient as defined above, and a
5 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
10 the condition or disorder to be treated.

In one embodiment of the present invention, the first and second active ingredients of the present invention are each administered by inhalation. In this embodiment, the active ingredients may be inhaled simultaneously. In another embodiment the active ingredients
15 may be inhaled sequentially. Or in a further embodiment the active ingredients may be inhaled separately.

The active ingredients are conveniently administered via inhalation (e.g. topically to the lung and/or airways) in the form of solutions, suspensions, aerosols or dry powder
20 compositions. Administration may be by inhalation, orally or intranasally. The active ingredients are preferably adapted to be administered, either together or individually, from a dry powder inhaler, pressurised metered dose inhaler, or a nebuliser.

The active ingredients may be used in admixture with one or more pharmaceutically
25 acceptable additives, diluents or carriers. Examples of suitable diluents or carriers include lactose (e.g. the monohydrate), dextran, mannitol or glucose.

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, a surfactant,
30 a lubricant, an anti-oxidant or a stabilising agent. 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, solutions may also be employed, with or
5 without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose compositions.

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
10 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.

When the active ingredients are adapted to be administered, either together or individually, via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with
15 or without a suitable pH or tonicity adjustment, either as a single dose or multidose device.

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

20 In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), and a second active ingredient, which is muscarinic antagonist, wherein each active ingredient is
25 formulated for inhaled administration.

In another embodiment of the present invention, the first active ingredient, which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of
30 formula (III) mentioned above), may be formulated for oral administration and the second

active ingredient(s) , which is a muscarinic antagonist, as defined above, may be formulated for inhaled administration.

In yet another embodiment of the present invention, the first active ingredient, which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), may be formulated for inhaled administration and the second active ingredient(s), which is a muscarinic antagonist, as defined above, may be formulated for oral administration.

In yet a further embodiment of the present invention, the first active ingredient, which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), and the second active ingredient(s), which is a muscarinic antagonist, as defined above, wherein each active ingredient is formulated for oral administration.

Medical use

The use of compounds of formula (III) are contemplated to demonstrate particular effects when used in combination with a muscarinic antagonist. For example, *in vivo* animal experiments may indicate that a combination of a muscarinic antagonist and a compound of formula (III), at dose levels where neither component alone significantly affects lung inflammation, in combination give significant reduction of inflammatory cell influx. The reduction in cell influx for the combination is contemplated to be greater than that expected from the additive effect of the two ingredients. This synergistic effect when combining the ingredients could be used, for example, to lower the therapeutic dose of muscarinic antagonist, or at the same dose, achieve enhanced efficacy on inflammation in comparison to the use of the muscarinic antagonist alone. The synergistic effect can be particularly advantageous where lower doses of the muscarinic antagonist are desirable, for example in individuals that have acquired resistance to such a muscarinic antagonist.

Examples of conditions diseases which may be treated using the combination of the invention are, but not limited to, airways/respiratory diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late
5 asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases,
10 fibroid lung and idiopathic interstitial pneumonia.

The compound of formula (III), or a pharmaceutically acceptable salt thereof, (first active ingredient) and the muscarinic antagonist or a pharmaceutically acceptable salt thereof, (second active ingredient) may be administered simultaneously, sequentially or separately
15 to treat airway diseases. By sequential it is meant that the active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately, but when administered in this manner they are generally 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
20 minutes apart.

Throughout the specification, the amount of the active ingredients used relate to unit doses unless explicitly defined differently.

25 When administered via inhalation the dose of the first active ingredient (compound of formula (III) or a pharmaceutically acceptable salt thereof), will generally be in the range of from 0.1 µg to 10000 µg, 0.1 to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 200 µg, 0.1 to 200 µg, 0.1 to 100 µg, 0.1 to 50 µg, 5 µg to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 200 µg, 5 to 100 µg, 5 to 50 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 200 µg,
30 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 200 µg, 20 to

100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 200 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg.

In one embodiment, the amount of the first active ingredient used is in the range of
5 from 1 µg to 200 µg, and that of the second active ingredient is in the range of from 1 µg to 200 µg.

