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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ERIKSSON, Tomas** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **HANSSON, Johan** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

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(54) **Title:** A COMBINATION OF COMPOUNDS, WHICH CAN BE USED IN THE TREATMENT OF RESPIRATORY DISEASES, ESPECIALLY CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND ASTHMA

(57) **Abstract:** The present invention provides pharmaceutical compositions comprising a β_2-agonist, and a compound of formula: wherein m, R^1, R^2, R^3, and R^4 are as defined in the specification, and their use in therapy.

A combination of compounds, which can be used in the treatment of respiratory diseases, especially chronic obstructive pulmonary disease (COPD) and asthma.

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of respiratory diseases, especially chronic obstructive pulmonary disease (COPD) and asthma.

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

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

COPD is a term which refers to a large group of lung diseases which can interfere with normal breathing. Current clinical guidelines define COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. The most important contributory source of such particles and

gases, at least in the western world, is tobacco smoke. COPD patients have a variety of symptoms, including cough, shortness of breath, and excessive production of sputum; such symptoms arise from dysfunction of a number of cellular compartments, including neutrophils, macrophages, and epithelial cells. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

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

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

Therapeutic agents used in the treatment of respiratory diseases include β_2–agonists. These agents (also known as beta2 (β_2) adrenoreceptor agonists) 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.

Whilst treatment with a β_2–agonist can yield important benefits, the efficacy of these agents is often far from satisfactory. Hence there is a pressing medical need for new therapies against respiratory diseases such as COPD and asthma, in particular for therapies with disease modifying potential.

WO01/98273 and WO03/051839 describe compounds having activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine

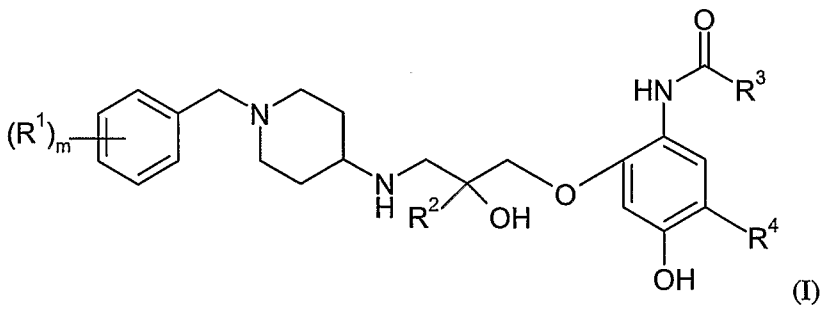
receptor), salts thereof and pharmaceutical formulations, and their potential use in treating various diseases.

The MIP-1α chemokine receptor CCR1 (chemokine receptor 1) is highly expressed in tissues affected in different autoimmune, inflammatory, proliferative, hyperproliferative and immunologically mediated diseases e.g. asthma and chronic obstructive pulmonary disease. Moreover, inflammatory cells (e.g. neutrophils and monocytes/macrophages) contribute to the pathogenesis of respiratory diseases such as COPD by secretion of proteolytic enzymes, oxidants and pharmacologic mediators. These cells are dependent on the function of CCR1 for recruitment and activation in lung tissues.

Surprisingly, it has now been found that an unexpectedly beneficial therapeutic effect may be observed in the treatment of respiratory diseases if a CCR1 receptor antagonist is used in combination with a β_2–agonist. The beneficial effect may be observed when the two active substances are administered simultaneously (either in a single pharmaceutical preparation or via or separate preparations), or sequentially or separately via separate pharmaceutical preparations.

Thus, according to the present invention, there is provided a pharmaceutical product comprising, in combination,

(a) a first active ingredient which is a compound of general formula



(I)

wherein

m is 0, 1 or 2;

each R^1 independently represents halogen or cyano;

R^2 represents a hydrogen atom or methyl;

R^3 represents the group C_1-C_4 alkyl;

and

R^4 represents hydrogen or halogen;

or a pharmaceutically acceptable salt thereof; and

(b) a second active ingredient which is a β_2-agonist.

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

In the context of the present specification, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched.

The integer m is preferably 1 or 2.

Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine) or cyano.

In one embodiment of the invention, m is 1 and R^1 represents a halogen atom, particularly a chlorine atom.

In a further embodiment, m is 1 and R^1 represents a halogen atom (e.g. chlorine) in the 4-position of the benzene ring relative to the carbon atom to which the CH_2 linking group is attached.

