NOVEL COMBINATIONS

The present invention relates to a combination of two or more pharmaceutically active substances for use in the treatment of respiratory diseases (for example chronic obstructive pulmonary disease (COPD) or 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 that 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 that 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 that 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 corticosteroids. Corticosteroids (also known as glucocorticosteroids or glucocorticoids) are potent anti-inflammatory agents. Whilst their exact mechanism of action is not clear, the end result of corticosteroid treatment is a decrease in the number, activity and movement of inflammatory cells into the bronchial submucosa, leading to decreased airway responsiveness. Corticosteroids may also cause reduced shedding of bronchial epithelial lining, vascular permeability, and mucus secretion. Whilst corticosteroid treatment can yield important benefits, the efficacy of these agents is often far from satisfactory, particularly in COPD. Moreover, whilst the use of steroids may lead to therapeutic effects, it is desirable to be able to use steroids in low doses to minimise the occurrence and severity of undesirable side effects that may be associated with regular administration. Recent studies have also highlighted the problem of the acquisition of steroid resistance amongst patients suffering from respiratory diseases. For example, cigarette smokers with asthma have been found to be insensitive to short term inhaled corticosteroid therapy, but the disparity of the response between smokers and non-smokers appears to be reduced with high dose inhaled corticosteroid (Tomlinson *et al.*, Thorax 2005; 60:282-287).

A further class of therapeutic agent used in the treatment of respiratory diseases are bronchodilators. Bronchodilators may be used to alleviate symptoms of respiratory diseases by relaxing the bronchial smooth muscles, reducing airway obstruction, reducing lung hyperinflation and decreasing shortness of breath. Types of bronchodilators in clinical use include β_2 adrenoceptor agonists, muscarinic receptor antagonists and methylxanthines. Bronchodilators are prescribed mainly for symptomatic relief and they are not considered to alter the natural history of respiratory diseases.

Combination products comprising a β_2 adrenoceptor agonist and a corticosteroid are available. One such product is a combination of budesonide and formoterol fumarate dihydrate (marketed by AstraZeneca under the trade mark Symbicort ®), which has proven to be effective in controlling asthma and COPD, and improving quality of life in many patients.

In view of the complexity of respiratory diseases such as asthma and COPD, it is unlikely that any one mediator can satisfactorily treat a respiratory disease alone. Whilst the known combination treatments using a β_2 adrenoceptor agonist and a corticosteroid deliver significant patient benefits, there remains a medical need for new therapies against respiratory diseases such as asthma and COPD, in particular for therapies with disease modifying potential.

The present invention provides a new combination product comprising (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate, or a pharmaceutically acceptable salt thereof.

The compound, (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate (and pharmaceutically acceptable salts thereof), is disclosed in our co-pending International

Patent Application No. PCT/SE2010/050367 (WO2010/114476) and has glucocorticosteroid receptor agonist activity.

In accordance with the present invention there is provided a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β2 adrenoreceptor agonist, a dual β2 adrenoreceptor agonist/M3 receptor antagonist (hereinafter referred to as a "MABA compound"), a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor (GR receptor) agonist; and optionally one or more pharmaceutically acceptable excipients.

In accordance with the present invention there is also provided a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β2 adrenoreceptor agonist, a dual β2 adrenoreceptor agonist/M3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor; and optionally one or more pharmaceutically acceptable excipients.

In accordance with the present invention there is also provided a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β2

adrenoreceptor agonist, a dual β2 adrenoreceptor agonist/M3 receptor antagonist or a muscarinic antagonist; and optionally one or more pharmaceutically acceptable excipients.

In accordance with the present invention there is also provided a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β2 adrenoreceptor agonist or a dual β2 adrenoreceptor agonist/M3 receptor antagonist; and optionally one or more pharmaceutically acceptable excipients.

Thus, in this embodiment the first and second active ingredients are in admixture.

The invention also provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor (GR receptor) agonist, wherein the preparations are for simultaneous, sequential or separate administration to a patient in need thereof.

The invention also provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient

selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor, wherein the preparations are for simultaneous, sequential or separate administration to a patient in need thereof.

The invention also provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist, wherein the preparations are for simultaneous, sequential or separate administration to a patient in need thereof.

The invention also provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, wherein the preparations are for simultaneous, sequential or separate administration to a patient in need thereof.

The present invention further provides a kit comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a

phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor (GR receptor) agonist, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The present invention further provides a kit comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The present invention further provides a kit comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The present invention further provides a kit comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor

antagonist, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

By "simultaneous" is meant that the preparations of the first and second active ingredients are administered at the same time. By "sequential" is meant that the preparations of the first and second 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, conveniently less than two hours apart, more conveniently less than 30 minutes apart and most conveniently less than 20 minutes apart, for example less than 10 minutes but not one immediately after the other.

Examples of possible salts of the first active ingredient, (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate, include, for example, an acid addition salt such as a hydrochloride, sulfate, methanesulfonate or *p*-toluenesulfonate salt, or a salt with a suitable base such as a hydroxide or methoxide salt.

The first active ingredient, (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate (and pharmaceutically acceptable salts thereof), may exist in solvated, for example hydrated, as well as unsolvated forms, and the present invention encompasses all such solvated forms.

For the avoidance of doubt, unless otherwise stated, any reference to any of the second active ingredients includes any active salt, solvate or derivative that may be formed from said active ingredient, or any enantiomer or mixture thereof.

A β_2-adrenoreceptor agonist is any compound or substance capable of stimulating the

β_2-receptors and acting as a bronchodilator. In the context of the present specification, unless otherwise stated, any reference to a β_2- adrenoreceptor agonist includes an active salt, solvate or derivative that may be formed from said β_2- adrenoreceptor agonist or any enantiomer or mixture thereof. Examples of possible salts or derivatives of a β_2-adrenoreceptor agonist are (1) acid addition salts such as the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, maleic acid, and (2) pharmaceutically acceptable esters (e.g. C_1-C_6 alkyl esters). The β_2-adrenoreceptor agonists may also be in the form of solvates, e.g. hydrates.

Examples of β_2- adrenoreceptor agonists that may be used in the pharmaceutical product according to the invention include:
metaproterenol,
isoproterenol,
isoprenaline,
albuterol,
salbutamol (e.g. as sulphate),
formoterol (e.g. as fumarate or fumarate dihydrate),
salmeterol (e.g. as xinafoate),
terbutaline,
orciprenaline,
bitolterol (e.g. as mesylate),
pirbuterol or
indacaterol (chemically identified as 5-{(1R)-2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1H)-one, and which is commercially available).