When administered via inhalation the dose of the second active ingredient (muscarinic antagonist), will generally be in the range of from 0.1 microgram (µg) to 1000 µg, 0.1 to
10 500 µg, 0.1 to 200 µg, 0.1 to 100 µg, 0.1 to 50 µg, 0.1 to 5 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 200 µg, 5 to 50 µg, 5 to 10 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 200 µg, 10 to 100 µg, 10 to 50 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 200 µg, 20 to 100 µg, 20 to 50 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 200 µg, 50 to 100 µg, 100 to 1000 µg, or 100 to 500 µg.

15 The molar ratio of the second active ingredient to the first active ingredient in a dose may typically be in the range of from 300:1 to 1:300. In one embodiment the ratio is in the range of from 100:1 to 1:100. In another embodiment the ratio is in the range of from 50:1 to 1:50. In a further embodiment the ratio is in the range of from 10:1 to 1:10. In yet another embodiment the ratio is in the range of from 5:1 to 1:5.

20 In one embodiment the ratio is in the range of 1:10 to 1:50. In another embodiment the ratio is in the range of 1:15 to 1:40.

The M3 antagonists are likely to have a lower molecular weight but may be as potent at their receptor as the glucocorticoid receptor modulators.

25 The doses of the first and second active ingredients will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

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

The present invention further provides the use of a pharmaceutical product, kit or pharmaceutical composition, which comprises:

(a) a (therapeutically effective) dose of a first active ingredient, which is a compound of formula (III) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above) or a pharmaceutically acceptable salt thereof; and
(b) a (therapeutically effective) dose of a second 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-dichlorobenzoyloxy)-ethyl]- dimethyl-ammonium salt;

[2-(4-Chloro-benzoyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt,

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt, and

(R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-

bicyclo[2.2.2]octane salt, in the manufacture of a medicament for the treatment of airway diseases.

The present invention further provides the use of a pharmaceutical product, kit or pharmaceutical composition, which comprises:

(a) a (therapeutically effective) dose of a first active ingredient, which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as defined above or any one of the compounds or salts of compounds of formula (III) mentioned above), or a pharmaceutically acceptable salt thereof; and

5 (b) a (therapeutically effective) dose of a second active ingredient, which is a muscarinic antagonist selected from

[2-((S)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt,

10 [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-dichloro-phenoxy)-propyl] dimethyl-ammonium salt,

15 [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt;

[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt,

20 (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt, and

(R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease or asthma, or any other disorder mentioned above.

25 The present invention still further provides a method of treating airway diseases, or chronic obstructive pulmonary disease or asthma, or any other disorder mentioned above which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient, which is a compound of formula (III)) (i.e. any one of the compounds falling within the scope of formula (III) as

defined above or any one of the compounds or salts of compounds of formula (III) mentioned above) or a pharmaceutically acceptable salt thereof; and

(b) a (therapeutically effective) dose of a second 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-dichloro-phenoxy)-propyl] dimethyl-ammonium salt,

[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt;

[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt,

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt, and

(R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt to a patient in need thereof.

One embodiment of the invention relates to the combination as described above wherein phosphodiesterase (PDE) inhibitors as well as glucocorticoid receptor agonists are excluded from the combination of the invention.

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.

5 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 “ingredient” means the compounds comprised in the combination of the present invention, i.e. glucocorticoid receptor modulators or a muscarinic antagonist.

10

Examples

The present invention will now be further understood by reference to the following illustrative examples.

15 Example 1

Inflammatory cell influx experiment in LPS-challenged rats

The effect of glucocorticoid receptor modulator referred to here as Compound A, and a muscarinic antagonist, referred to here as Compound B, and their combination, on inflammatory cell influx is examined by monitoring the effect on total and neutrophil cell number in bronchoalveolar lavage (BAL) fluid of rats challenged intra-tracheally (i.t.) with Lipopolysaccharide (LPS) N=10 [N = 7 rats per treatment group]. Saline group n=2

20

Methodology

Preparation of solutions: Both Compound A and compound B are dissolved in a Vehicle containing the following ingredients (mg/mL): Sodium chloride (8.5), EDTA (0.1), Citric acid dried (0.15), Sodium citrate (0.5), Polysorbate 80 (0.2) in Milli-Q water) to the final concentrations of 0.001 or 0.01 µg/ml (compound A) and 0.1 µg/ml (compound B).