R^2 represents a hydrogen atom or methyl. In one embodiment of the present invention, R^2 represents methyl.

R^3 represents the group C_1-C_4 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl). Typically, R^3 is methyl or ethyl, particularly methyl.

R^4 represents hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine). In an embodiment of the present invention, R^4 represents hydrogen or chlorine.

The compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Preferred optical isomers are the (S)-enantiomers (i.e. compounds with the S configuration at the stereocentre with R^2 and OH attached).

The compounds of formula (I) according to the present invention may be synthesised using the procedures set out in WO01/98273 and WO03/051839.

The compounds of formulas (I) may be used in the form of a pharmaceutically acceptable salt, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, sulfphate, acetate, ascorbate, benzoate, fumarate, hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate or *p*-toluenesulphonate. A pharmaceutically acceptable salt also includes internal salt (zwitterionic) forms. Any reference to compounds of formula (I) or salts thereof also encompasses solvates of such compounds and salts thereof (e.g. hydrates).

It will be appreciated that the compounds of formula (I) and salts thereof may exist as zwitterions. Thus, whilst the compounds are drawn and referred to in the hydroxyl form,

they may exist also in internal salt (zwitterionic) form. The representation of formula (I) and the examples of the present invention covers both hydroxyl and zwitterionic forms and mixtures thereof in all proportions.

In another embodiment of the present invention, the compound of formula (I) is selected from
N-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide,
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide,
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl}acetamide,
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl} propaneamide, or
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide,
or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the compound of formula (I) is a salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide, for example hydrochloride, hydrobromide, phosphate, sulfphate, acetate, ascorbate, benzoate, fumarate, hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate or *p*-toluenesulphonate salt. Salts with particularly good properties (e.g. favourable crystallinity and other physio properties suitable for e.g. being formulated in a dry powder formulation for pulmonary administration) are the benzoate, fumarate, or hemifumarate salts of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide, including any forms of the salts referred to in the Examples.

In an embodiment of the invention, the compound of formula (I) or salt thereof has crystalline properties and is e.g. at least 50% crystalline, at least 60% crystalline, at least 70% crystalline or at least 80% crystalline. Crystallinity can be estimated by conventional X-ray diffractometry techniques.

In another embodiment of the invention, the compound of formula (I) or salt thereof is from 50%, 60%, 70%, 80% or 90% to 95%, 96%, 97%, 98%, 99% or 100% crystalline.

It should be noted that where X-ray powder diffraction peaks are expressed (in degrees 2θ), the margin of error is consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089).

In an embodiment of the invention, the compound of formula (I) is a hemifumarate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

(1) 6.2, 10.7 and 12.5, or
(2) 6.2, 10.7 and 18.8, or
(3) 6.2, 10.7 and 18.0, or
(4) 6.2, 10.7, 12.5, 18.0 and 18.8, or
(5) 6.2, 10.7, 12.5, 18.0, 18.8, 19.7 and 19.8.

In another embodiment of the invention, the compound of formula (I) is a furoate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

(1) 6.3, 11.0 and 12.7, or

(2) 6.3, 10.7 and 12.7, or

(3) 6.3, 11.0, 12.7 and 15.9, or

(4) 6.3, 10.7, 11.0, 12.7, 13.9, 14.2 and 15.9, or

(5) 6.3, 10.7, 11.0, 12.7, 15.9, 17.7, 19.1, 19.7 and 25.5, or

(6) 6.3, 10.7, 11.0, 12.7, 13.9, 14.2, 15.9, 17.7, 19.1, 19.7, 19.9, 21.6 and 25.5.

In another embodiment of the invention, the compound of formula (I) is a furoate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

(1) 6.7, 11.0 and 13.4, or

(2) 6.7, 10.4, 11.0 and 13.4, or

(3) 6.7, 10.4, 12.4, 13.4 and 13.7, or

(4) 6.7, 10.4, 13.4 and 20.9, or

(5) 6.7, 10.4, 11.0, 12.4, 13.4, 13.7, 15.6, 16.0 and 17.6, or

(6) 6.7, 10.4, 11.0, 12.4, 13.4, 13.7, 15.6, 16.0, 16.1, 17.6, 18.0, 18.6, 18.9, 20.1, 20.9 and 23.4.