In one embodiment of the invention, the β_2-adrenoreceptor agonist is a long-acting β_2-adrenoreceptor agonist (i.e. a β_2-adrenoreceptor agonist with activity that persists for more than 24 hours), examples of which include:

indacaterol

salmeterol (e.g. as xinafoate),

formoterol (e.g. as fumarate or fumarate dihydrate),

bambuterol (e.g. as hydrochloride),

carmoterol (TA 2005, chemically identified as [R-(R*,R*)]-8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-phenyl)-1-methylethyl]-amino]ethyl]-2(1H)-quinolone monohydrochloride, also identified by Chemical Abstract Service Registry Number 137888-11-0 and disclosed in U.S. Patent No 4,579,854),

a benzothiazolone as disclosed in WO 2005/074924, or WO 2006/056741 (for example, 7-[(R)-2-((1S,2S)-2-Benzyloxy-cyclopentylamino)-1-hydroxyethyl]-4-hydroxy-3H-benzothiazol-2-one),

an aryl aniline as disclosed in WO 2003/042164 or WO 2006/133942 (for example, N-[2-[4-[(3-phenyl-4-methoxyphenyl)amino]phenyl]ethyl]-(R)-2-hydroxy-2-(8-hydroxy-1,2-dihydro-2-oxoquinolin-5-yl)ethylamine),

compounds disclosed in WO 2006/07489 (for example, 5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one),

a formanilide as disclosed in WO 2004/011416, WO 2005/030678, or WO 2006/066907 (for example, N-(2-[4-((R)-2-hydroxy-2-phenylethylamino)phenyl]ethyl)-(R)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine),

compounds disclosed in WO 2005/121065 (for example, 8-hydroxy-5-[(1R)-1-hydroxy-2-[6-(phenethylamino)hexylamino]ethyl]-1H-quinolin-2-one),

compounds disclosed in WO 2003/024439 (for example, (1R)-4-[2-[6-[2-[(2,6-dichlorophenyl)methoxy]ethoxy]hexylamino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol),

compounds disclosed in WO 2004/037773 (for example, 4-[(1R)-2-[6-[4-(3-cyclopentylsulfonylphenyl)butoxy]hexylamino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol),

a benzenesulfonamide derivative as disclosed in WO 2002/066422 (for example, 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)phenyl]ethyl}amino)-hexyl]oxy}butyl)benzenesulfonamide),

a formanilide disclosed in WO 2002/076933 (for example, 3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}-butyl)-benzenesulfonamide),
a compound GSK159797 (chemically identified as N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[2-[4-[[(2R)-2-hydroxy-2-phenyl-ethyl]amino]phenyl]ethylamino]ethyl]phenyl]formamide),
GSK159802, GSK597901, GSK642444 (chemically identified as 4-[(1R)-2-[6-[2-[(2,6-dichlorophenyl)methoxy]ethoxy]hexylamino]-1-hydroxy-ethyl]-2-(hydroxymethyl)phenol) or GSK678007,
an indole derivative as disclosed in WO 2004/032921 (for example, N-[(2,6-dimethoxyphenyl)methyl]-5-[2-[[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]-1H-indole-2-carboxamide),
compounds disclosed in WO 2006/051375 (for example, N-(1-adamantyl)-2-[3-[(2R)-2-[[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]propyl]phenyl] acetamide),
compounds disclosed in WO 2008/017637 (for example 8-[(1R)-2-[[4-[3-(4-chlorophenyl)-5-methyl-1,2,4-triazol-1-yl]-2-methylbutan-2-yl]amino]-1-hydroxyethyl]-6-hydroxy-4H-1,4-benzoxazin-3-one),
compounds disclosed in WO 2008/023003 (for example, N-[5-[(1R)-2-[[4-(4,4-diethyl-2-oxo-3,1-benzoxazin-1-yl)-2-methylbutan-2-yl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide),
compounds disclosed in WO 2006/122788, and WO 2008/095720 (for example, 5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one),
compounds disclosed in WO 2008/046598 (for example, 5-[(1R)-2-[2-[4-(2,2-difluoro-2-phenylethoxy)phenyl]ethylamino]-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one), and
compounds disclosed in WO 2007/124898 (for example, 5-(2-[(6-(2-[(2,6-dichlorobenzyl)(methyl)amino]ethoxy)hexyl)amino]-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one).

In another embodiment of the invention, the β_2-adrenoreceptor agonist is selected from:

N-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide as disclosed in WO 2008/096111,

N-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(3-chlorophenyl)ethoxy]propanamide as disclosed in WO 2008/096121,

7-[(1*R*)-2-({2-[(3-{[2-(2-Chlorophenyl)ethyl]amino}propyl)thio]ethyl}amino)-1-hydroxyethyl]-4-hydroxy-1,3-benzothiazol-2(3*H*)-one as outlined in WO 2008/104776,

4-Hydroxy-7-[1-hydroxy-2-(2-{3-[(2-methoxy-benzylamino)-methyl]-phenyl}-ethylamino)-ethyl]-3H-benzothiazol-2-one as disclosed in WO 2008/106016, or

N-Cyclohexyl-3-[2-(3-fluorophenyl)ethylamino]-N-[2-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]ethyl]propanamide as disclosed in WO 2008/075026,

or a pharmaceutically acceptable salt of any one thereof.

In another embodiment of the invention, the β_2-adrenoreceptor agonist is formoterol (e.g. as fumarate or fumarate dihydrate).

In another embodiment of the invention, the β_2-adrenoreceptor agonist is selected from *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide or indacaterol, or a pharmaceutically acceptable salt of any one thereof.

In another embodiment of the invention, the β_2-adrenoreceptor agonist is indacaterol, or a pharmaceutically acceptable salt thereof (for example indacaterol 2(Z)-but-2-ene dioate).

In another embodiment of the invention, the β_2-adrenoreceptor agonist is *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide, or a pharmaceutically acceptable salt thereof (for example *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-

oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide hydrobromide).

In yet another embodiment of the invention, the β_2-adrenoreceptor agonist is selected from indacaterol 2(Z)-but-2-ene dioate or *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide hydrobromide.

In yet another embodiment of the invention, the β_2-adrenoreceptor agonist is selected from:

N-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide dihydrobromide,

N-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(3-chlorophenyl)ethoxy]propanamide dihydrobromide,

7-[(1*R*)-2-({2-[(3-{[2-(2-Chlorophenyl)ethyl]amino}propyl)thio]ethyl}amino)-1-hydroxyethyl]-4-hydroxy-1,3-benzothiazol-2(3*H*)-one dihydrobromide,

4-Hydroxy-7-[1-hydroxy-2-(2-{3-[(2-methoxy-benzylamino)-methyl]-phenyl}-ethylamino)-ethyl]-3H-benzothiazol-2-one dihydrobromide, or

N-Cyclohexyl-3-[2-(3-fluorophenyl)ethylamino]-N-[2-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]ethyl]propanamide di-D-mandelate salt.

In yet another embodiment of the invention, the β_2-adrenoreceptor agonist is *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide dihydrobromide.