25

Compound A/Compound B mixed formulations are made by mixing 0.002 or 0.02 µg/ml Compound A in Vehicle and 0.2 µg/ml Compound B in Vehicle to the final concentrations

of 0.001/0.1 µg/mL Compound A/Compound B and 0.01/0.1 µg/mL Compound A/Compound B.

LPS (Lipopolysaccharide B. E.coli 026:B6) is dissolved in saline to a final concentration of 2.5 µg/ml

5

Treatments: Rats are anaesthetized with Isofluran and put in a supine position, head up, on a board tilted at 30°. Animals are intratracheally instilled with solutions (1 ml/kg) of Compound A/Compound B (0.001/ 0.1 µg/kg), Compound A/Compound B (0.01/0.1 µg/kg), Compound A (0.001 or 0.01 µg/kg) alone, Compound B (0.1 µg/kg) alone, or with Saline (negative and positive control animals). Rats remain in this position until regaining consciousness. The drugs are administrated 30 min before LPS instillation.

10

LPS instillation: Rats are anaesthetized with Isofluran and put in a supine position, head up, on a board tilted at 30°. LPS or saline alone (negative control) in a volume of 200 µl is administered i.t. using a modified metal cannula. Rats remain in this position until regaining consciousness.

15

Termination: 4 hours after the LPS challenge, rats are intraperitoneally injected with 2 mL of a mixture of pentobarbital (60 mg/ml, Apoteksbolaget, Sweden) and PBS (1:1) for 1 – 2 min.

20

Bronchoalveolar lavage (BAL): After termination, collection of BAL fluid is performed twice with PBS. The BAL fluid is centrifuged and the cell pellet is resuspended in PBS. The total numbers of BAL cells are counted in a SYSMEX cell counter.

25

It is contemplated that these in vivo studies show that the combination of two non-effective dosages of a muscarinic antagonist and a glucocorticoid receptor modulator leads to a significant reduction in the influx of pro-inflammatory cells, like neutrophils, in the bronchial lavage fluid, over both the LPS challenged group, as well as those groups treated with a muscarinic antagonist or a glucocorticoid receptor modulator and that such a

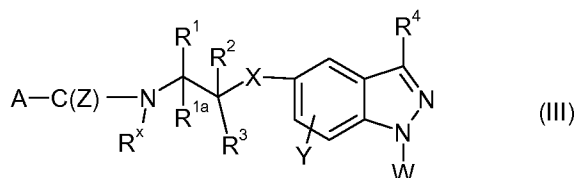
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combined treatment will lead to an improved control over the inflammatory element of the pathology of airway diseases, like COPD. The lowering in inflammatory cell levels following this combination treatment will lead to a decrease in exacerbations of disease, i.e. a reduction in bronchoconstriction and a diminished mucus production and plugging. In
5 addition, it is contemplated that patients that receive a combination treatment containing both a muscarinic antagonist and a glucocorticoid receptor modulator will need to be treated with less amount of both active ingredients, compared to patients that are on single treatment.

CLAIMS

1. A pharmaceutical product for treating an airway disease comprising, in combination,
(a) a first active ingredient, which is a compound of formula (III)

5



wherein:

A is C₁₋₃hydroxyalkyl, C₃₋₅cycloalkyl, C₁₋₃haloalkyl or NR⁵R⁶C(O);

R¹ and R^{1a} are independently selected from hydrogen and C₁₋₃alkyl;

10 R² is hydrogen;

R³ is C₅₋₁₀aryl C₅₋₁₀arylOC₁₋₂alkyl or C₅₋₁₀heteroaryl, which may be optionally substituted by one or more substituents independently selected from B;

B is C₁₋₃alkoxy or C₁₋₃alkylS(O)_n;

n is 2;

15 R⁴ is hydrogen;

W is phenyl which is optionally substituted by one or more halo;

X is O;

Y is hydrogen;

Z is O;