In another embodiment of the invention, the compound of formula (I) is a benzoate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

(1) 6.1, 10.7 and 19.3, or

(2) 6.1, 12.2 and 14.1, or

(3) 6.1, 10.7, 12.2, 14.1, 18.1 and 19.3, or

(4) 6.1, 10.7, 12.2, 14.1, 15.7, 18.1 and 19.3, or

(5) 6.1, 10.7, 12.2, 14.1, 15.1 and 19.3, or

(6) 6.1, 10.7, 12.2, 14.1, 15.1, 15.7, 18.1 and 19.3, or

(7) 6.1, 10.7, 12.2, 14.1, 15.1, 15.7, 18.1, 19.3, 21.2 and 24.6.

In another embodiment of the invention, the compound of formula (I) is a benzoate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):

(1) 6.5, 9.3 and 10.5, or

(2) 6.5, 9.3, 17.6 and 17.8, or

(3) 6.5, 9.3, 10.5,12.0 and 12.4, or

(4) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6 and 17.8, or

(5) 6.5, 13.0 and 20.2, or

(6) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8 and 19.2, or

(7) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8 and 26.0, or

(8) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8, 24.2, 26.0 and 30.7.

In an embodiment of the invention, the compound of formula (I) is the furoate or benzoate salt of *N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide.

The second active ingredient in the combination of the present invention is a β_2-agonist. The β_2-agonist of the present invention may be any compound or substance capable of stimulating the β_2-receptor and acting as a bronchodilator. Examples of β_2-agonists that may be used in the present invention include bambuterol, bitolterol, carbuterol, indacaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, TA 2005 (chemically identified as 2(1H)-Quinolone, 8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-phenyl)-1-methylethyl]-amino]ethyl]-monohydrochloride, [R-(R*,R*)] also identified by Chemical

Abstract Service Registry Number 137888-11-0 and disclosed in U.S. Patent No 4.579.854 (= CHF-4226), GSK159797, formanilide derivatives e.g. 3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}-butyl)-benzenesulfonamide as disclosed in WO 2002/76933, benzenesulfonamide derivatives e.g. 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)phenyl]ethyl}amino)-hexyl]oxy}butyl)benzenesulfonamide as disclosed in WO 2002/88167, aryl aniline receptor agonists such as those disclosed in WO 2003/042164 and WO 2005/025555, and indole derivatives such as those disclosed in WO 2004/032921.

In one aspect, the β_2-agonist of the invention is a long acting β_2-agonist, i.e. a β_2-agonist with activity that persists for more than 12 hours. Examples of long acting β_2-agonists include formoterol, bambuterol and salmeterol.

In the context of the present specification, unless otherwise stated, any reference to a β_2-agonist includes active salts, solvates or derivatives that may be formed from said β_2-agonist and any enantiomers and mixtures thereof, including racemates. Examples of possible salts or derivatives of β_2-agonists are 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 pharmaceutically acceptable esters (e.g. C_1-C_6 alkyl esters). The β_2-agonists (including salts and derivatives thereof) may also be in the form of a solvate, e.g. a hydrate.

In an embodiment of the present invention, the β_2-agonist is formoterol. The chemical name for formoterol is *N*-[2-hydroxy-5-[(1)-1-hydroxy-2-[[(1)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide. The preparation of formoterol is described, for example, in WO 92/05147. As will be clear from the above, the term formoterol is intended to include all pharmaceutically acceptable salts thereof. In one aspect of this embodiment, the β_2-agonist is formoterol fumarate, for example formoterol fumarate dihydrate.

As emphasised above, it will be understood that the invention encompasses the use of all optical isomers of formoterol and mixtures thereof including racemates. Thus for example, the term formoterol encompasses *N*-[2-hydroxy-5-[(1*R*)-1-hydroxy-2-[[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide, *N*-[2-hydroxy-5-[(1*S*)-1-hydroxy-2-[[(1*S*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide or a mixture of such enantiomers, including a racemate.

In a further embodiment of the present invention, the β_2-agonist is indacaterol. As will be clear from the above, the term indacaterol is intended to include all pharmaceutically acceptable salts thereof, including for example, indacaterol maleate and indacaterol hydrochloride.

The compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof (first active ingredient) and β_2–agonist (second active ingredient) of the present invention may be administered simultaneously, sequentially or separately to treat respiratory diseases. By sequential it is meant that the active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately, but when administered in this manner they are generally administerted less than 4 hours apart, more conveniently less than two hours apart, more conveniently less than 30 minutes apart and most conveniently less than 10 minutes apart.

The active ingredients of the present invention may be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. The active ingredients may also be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders,

lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

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

Therefore, in one aspect, the present invention provides a kit comprising a preparation of a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient which is a β_2–agonist, and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

In another embodiment the active ingredients may be administered via a single pharmaceutical composition. Therefore, the present invention further provides a pharmaceutical composition comprising, in admixture, a first active ingredient which is compound of formula (I) or pharmaceutically acceptable salt thereof, and a second active ingredient which is β_2–agonist. The present invention also provides a process for the preparation of a pharmaceutical composition which comprises mixing the first active ingredient with the second active ingredient.

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 (I) or pharmaceutically acceptable salt thereof, with a β_2–agonist and a pharmaceutically acceptable adjuvant, diluent or carrier.

It will be understood that the therapeutic dose of each active ingredient administered in accordance with the present invention will vary depending upon the particular active ingredient employed, the mode by which the active ingredient is to be administered, and the condition or disorder to be treated.

In one aspect of the present invention, the first, second (and when present, the third) active ingredients of the present invention are each administered by inhalation. In this aspect, the active ingredients are inhaled simultaneously, sequentially or separately.

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

When administered via inhalation the dose of the first active ingredient (compound of formula (I) or a pharmaceutically acceptable salt or solvate 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, 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.

When administered via inhalation the dose of the second active ingredient (β_2-agonist), may conveniently be administered by inhalation at a dose generally in the range of from 0.1 to 100 μg, 0.1 to 50 μg, 0.1 to 40 μg, 0.1 to 30 μg, 0.1 to 20 μg, 0.1 to 10 μg, 5 to 100 μg, 5 to 50 μg, 5 to 40 μg, 5 to 30 μg, 5 to 20 μg, 5 to 10 μg, 10 to 100 μg, 10 to 50 μg, 10 to 40 μg, 10 to 30 μg, or 10 to 20 μg. In an embodiment of the present invention, the dose of the third active ingredient is in the range 1 to 30 μg.

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.

In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a second active ingredient which is a β_2-agonist, wherein each active ingredient is formulated for inhaled administration.

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 formulations. 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 acceptable additives, diluents or carriers. Examples of suitable diluents or carriers include lactose (e.g. the monohydrate), dextran, mannitrol 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 surfactants, 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 or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

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

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 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.

In an embodiment of the present invention, the compound of formula (I) or pharmaceutically acceptable salt thereof may be administered orally and the other active ingredient(s) administered by inhalation.

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

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

The present invention still further provides a method of treating a respiratory disease which comprises simultaneously, sequentially or separately administering:
(a) a (therapeutically effective) dose of a first active ingredient which is a compound of formula (I) or a pharmaceutically acceptable salt thereof; and
(b) a (therapeutically effective) dose of a second active ingredient which is a β_2-agonist.;
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and

"therapeutically" should be construed accordingly. Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The pharmaceutical product, kit or composition of the present may optionally comprise a third active ingredient which third active ingredient is a substance suitable for use in the treatment of respiratory diseases. However, in one embodiment of the present invention there is a provided a pharmaceutical product, kit or composition according to the present invention that does not include a glucocorticosteroid as an active ingredient.

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

^{1}H NMR spectra were recorded on a Varian Unity Inova 400 or a Varian Mercury VX 300 and data are quoted in the form of delta values, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard.

The central solvent peak of chloroform–*d* (δ_H 7.27 ppm), acetone-d_6 (δ_H 2.05 ppm), or DMSO-d_6 (δ_H 2.50 ppm) were used as internal standard.

Low resolution mass spectra and accurate mass determination were recorded on an Agilent MSD 1100 LC-MS system equipped with APCI /ESI ionisation chambers.

All solvents and commercial reagents were laboratory grade and used as received.