An alternative chemical name for *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide is *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-(2-naphthalene-1-ylethoxy)propanamide.

In one embodiment of the invention, the second active ingredient is a β_2 adrenoreceptor agonist, for example a long-acting β_2-adrenoreceptor agonist.

The dual β2 adrenoreceptor agonist/M3 receptor antagonist is also known as a MABA compound. A MABA compound is a compound having dual activity as both a muscarinic antagonist and as a β_2-adrenoreceptor agonist, examples of which are disclosed in WO 2004/089892, WO 2004/106333, US 2004/0167167, WO 2005/111004, WO 2005/051946, US 2005/0256114, WO 2006/023457, WO 2006/023460, US 2006/0223858, US 2006/0223859, WO 2007/107828, WO 2008/000483, US 7317102 and WO 2008/041095.

Specific examples of MABA compounds include:

biphenyl-2-ylcarbamic acid 1-[2-(4-{[(R)-2-(3-formylamino-4-hydroxypheny1)-2-hydroxyethylam-2,5-dimethylphenylcarbamoyl)ethyl]piperidin-4-yl ester,

succinic acid salt of biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylmino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester,

naphthalene-1,5-disulfonic acid salt of biphenyl-2-ylcarbamic acid 1-(9-[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydro-quinolin-5-yl)ethylamino]nonyl}piperidin-4-yl ester,

N-{5-[(1R)-2-((2-[4-(2-{3-[(1R)-3-(diisopropylamino)-1- phenylpropyl)-4-hydroxyphenyl}ethoxy)-phenyl]ethyl}amino)-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide (optionally as the succinate salt), and

7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one, or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, the dual β2 adrenoreceptor agonist/M3 receptor antagonist is 7-[-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one, or a pharmaceutically acceptable salt thereof. In another

embodiment of the invention, the dual β2 adrenoreceptor agonist/M3 receptor antagonist is 7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one, or a pharmaceutically acceptable salt thereof. 7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one (and salts thereof) is disclosed in WO 2009/098448 and WO 2011/012897. Suitable salts include the trifluoroacetate or dicamphor sulfonate (dicamsylate) salts.

An alternative chemical name for 7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one is 7-{(1R)-2-[(2-{2-fluoro-5-[(4-{[2-(1-methylethyl)-1,3-thiazol-4-yl]carbonyl}-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-4-hydroxy-1,3-benzothiazol-2(3H)-one or (R)-7-(2-(2-fluoro-5-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethylamino)-1-hydroxyethyl)-4-hydroxybenzo[d]thiazol-2(3H)-one.

In one embodiment of the invention, the second active ingredient is a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist.

Examples of muscarinic antagonists (also known as LAMA compounds) that may be used in the pharmaceutical product according to the invention include:

aclidinium bromide,

glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide),

oxitropium bromide,

pirenzepine,

telenzepine,

tiotropium bromide,

darotropium ((1R, 3R, 5S)-3-(2-cyano-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3,2,1]octane bromide),

3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide (see WO 01/04118),

3(R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane bromide, (3R)-3-[(2S)-2-cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]actane bromide (see WO 01/04118),

((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt, e.g. bromide salt, as described in WO 2009/138707 and WO 2009/139708, and

quaternary ammonium salts such as [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 or [2-(4-Chloro-benzyloxy)-ethyl]-[2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-ammonium salt, or (*R*)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((*S*)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane where the counter ion is, for example, chloride, bromide, sulfate, methanesulfonate, benzenesulfonate (besylate), toluenesulfonate (tosylate), napthalene-bissulfonate (napadisylate), hemi- napthalenebissulfonate (hemi-napadisylate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, fumarate or succinate.

In an embodiment, the muscarinic antagonist is selected from ((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt (particularly the bromide salt) or tiotropium (particularly tiotropium bromide).

In another embodiment, the muscarinic antagonist is ((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt, particularly ((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane bromide.

In another embodiment, the muscarinic antagonist is 3-(1-phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane salt, particularly 3-(1-phenyl-cycloheptanecarbonyloxy)-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane bromide.

In another embodiment, the muscarinic antagonist is tiotropium (particularly tiotropium bromide).

An alternative chemical name for ((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane is (3R)-1-[2-oxo-2-(pyridin-2-ylamino)ethyl]-3-{[(1-phenylcycloheptyl)carbonyl]oxy}-1-azoniabicyclo[2.2.2]octane.

Tiotropium is chemically identified as (1*R*,2*R*,4*S*,5*S*,7*S*)-7-{[hydroxy(dithiophen-2-yl)acetyl]oxy}-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane.

In one embodiment of the invention, the second active ingredient is a muscarinic antagonist.

p38 Kinase inhibitors are known, for example, from WO 2009/001132. One such compound described in WO 2009/001132 is *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide and pharmaceutically acceptable salts thereof.

A suitable salt of *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide is, for example, a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate, *p*-toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic

acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulphonate, for example (1S)-(+)-10-Camphorsulfonic acid salt), formate, glutamate, glutarate, glycolate, hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulphonate), pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate), palmitate or furoate. It is to be understood for the avoidance of confusion that salts may exist in varying stoichiometries, for example, but not limited to, hemi-, mono-, and di-, and that the invention encompasses all such forms.

Another known p38 Kinase inhibitor is N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide (as disclosed in WO 2009/001132) and pharmaceutically acceptable salts thereof.

In one embodiment, the p38 Kinase inhibitor is selected from *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide and N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide, or a pharmaceutically acceptable salt of any one thereof.

In another embodiment, the p38 Kinase inhibitor is *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide, or a pharmaceutically acceptable salt thereof.

In another embodiment, the p38 Kinase inhibitor is N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide, or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, the second active ingredient is a p38 kinase inhibitor.

A neutrophil elastase inhibitor is, for example, 6-[2-(4-Cyano-phenyl)-2H-pyrazol-3-yl]-5-methyl-3-oxo-4-(3-trifluoromethyl-phenyl)-3,4-dihydro-pyrazine-2-carboxylic acid ethylamide (WO 2007/129963).

In one embodiment of the invention, the second active ingredient is a neutrophil elastase inhibitor.

Phosphodiesterase PDE4 inhibitors are known in the art and include, for example, 6-fluoro-N-((1s,4s)-4-(6-fluoro-2,4-dioxo-1-(4'-(piperazin-1-ylmethyl)-biphenyl-3-yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl)imidazo[1,2-a]pyridine-2-carboxamide (as disclosed in WO 2008/084223), or a pharmaceutically acceptable salt thereof, for example, a (1S)-(+)-10-camphorsulfonic acid or trihydrochloride salt; and 6-Fluoro-N-((1s,4s)-4-(6-fluoro-2,4-dioxo-1-(4'-(piperazin-1-ylmethyl)-biphenyl-3-yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl)imidazo[1,2-a]pyridine-2-carboxamide (as described in International Patent Application No. PCT/GB2008/000061), or a pharmaceutically acceptable salt thereof such as a (1S)-(+)-10-camphorsulfonic acid salt.