20 R⁵ and R⁶ are independently selected from hydrogen and C₁₋₃alkyl; and

R^x is hydrogen;

or a pharmaceutically acceptable salt thereof,

and

(b) a second active ingredient, which is a muscarinic antagonist selected from a

25 [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,

5 [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- [3-(3,4-dichloro-phenoxy)-propyl] dimethyl-ammonium salt,

[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt;

10 [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt,

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt and

(R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt

15

2. The pharmaceutical product according to claim 1, wherein the first active ingredient is selected from:

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]cyclopropanecarboxamide,

20 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]propanamide, methyl N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]carbamate,

25 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-2-methyl-propanamide,

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide,

30 N-[(1R,2S)-1-(4-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]-2,2-dimethyl-propanamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(4-methylsulfonylphenyl)propan-2-yl]-2-hydroxy-acetamide,

5 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide,

10 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide,

N-[(1R,2S)-1-(2,5-dioxabicyclo[4.4.0]deca-7,9,11-trien-8-yl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2,2,2-trifluoro-acetamide,

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-naphthalen-2-yl-propan-2-yl]acetamide,

15 N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-naphthalen-2-yl-propan-2-yl]-2-hydroxy-acetamide,

N-[(1R,2S)-1-(3-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2,2,2-trifluoro-acetamide,

20 N-[(1R,2S)-1-(3-ethylphenyl)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-propan-2-yl]-2-hydroxy-acetamide, and

2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methylphenyl)propan-2-yl]acetamide,

or a pharmaceutically acceptable salt thereof.

25 3. The pharmaceutical product according to any one of claims 1 to 2, wherein both active ingredients are in a composition suitable for inhalation.

4. Use of the pharmaceutical product according to any one of claims 1 to 3, in the manufacture of a medicament for the treatment of airway diseases.

5. Use according to claim 4, wherein the airway disease is chronic obstructive pulmonary disease or asthma.

6. A method of treating airway diseases, or chronic obstructive pulmonary disease or asthma, which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient, which is a glucocorticoid receptor modulator as defined in any one of claims 1, 2 or 3, or a pharmaceutically acceptable salt thereof; and

(b) a (therapeutically effective) dose of a second active ingredient, which is a muscarinic antagonist selected from a

[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-dichloro-phenoxy)-propyl] dimethyl-ammonium salt,

[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-(3,4-dichloro-benzyloxy)-ethyl]- dimethyl-ammonium salt;

[2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]- dimethyl-ammonium salt,

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane salt, and

(R)-3-(1-Phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/050900

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008076048 A1 (ASTRAZENECA AB ET AL), 26 June 2008 (26.06.2008), claims 1-4,13,21, examples 5-7,12,16,18-24,40 --	1-6
Y	WO 2007017669 A1 (ARGENTA DISCOVERY LTD.), 15 February 2007 (15.02.2007), page 21, line 16 - line 20, claims 33-35, examples 7-12,44, 46,49,56-57,65,68-69,80-81,83,85-87 --	1-6
Y	WO 2008075005 A1 (ASTRAZENECA AB), 26 June 2008 (26.06.2008), claims 1,16, example 44 --	1-6

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

15 October 2009

Date of mailing of the international search report

20-10-2009

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/050900

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008059245 A1 (ASTRAZENECA AB), 22 May 2008 (22.05.2008), claims 1,16 --	1-6
A	WO 2008063116 A1 (ASTRAZENECA AB ET AL), 29 May 2008 (29.05.2008), claims 1,17, example 5 --	1-6
A	WO 2008079073 A1 (ASTRAZENECA AB ET AL), 3 July 2008 (03.07.2008), claims 1,17, example 1 -- -----	1-6

International patent classification (IPC)**A61K 31/416** (2006.01)**A61K 31/421** (2006.01)**A61K 31/46** (2006.01)**A61P 11/00** (2006.01)**A61P 11/06** (2006.01)**Download your patent documents at www.prv.se**

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Use the application number as username. The password is **QSYHSJTMXR**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050900

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 6 relates to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic
.../...
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050900

Box II.1

methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/SE2009/050900

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				EC	SP099394 A	31/07/2009
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