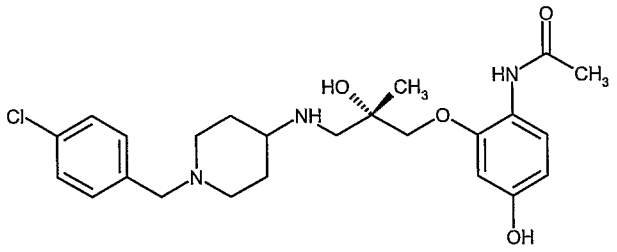
The following abbreviations are used:

DMSO	dimethyl sulfoxide;
DMF	*N*-dimethylformamide;
THF	tetrahydrofuran;
TFA	trifluoroacetic acid;

Prepration of CCR1 receptor antagonists

Example 1 (a)

***N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide hemi-fumarate (2:1 salt)**



To a stirred solution of crude *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (24.0 g, 36.5 mmol; obtained by extraction at pH 9 from the corresponding salt with trifluoroacetic acid as described in Example 1 of WO 03/051839) in methanol (240 ml), a solution of fumaric acid (2.13 g, 18.3 mmol) in methanol (55 ml) was added over a period of 15 minutes. It was observed that a precipitate began to form when about two thirds of the fumaric acid solution had been added. When all the fumaric acid solution had been added, the stirring was stopped and the reaction mixture was left overnight at ambient temperature (20°C) in a closed flask. The precipitate was isolated on a filter funnel, washed with methanol (3 x 50 ml) and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid (14.0 g, 73%).

^{1}H NMR (399.99 MHz, dmso) δ 8.91 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.50 (s, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.79 (s, *strongly coupled AB-system*, 2H), 3.44 (s, 2H), 2.88 (d, *J* = 12.2 Hz, 1H), 2.82 – 2.72 (m, 3H), 2.64 - 2.55 (m, 1H), 2.02 (s, 3H), 2.00 – 1.92 (m, 2H), 1.91 – 1.83 (m, 2H), 1.47 – 1.35 (m, 2H), 1.23 (s, 3H)

APCI-MS: m/z 462 [MH+]

The stoichiometry, base to acid, of 2:1 was confirmed by NMR.

The hemi-fumarate salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089):

(2) 6.2, 10.7 and 12.5, or
(3) 6.2, 10.7 and 18.8, or
(4) 6.2, 10.7 and 18.0, or
(5) 6.2, 10.7, 12.5, 18.0 and 18.8, or
(6) 6.2, 10.7, 12.5, 18.0, 18.8, 19.7 and 19.8.

Example 1(b)

Preparation of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide benzoate (1:1 salt), Form A

(a) Hot solutions of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (which may be prepared by processes described in WO 03/051839; 462 mg, 1.0 mmol) in ethyl acetate (10 ml) and benzoic acid

(244 mg, 2.0 mmol) in ethyl acetate (10 ml) were mixed. The resulting mixture was left to cool down to ambient temperature (20°C) in a closed vial. A white precipitate was formed without turbidity. After standing at ambient temperature overnight the precipitate obtained was washed with ethyl acetate (3 x 10 ml) and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid (506 mg, 86%). The salt contained traces of ethyl acetate.

^{1}H NMR (399.99 MHz, acetone-d_6) δ 8.77 (s, 1H), 8.07 - 8.04 (m, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.55 - 7.50 (m, 1H), 7.46 - 7.41 (m, 2H), 7.36 - 7.31 (m, 4H), 6.52 (d, J = 2.6 Hz, 1H), 6.40 (dd, J = 8.7, 2.6 Hz, 1H), 3.97 (d, J = 9.3 Hz, 1H), 3.89 (d, J = 9.3 Hz, 1H), 3.48 (s, 2H), 3.29 (d, J = 12.1 Hz, 1H), 2.94 (d, J = 12.2 Hz, 1H), 2.91 - 2.77 (m, 3H), 2.09 - 2.00 (m, 4H), 1.98 (s, 3H), 1.72 - 1.59 (m, 2H), 1.30 (s, 3H)

APCI-MS: m/z 462 [MH+]

The stoichiometry, base to acid, of 1:1 was confirmed by NMR.

Further quantities of the titled salt were prepared by the following method:

(b) Hot solutions of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (4.0 g, 8.65 mmol) in ethyl acetate (75 ml) and benzoic acid (1.16 g, 9.5 mmol) in ethyl acetate (75 ml) were mixed. When the resulting mixture had cooled down to ambient temperature (20°C) it was seeded with a particle of the titled salt obtained in (a) above and was left overnight in a closed flask. The precipitate obtained was washed with ethyl acetate (3 x 50 ml) and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid (4.41 g, 87%). The salt contained traces of ethyl acetate.