In one embodiment of the invention, the second active ingredient is a phosphodiesterase PDE4 inhibitor.

An IKK2 kinase inhibitor is, for example, 2-{[2-(2-Methylamino-pyrimidin-4-yl)-1H-indole-5-carbonyl]-amino}-3-(phenyl-pyridin-2-yl-amino)-propionic acid or a compound as disclosed in WO 01/58890, WO 03/010158, WO 03/010163, WO 04/063185 or WO 04/063186.

In one embodiment of the invention, the second active ingredient is an IKK2 kinase inhibitor.

A non-steroidal glucocorticoid receptor (GR) agonist is, for example, a compound disclosed in WO 2008/076048, for example 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide, 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-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide, (2*S*)-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-propanamide, 2,2,2-trifluoro-N-[(2S*,3S*)-3-[1-(4-fluorophenyl)indazol-5-yl]oxy-4-phenoxy-butan-2-yl]acetamide, *N*'-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]-N-propan-2-yl-oxamide, or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, the second active ingredient is a non-steroidal glucocorticoid receptor agonist.

In a preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-(2-naphthalen-1-ylethoxy)propanamide,

(3R)-1-[2-(4-fluorophenyl)ethyl]-3-{[(2S)-2-phenyl-2-piperidin-1-ylpropanoyl]oxy}-1-azoniabicyclo[2.2.2]octane,

(3R)-1-[2-oxo-2-(pyridin-2-ylamino)ethyl]-3-{[(1-phenylcycloheptyl)carbonyl]oxy}-1-azoniabicyclo[2.2.2]octane,

N-cyclopropyl-3-fluoro-4-methyl-5-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide,

N-cyclohexyl-N-(2-{[2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}ethyl)-3-{2-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]ethoxy}propanamide,

N-cyclohexyl-N^3-[2-(3-fluorophenyl)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-β-alaninamide,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

(3R)-1-[2-(4-fluorophenyl)ethyl]-3-{[(2S)-2-phenyl-2-piperidin-1-ylpropanoyl]oxy}-1-azoniabicyclo[2.2.2]octane,

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

N-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide

N-cyclohexyl-N-(2-{[2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}ethyl)-3-{2-[3-(1-methyl-1H-pyrazol-4-yl)phenyl]ethoxy}propanamide,

N-cyclohexyl-N^3-[2-(3-fluorophenyl)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-β-alaninamide,

indacaterol,

N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide,

tiotropium,

7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt of any one thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

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

N-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide

indacaterol,

N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide,

tiotropium,

7-[2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

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

N-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide

indacaterol,

N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide,

tiotropium,

7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

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

indacaterol,

tiotropium,

7-[2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

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

indacaterol,

tiotropium,

7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

indacaterol,

7-[2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

In another preferred aspect of the invention, the second active ingredient is selected from:

N-[2-(diethylamino)ethyl]-N-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide,

indacaterol,

7-[(1R)-2-[2-[2-fluoro-5-[[8-(2-isopropylthiazole-4-carbonyl)-11-oxa-3,8-diazaspiro[5.5]undecan-3-yl]methyl]phenyl]ethylamino]-1-hydroxy-ethyl]-4-hydroxy-3H-1,3-benzothiazol-2-one,

or a pharmaceutically acceptable salt thereof.

All the above second *et seq* active ingredients may be in the form of solvates, for example hydrates.

The active ingredients may be delivered to the lung and/or airways via oral administration in the form of a solution, suspension, aerosol or dry powder formulation. These dosage

forms will usually include one or more pharmaceutically acceptable excipients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings or colorants. Examples of such excipients are described in the Handbook of Pharmaceutical Excipients (Fifth Edition, 2005, edited by Ray C. Rowe, Paul J. Sheskey and Sian C. Owen, published by the American Pharmaceutical Association and the Pharmaceutical Press). The active ingredients of the present invention may also 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. 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.

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 first active ingredient is administered via inhalation. When administered via inhalation the dose of the first active ingredient 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, 0.1 to 5 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 is administered by inhalation. When administered via inhalation the dose of the second active ingredient 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, 0.1 to 5 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 another embodiment the present invention provides a pharmaceutical product wherein the molar ratio of first active ingredient to second active ingredient is from 1:1000 to 1000:1, such as from 1:100 to 100:1, for example from 1:50 to 50:1, for example 1:20 to 20:1.

In one preferred embodiment, the pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist; and optionally one or more pharmaceutically acceptable excipients, is formulated for inhaled administration.

In another preferred embodiment, the pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β_2

adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor; and optionally one or more pharmaceutically acceptable excipients, is formulated for inhaled administration.

In another preferred embodiment, the pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist; and optionally one or more pharmaceutically acceptable excipients, is formulated for inhaled administration.

In another preferred embodiment, the pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist; and optionally one or more pharmaceutically acceptable excipients, is formulated for inhaled administration.

In still another preferred embodiment, the preparations of the first and second active ingredients for simultaneous, sequential or separate administration are each formulated for inhaled administration.

Administration by inhalation may be via the oral or nasal route using a pressurised metered dose inhaler (pMDI), a nebuliser or a dry powder inhaler.

If a pMDI is used, the first and/or second active ingredient(s) may be dispersed in a suitable propellant optionally together with an additional excipient such as an alcohol (e.g. ethanol), a surfactant, a lubricant or a stabilising agent. A suitable propellant includes a hydrocarbon, chlorofluorocarbon or a hydrofluoroalkane (e.g. heptafluoroalkane) propellant, or a mixture of any such propellants. Preferred propellants are P134a and P227, each of which may be used alone or in combination with other another propellant and/or surfactant and/or other excipient.

If a nebuliser is used, the first and/or second active ingredient(s) will typically be formulated as an aqueous suspension or, preferably, solution, with or without suitable pH and/or tonicity adjustment.

A dry powder inhaler may be used to administer the active ingredients, alone or in combination with a pharmaceutically acceptable carrier (such as lactose), in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be "passive" or breath-actuated, or "active" where the powder is dispersed by some mechanism other than the patient's inhalation, for instance, an internal supply of compressed air. At present, three types of passive dry powder inhalers are available: single-dose, multiple unit dose or multidose (reservoir) inhalers. In single-dose devices, individual doses are provided, usually in capsules, and have to be loaded into the inhaler before use, examples of which include Spinhaler® (Aventis), Rotahaler® (GlaxoSmithKline), Aeroliser™ (Novartis), Inhalator® (Boehringer) and Eclipse (Aventis) devices. Multiple unit dose inhalers contain a number of individually packaged doses, either as multiple gelatine capsules or in blisters, examples of which include Diskhaler® (GlaxoSmithKline), Diskus® (GlaxoSmithKline), Aerohaler® (Boehringer) and Handihaler® (Boehringer) devices. In multidose devices, drug is stored in a bulk powder reservoir from which individual doses are metered, examples of which include Turbuhaler® (AstraZeneca), Easyhaler® (Orion), Novolizer® (ASTA Medica), Clickhaler® (Innovata Biomed) and Pulvinal® (Chiesi) devices.

Thus, the present invention further provides a dry powder inhaler, in particular a multiple unit dose dry powder inhaler, containing a pharmaceutical product as hereinbefore described.

The pharmaceutical product of the present invention may be used to treat diseases of the respiratory tract such as obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

Accordingly, the present invention further provides a pharmaceutical product as hereinbefore defined for use in therapy.

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

disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The present invention further provides the use of first and second active ingredients, wherein the first active ingredient is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and the second active ingredient is a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist, in the manufacture of a medicament or pharmaceutical product for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides the use of first and second active ingredients, wherein the first active ingredient is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and the second active ingredient is a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor in the manufacture of a medicament or pharmaceutical product for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

In one embodiment, the present invention provides the use of first and second active ingredients, wherein the first active ingredient is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-

2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and the second active ingredient is a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist, in the manufacture of a medicament or pharmaceutical product for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

In one embodiment, the present invention provides the use of first and second active ingredients, wherein the first active ingredient is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and the second active ingredient is a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, in the manufacture of a medicament or pharmaceutical product for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

The present invention further provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist or a p38 kinase inhibitor, for use in treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

In one embodiment, the present invention provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist or a muscarinic antagonist, for treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

In one embodiment, the present invention provides a pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof and a second active ingredient selected from a β_2 adrenoreceptor agonist or a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, for treating a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

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

(a) a therapeutically effective dose of a first active ingredient as defined above; and

(b) a therapeutically effective dose of a second active ingredient as defined above.

The present invention will now be further explained by reference to the following illustrative examples in which the following abbreviations are used:

EtOAc	ethyl acetate
HCl	hydrochloric acid
H_2S	hydrogen sulphide
CH_2Cl_2	dichloromethane (DCM)
DMF	*N,N*-dimethylformamide
NaH	sodium hydride
$MgSO_4$	magnesium sulphate
$NaNO_2$	sodium nitrite
K_2CO_3	potassium carbonate
$SnCl_2$	tin (II) chloride

NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NH_4Cl	ammonium chloride
DIEA	diisopropylethylamine
DME	dimethyl ether
DCM	dichloromethane
DMSO	dimethylsulfoxide
EtOH	ethanol
Et_2O	diethyl ether
THF	tetrahydrofuran
TFA	trifluoroacetic acid
HCl	hydrochloric acid
$NaHCO_3$	sodium hydrogen carbonate
Et_3N	triethylamine
MeOH	methanol
MeCN / CH_3CN	acetonitrile
EDTA	ethylenediaminetetraacetic acid
NMP	N-methylpyrrolidine
conc.	concentrated
rt	room temperature
h	hours
min	minutes
M	molar
MS	mass spectrometry
APCI	atmospheric chemical ionisation method
ESI	electron spray ionisation method
NMR	nuclear magnetic resonance
SCX	solid phase extraction with a sulfonic acid sorbent
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography with mass spectrometry detection

In the Examples, the following Figures are presented:

Figure 1 shows a graph of % inhibition against concentration for Compound A in combination with compound B,

Figure 2 shows a graph of % inhibition against concentration for Compound A in combination with compound C,

Figure 3 shows a graph of % inhibition against concentration for Compound A in combination with compound D,

Figure 4 shows a graph of % inhibition against concentration for Compound A in combination with compound E,

Figure 5 shows a graph of % inhibition against concentration for Compound A in combination with compound F,

Figure 6 shows a graph of % inhibition against concentration for Compound A in combination with compound G, and

Figure 7 shows a graph of % inhibition against concentration for Compound A in combination with compound H.

General Methods

NMR spectra were recorded on a Varian Mercury-VX 300 MHz instrument or a Varian Inova 400MHz instrument. The central peaks of chloroform-*d* (H 7.26 ppm), acetone-d_6 (H 2.05 ppm), acetonitrile-d_3 (δ_H 1.94 ppm) or DMSO-d_6 (H 2.50 ppm) were used as internal references.

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.

Column chromatography was carried out using silica gel (0.040-0.063 mm, Merck).

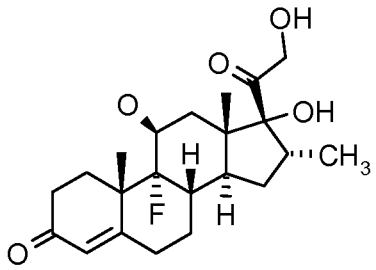
For preparative HPLC either a Kromasil® KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water (0.1% TFA) at a flow rate of 10 ml/min or a

XTerra® Prep MS C_{18} OBD™ Column, 5μm, 19 x 50 mm (acetonitrile/water/0.1% NH_3) at a flow rate of 20 ml/min was used. UV=254 nm or 220 nm was used for detection.

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

Intermediate 1

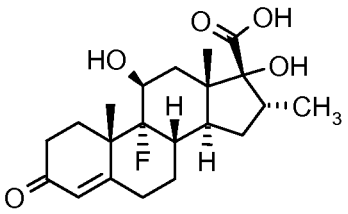
(8S,9R,10S,11S,13S,14S,16R,17R)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one



In a 1000 mL round-bottomed flask was suspended dexamethasone (10 g, 25.48 mmol) in EtOAc (400 mL) and ethanol (100 mL) and tris(triphenylphosphine)rhodium(I)chloride (Wilkinson´s catalyst, 2.5 g, 2.70 mmol) was added together with a magnetic stirrer bar. The mixture was vigorously stirred in a hydrogen atmospere (1 atm) at room temperature for 1 week and another 1.0g of the catalyst was added. The reaction was allowed to proceed for another week and the resulting mixture was concentrated *in vacuo* to obtain a solid that was suspended in DCM (100 ml) and the suspension was filtered. The obtained solid was washed with 3 portions of DCM (50ml) and dried on the sinter in air, yielding 9.6g of the target compound as an off white solid. APCI-MS m/z: 395 [MH^+].