The benzoate Form A salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see

the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089):

(1) 6.1, 10.7 and 19.3, or
(2) 6.1, 12.2 and 14.1, or
(3) 6.1, 10.7, 12.2, 14.1, 18.1 and 19.3, or
(4) 6.1, 10.7, 12.2, 14.1, 15.7, 18.1 and 19.3, or
(5) 6.1, 10.7, 12.2, 14.1, 15.1 and 19.3, or
(7) 6.1, 10.7, 12.2, 14.1, 15.1, 15.7, 18.1 and 19.3, or
(8) 6.1, 10.7, 12.2, 14.1, 15.1, 15.7, 18.1, 19.3, 21.2 and 24.6.

Preparation of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide benzoate (1:1 salt), Form B

(a) The benzoate salt prepared by the method of Example 1(b) (Form A, 10 to 15 mg) was placed in a Differential Scanning Calorimetry pan (with a lid crimped) and using a heating rate of 5 K.min-1, heated until a temperature of 155°C was reached. Once the salt had melted (an onset melting temperature of 146.5°C was recorded under the conditions used), the melted sample was cooled down at a rate of 5 K.min-1 to ambient temperature (20°C). Then the same pan was heated again at a heating rate of 5 K.min-1 until a temperature of 151°C was reached and the scan recorded an isotherm at 148°C over a 10 minute period. The pan was then cooled rapidly to ambient temperature resulting in the formation of crystals which were subsequently confirmed by X-ray powder diffraction (XRPD) to be a new physical form of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide benzoate (Form B). Some amorphous benzoate salt may be formed as a by-product of the process.

(b) The Form B salt described in (a) above was also prepared by dissolving, in a vial, 20%w of a sample of the benzoate salt prepared by the method of Example 1(b) (Form A)

in a solvent such as methanol (>20 mg/ml), ethanol (>20 mg/ml), n-propanol (>20 mg/ml), isopropanol (8.5 mg/ml) or acetone (9.6 mg/ml). The figures in brackets indicate the estimated solubility of the salt in these solvents. The vial was then sealed and the suspension was homogenised at ambient temperature (20°C) using a magnet. Stirring and temperature were maintained for a period of at least 7 days after which time a sample of the material obtained was dried and tested by XRPD. XRPD confirmed that there had been complete transformation of Form A to Form B.

(c) The Form B salt described in (a) above was also prepared by dissolving benzoate salt prepared by the method of Example 1(b) (Form A) (22.0g, 37.7mmol) and benzoic acid (0.46 g, 3.8 mmol) in hot 2-propanol (190 ml) in a round-bottomed flask to give a reddish solution. The flask was rotated using a Rotavapor device on a waterbath at 40°C until the solution had cooled down to 40 °C, whereupon it was seeded with some crystals of the Form B salt. The waterbath was allowed to cool down slowly to ambient temperature overnight while the flask was rotating and the mixture was seeded occasionally with some crystals of the Form B salt. A pink precipitate which formed was isolated by suction, washed with 2-propanol (2 x 50 ml) and dried *in vacuo* at 100°C for 20 hours to give the titled salt (as confirmed by XRPD) as a pale pink solid (18.5 g, 84%). The salt contained traces of 2-propanol.

^{1}H NMR (299.95 MHz, DMSO-*d6*) δ 8.87 (s, 1H), 7.96 - 7.91 (m, 2H), 7.59 - 7.52 (m, 1H), 7.49 - 7.47 (m, 1H), 7.46 - 7.42 (m, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 6.39 (d, J = 2.5 Hz, 1H), 6.29 (dd, J = 8.5, 2.5 Hz, 1H), 3.78 – 3.72 (m, 2H), 3.41 (s, 2H), 2.79 - 2.66 (m, 4H), 1.98 (s, 3H), 1.97 - 1.88 (m, 2H), 1.85 - 1.76 (m, 2H), 1.41 - 1.25 (m, 2H), 1.19 (s, 3H)

APCI-MS: m/z 462 [MH+]

The stoichiometry, base to acid, of 1:1 was confirmed by NMR.

The benzoate Form B salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089):

(1) 6.5, 9.3 and 10.5, or

(2) 6.5, 9.3, 17.6 and 17.8, or

(3) 6.5, 9.3, 10.5,12.0 and 12.4, or

(4) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6 and 17.8, or

(5) 6.5, 13.0 and 20.2, or

(6) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8 and 19.2, or

(7) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8 and 26.0, or

(8) 6.5, 9.3, 10.5, 12.0, 12.4, 13.0, 13.6, 15.5, 17.6, 17.8, 19.2, 20.2, 22.8, 24.2, 26.0 and 30.7.