Intermediate 2

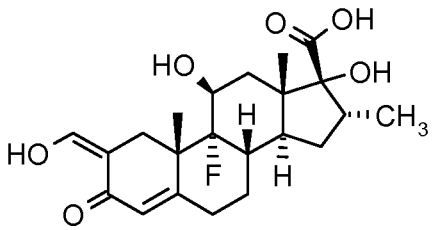
(8S,9R,10S,11S,13S,14S,16R,17R)-9-Fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-17-carboxylic acid



In a 500 mL round-bottomed flask was dissolved intermediate 1 (9.5g, 24.08 mmol) in THF (200 mL) and a solution of orthoperiodic acid (10.98 g, 48.17 mmol) in 80 ml of water was added at room temperature. The obtained mixture was stirred for 2 hours at the same temperature, the organic solvent was removed *in vacuo*, and the resulting wet slurry was diluted with water (100 ml). The obtained solid was filtered, washed with water on the filter and dried on the sinter in a stream of air, giving 9.0 g of the desired product as an off-white solid. APCI-MS m/z: 381 [MH^+].

Intermediate 3

(8S,9R,10S,11S,13S,14S,16R,17R,Z)-9-Fluoro-11,17-dihydroxy-2-(hydroxymethylene)-10,13,16-trimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-17-carboxylic acid

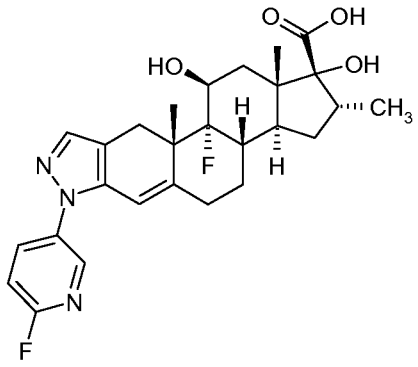


In a 1000 mL round-bottomed flask, equipped with a magnetic stirrer bar and a reflux condenser was added sodium hydride (60% in mineral oil, 10.32 g, 236.56 mmol) and dry THF (150 mL) to give a white suspension that was stirred in an atmosphere of argon at room temperature. Intermediate 2 (9 g, 23.66 mmol) was added followed by ethyl formate (96 mL, 1182.81 mmol) and the resulting mixture was stirred at the same temperature for approximately 2 hours. The reaction was quenched by careful addition of 2M NaOH (50 ml), the resulting mixture was stirred for 5 minutes and subsequently transferred to a separation funnel where the phases were allowed to separate. The aqueous phase was collected, and the organic phase was extracted with an additional 40 ml of 2M NaOH. The combined aqueous phases were diluted with water (50 ml), washed with Et_2O (50 ml) and acidified with 4M HCl (90 ml). The product was extracted with EtOAc (2x150 ml), and the

combined organic phases were washed with brine (100 ml) and dried over Na_2SO_4. Filtration and evaporation of the organic solution *in vacuo* yielded 7.2 g of the desired product as an orange foam that was used in the next step without any further purification. APCI-MS m/z: 409 [MH^+].

Intermediate 4

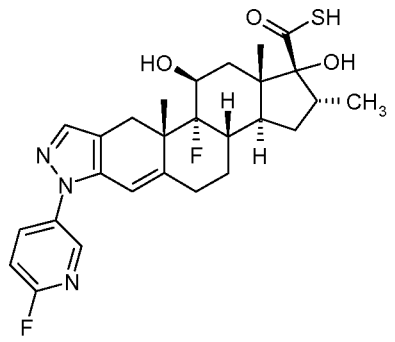
(1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-7-(6-fluoropyridin-3-yl)-1,11-dihydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazole-1-carboxylic acid



In a 500 mL round-bottomed flask was dissolved intermediate 3 (7.2 g, 17.63 mmol) in acetic acid (100 mL) and the solution was degassed with nitrogen gas, N_2. 2-Fluoro-5-hydrazinylpyridine (2.465 g, 19.39 mmol) was added at room temperature and the mixture was stirred with a magnetic stirrer for 30 minutes. The solution was freeze-dried overnight to yield 8.7g of the desired product as an orange solid. APCI-MS m/z: 500 [MH^+].

Intermediate 5

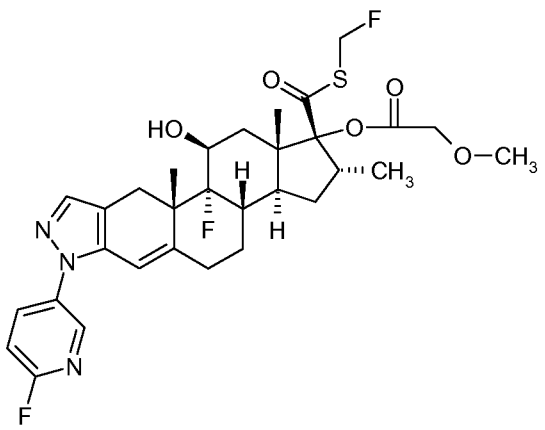
(1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-7-(6-fluoropyridin-3-yl)-1,11-dihydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazole-1-carbothioic S-acid



In a 100 mL round-bottomed flask was dissolved intermediate 4 (8.7 g, 17.62 mmol) in DMF (20 mL) and di(1H-imidazol-1-yl)methanone (CDI, 5.71 g, 35.23 mmol) was added at room temperature. After the gas evolution had ceased, the mixture was stirred in a sealed flask overnight. Hydrogen sulfide (H_2S) was subsequently bubbled through the solution for 10 minutes and the resulting solution was allowed to stir for another 10 minutes. The solution was added to 200 ml 1M HCl in a separation funnel and the mixture was extracted with EtOAc (2x150 ml). The combined organic phases were washed with 0.5M HCl (3x100 ml) and brine (40 ml), were subsequently dried over Na_2SO_4, filtered and the organic solvent was evaporated *in vacuo* to give 9.0g of the desired product as an orange foam which was used in the next step without any further purification. APCI-MS m/z: 516 [MH^+].

Example 1

(1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate (Compound A)



In a 250 mL round-bottomed flask was dissolved intermediate 5 (8.8 g, 17.07 mmol) in DCM (80 mL) and triethylamine (5.91 mL, 42.67 mmol) was added. To the stirred mixture was added 2-methoxyacetyl chloride (3.89 g, 35.84 mmol), whilst cooling in a water bath, and the mixture was stirred for 10 minutes. N_1-ethyl-N_2,N_2-dimethylethane-1,2-diamine (3.48 mL, 22.19 mmol) was added and the mixture was stirred for another 10 minutes A solution of 60% bromofluoromethane (4.82 g, 25.60 mmol) in DMF was added, followed by triethyl amine (2 ml) and the reaction was allowed to stir for an additional 30 minutes. The resulting mixture was concentrated *in vacuo* and partitioned between EtOAc (150 ml) and 1M HCl (150 ml). The aqueous phase was extracted with EtOAc (150 ml) and the combined organic phases were washed with 0.5M HCl (2x100 ml), water (100 ml) and brine (50 ml). Drying over Na_2SO_4 was followed by filtration and evaporation *in vacuo* to yield the crude product as a foam which was purified on silica (Heptane:EtOAc 3:1 to 2:1) to give 2.9g of the target compound as a yellowish solid.

A small sample (0.35g) of this material was purified on a preparative HPLC column (Kromasil C18, CH3CN / water), the compound containing fraction were freeze-dried to yield 0.26g of the target compound as a colourless solid. The solid was suspended in Et_2O (10 ml) and the suspension was stirred at room temperature for 2 hours. The solid was isolated by filtration to give 0.23g of the tartet compound as a white crystalline solid.

APCI-MS m/z: 620 [MH^+].

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, s), 7.99 (1H, m), 7.51 (1H, s), 7.07 (1H, dd), 6.18 (1H, s), 6.01-5.76 (2H, m), 4.45 (1H, bs), 4.12 (2H, s), 3.45 (3H, s), 3.45-3.40 (1H, m), 3.32 (1H, d), 2.80 (1H, d), 2.61 (1H, t), 2.49-2.19 (4H, m), 1.96-1.82 (2H, m), 1.76-1.66 (1H, m), 1.65-1.51 (1H, m), 1.41 (3H, s), 1.41-1.33 (1H, m), 1.28 (1H, bs), 1.12 (3H, s), 1.04 (3H, d).

Example 2

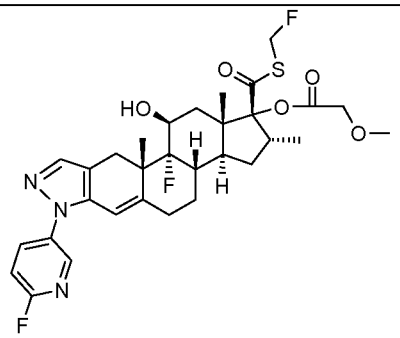
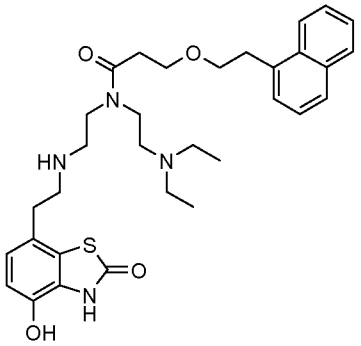
Inhibition of lipopolysaccharride (LPS)–induced TNFα production in human peripheral blood mononuclear cells

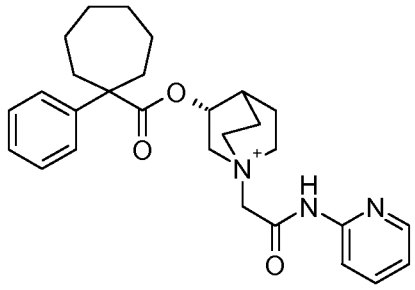
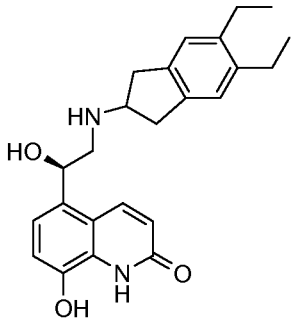
Human isolated peripheral blood mononuclear cells (PBMCs) were pre-incubated with a range of concentrations of the GR agonist (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-

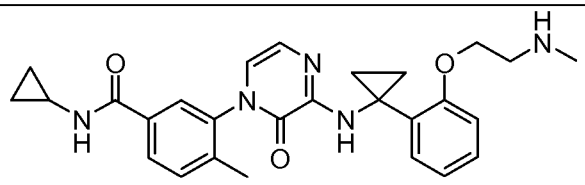
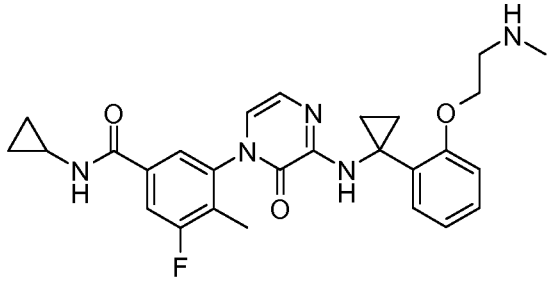
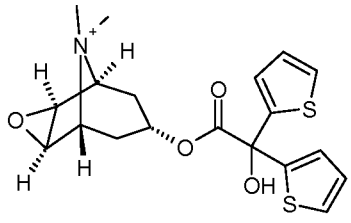
2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate (Compound A), alone or in the presence of a range of concentrations of a second compound with a distinct pharmacological activity for 45 minutes at 37°C. The second compound was selected from β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M3 receptor antagonist (hereinafter referred to as a "MABA compound"), a muscarinic antagonist or a p38 kinase inhibitor. After the pre-incubation period, the cells were then incubated with LPS (5ng/mL) for 18 hours at 37°C to induce TNFα production. The total assay volume was 200 μL. At the end of the incubation period, 10 μL of the culture supernatant diluted 1:5 was analysed to quantify the TNFα released using AlphaLISA (PerkinElmer). The fluorescence was detected on an EnVision Alphareader. Inhibition curves were fitted using a 4-parameter logistic equation in a non-linear curve fitting routine and activity was expressed as pIC50.

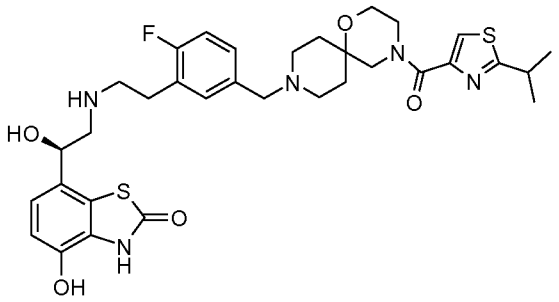
In this series of experiments, the test of Compound A alone gave a pIC50 for inhibition of LPS-induced TNFα production from human PBMC of 9.6 ±0.1 (n=7 exp).

In the particular series of experiments described below, compound A was tested in combination with each of the Compounds B to H described in the following table. In the table the chemical structure of each of the exemplified compounds is depicted together with the chemical name used in the present specification to denote the compound parent structure.

Compound	Chemical Structure and IUPAC name	Mechanism
A	 (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-ylmethoxyacetate	GR agonist
B	 *N*-[2-(Diethylamino)ethyl]-*N*-(2-{[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino}ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide	LABA

Compound	Chemical Structure and IUPAC name	Mechanism
C	 ((*R*)-3-(1-phenyl-cycloheptanecarbonyloxy))-1-(pyridin-2-ylcarbamoylmethyl)-1-azonia-bicyclo [2.2.2]octane	LAMA
D	 5-{(1R)-2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1H)-one	LABA

Compound	Chemical Structure and IUPAC name	Mechanism
E	 N-cyclopropyl-4-methyl-3-{3-[(1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl)amino]-2-oxopyrazin-1(2H)-yl}benzamide	p38
F	 *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide	p38
G	 (1R,2R,4S,5S,7S)-7-{[hydroxy(dithiophen-2-yl)acetyl]oxy}-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane	LAMA

Compound	Chemical Structure and IUPAC name	Mechanism
H	 7-{(1R)-2-[(2-{2-fluoro-5-[(4-{[2-(1-methylethyl)-1,3-thiazol-4-yl]carbonyl}-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)methyl]phenyl}ethyl)amino]-1-hydroxyethyl}-4-hydroxy-1,3-benzothiazol-2(3H)-one	MABA

The pIC_{50} and maximal inhibition achieved for combinations of Compound A with each of Compounds B to H are shown in Tables 1 to 7 below and in Figures 1 to 7 respectively.

In tables 2 and 4 to 7, the data represents the mean of two separate experiments using PBMC from healthy blood donors (n=2). In table 3, the data represents the mean of three separate experiments using PBMC from healthy blood donors (n=3). In table 1, the data represents the mean of four separate experiments using PBMC from healthy blood donors (n=4).

Table 1. Compound A in combination with Compound B

Compound	**Concentration (μM)**	**pIC50 compound A**	**pEC50 compound A**	**% Max inhibition**
Compound B	1	9.7	9.4	84.4
Compound B	0.1	9.7	9.4	83.3
Compound B	0.01	9.6	9.5	83.0
Compound B	0.001	9.3	9.6	78.6
Compound B	0.0001	9.4	9.7	81.3
Compound B	0.00001	9.3	9.6	80.5
Compound B	0.000001	9.2	9.5	77.1

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound B	0	9.2	9.6	79.0

Table 2. Compound A in combination with Compound C

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound C	1	9.2	9.5	75.2
Compound C	0.1	9.3	9.5	76.9
Compound C	0.01	9.2	9.5	75.9
Compound C	0.001	9.2	9.4	72.9
Compound C	0.0001	9.2	9.4	77.6
Compound C	0.00001	9.4	9.6	78.5
Compound C	0.000001	9.3	9.7	79.5
Compound C	0	9.2	9.6	79.0

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Table 3. Compound A in combination with Compound D

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound D	1	9.6	9.4	80.4
Compound D	0.1	9.6	9.3	80.5
Compound D	0.01	9.3	9.2	78.5
Compound D	0.001	9.4	9.5	79.1
Compound D	0.0001	9.3	9.6	73.0
Compound D	0.00001	9.3	9.6	74.0
Compound D	0.000001	9.1	9.5	73.1
Compound D	0	9.2	9.6	79.0

Table 4. Compound A in combination with Compound E

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound E	1	>13	9.1	93.6
Compound E	0.1	>13	9.1	90.4
Compound E	0.01	>13	9.1	90.4
Compound E	0.001	9.1	9.4	70.5
Compound E	0.0001	9.2	9.7	69.6
Compound E	0.00001	9.0	9.6	68.4
Compound E	0.000001	8.9	9.5	68.6
Compound E	0	9.2	9.6	79.0

Table 5. Compound A in combination with Compound F

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound F	1	>13	N/A	96.3
Compound F	0.1	>13	9.3	95.1
Compound F	0.01	>13	9.3	90.6
Compound F	0.001	9.3	9.6	74.7
Compound F	0.0001	9.3	9.8	72.3
Compound F	0.00001	9.4	9.7	71.7
Compound F	0.000001	9.1	9.6	72.4
Compound F	0	9.2	9.6	79.0

N/A = not available

Table 6. Compound A in combination with Compound G

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound G	1	9.1	9.3	73.2
Compound G	0.1	9.2	9.5	69.2
Compound G	0.01	9.0	9.2	68.0
Compound G	0.001	8.9	9.4	68.1
Compound G	0.0001	9.0	9.3	71.1
Compound G	0.00001	9.0	9.4	70.1
Compound G	0.000001	8.8	9.3	67.4
Compound G	0	9.2	9.6	79.0

Table 7. Compound A in combination with Compound H

Compound	Concentration (μM)	pIC50 compound A	pEC50 compound A	% Max inhibition
Compound H	1	>13	9.5	92.2
Compound H	0.1	10.4	9.5	85.4
Compound H	0.01	9.7	9.4	83.6
Compound H	0.001	9.5	9.5	82.2
Compound H	0.0001	9.5	9.8	78.8
Compound H	0.00001	9.3	9.6	76.8
Compound H	0.000001	9.2	9.7	81.0
Compound H	0	9.2	9.6	79.0

CLAIMS

1. A pharmaceutical product comprising a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist; and optionally one or more pharmaceutically acceptable excipients.

2. A pharmaceutical product according to claim 1 wherein the second active ingredient is a β_2 adrenoreceptor agonist.

3. A pharmaceutical product according to claim 1 wherein the second active ingredient is a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist.

4. A pharmaceutical product according to claim 1 wherein the second active ingredient is a muscarinic antagonist.

5. A pharmaceutical product according to claim 1 wherein the second active ingredient is a p38 kinase inhibitor.

6. A pharmaceutical product according to claim 1 which is in a form suitable for administration by inhalation.

7. A dry powder inhaler containing a pharmaceutical product according to claim 1 or claim 6.

8. A dry powder inhaler according to claim 7 which is a multiple unit dose dry powder inhaler.

9. A pharmaceutical product comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist, wherein the preparations are for simultaneous, sequential or separate administration to a patient in need thereof.

10. A pharmaceutical product according to claim 9, wherein the preparations of the first and second active ingredients are each in a form suitable for administration by inhalation.

11. A pharmaceutical product according to any one of the preceding claims for use in treating chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis.

12. Use of first and second active ingredients, wherein the first active ingredient is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and the second active ingredient is a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor

or a non-steroidal glucocorticoid receptor agonist, in the manufacture of a medicament for the treatment of a respiratory disease.

13. A method of treating a respiratory disease which comprises simultaneously, sequentially or separately administering to a patient in need thereof:
(a) a therapeutically effective dose of a first active ingredient being(1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof; and
(b) a therapeutically effective dose of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist.

14. A kit comprising a preparation of a first active ingredient which is (1R,2R,3aS,3bS,10aS,10bR,11S,12aS)-10b-Fluoro-1-{[(fluoromethyl)sulfanyl]carbonyl}-7-(6-fluoropyridin-3-yl)-11-hydroxy-2,10a,12a-trimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-yl methoxyacetate or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient selected from a β_2 adrenoreceptor agonist, a dual β_2 adrenoreceptor agonist/M_3 receptor antagonist, a muscarinic antagonist, a p38 kinase inhibitor, a neutrophil elastase inhibitor, a phosphodiesterase PDE4 inhibitor, an IKK2 kinase inhibitor or a non-steroidal glucocorticoid receptor agonist, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.