Example 1(c)

Preparation of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide furoate (1:1 salt), Form A

(a) To a stirred solution of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (which may be prepared by processes described in WO 03/051839; 46 mg, 0.1 mmol) and furoic acid (23 mg, 0.2 mmol) in methanol (0.2 ml) contained in a vial, diethylether (5 ml) was added and the vial was closed. The resulting mixture was stirred for 3 days and a precipitate that formed was isolated, washed with diethylether and dried *in vacuo* to give an off-white solid (38 mg). The solid contained the titled salt as a crystalline material together with some amorphous salt. The titled salt contained trace amounts of diethylether.

^{1}H NMR (299.946 MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.75 - 7.73 (m, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 4.4 Hz, 2H), 7.29 (d, J = 4.4 Hz, 2H), 6.97 - 6.94 (m, 1H), 6.54 (dd, J = 3.4, 1.7 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 6.29 (dd, J = 8.6, 2.4 Hz, 1H), 3.78 (s, 2H), 3.43 (s, 2H), 2.93 (d, J = 12.1 Hz, 1H), 2.84 - 2.71 (m, 3H), 2.70 - 2.58 (m, 1H), 1.99 (s, 3H), 1.96 - 1.83 (m, 4H), 1.51 - 1.34 (m, 2H), 1.22 (s, 3H)

APCI-MS: m/z 462 [MH+]

The stoichiometry, base to acid, of 1:1 was confirmed by NMR.

Further quantities of the titled salt were prepared by the following method:

(b) To a solution of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (230 mg, 0.5 mmol) in methanol (0.5 ml) contained in a vial, furoic acid (62 mg, 0.55 mmol) was added as a solid. The mixture was shaken until a solution was obtained. The solution was diluted with ethyl acetate (6ml), seeded with a particle of the titled salt obtained in (a) above and was left overnight in the closed vial. The precipitate obtained was washed with ethyl acetate and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid (200 mg, 70%). The titled salt contained trace amounts of ethyl acetate.

^{1}H NMR (299.946 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.73 - 7.71 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.94 - 6.91 (m, 1H), 6.52 (dd, J = 3.3, 1.8 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 6.30 (dd, J = 8.6, 2.2 Hz, 1H), 3.78 (s, 2H), 3.43 (s, 2H), 2.97 (d, J = 11.9 Hz, 1H), 2.87 - 2.61 (m, 4H), 1.98 (s, 3H), 1.96 - 1.85 (m, 4H), 1.53 - 1.38 (m, 2H), 1.23 (s, 3H)

APCI-MS: m/z 462 [MH+]

The stoichiometry, base to acid, of 1:1 was confirmed by NMR.

The furoate Form A salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089):

(1) 6.3, 11.0 and 12.7, or
(2) 6.3, 10.7 and 12.7, or
(3) 6.3, 11.0, 12.7 and 15.9, or
(4) 6.3, 10.7, 11.0, 12.7, 13.9, 14.2 and 15.9, or
(5) 6.3, 10.7, 11.0, 12.7, 15.9, 17.7, 19.1, 19.7 and 25.5, or
(6) 6.3, 10.7, 11.0, 12.7, 13.9, 14.2, 15.9, 17.7, 19.1, 19.7, 19.9, 21.6 and 25.5.

Preparation of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide furoate (1:1 salt), Form B

(a) Form B was prepared by dissolving, in a vial, 20%w of a sample of the furoate salt prepared by the method of Example 1(b) (Form A) in a solvent such as ethanol (16 mg/ml) or 2-butanol (8 mg/ml). The figures in brackets indicate the estimated solubility of the salt in these solvents. The vial was then sealed and the suspension was homogenised at ambient temperature (20°C) using a magnet. Stirring and temperature were maintained for a period of at least 7 days after which time a sample of the material obtained was dried and tested by XRPD. XRPD confirmed that there had been complete transformation of Form A to Form B.

Further quantities of the titled salt were prepared by the following method:

(b) Solutions of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (46 mg, 0.10 mmol) in 2-butanol (0.5 ml) and furoic acid (12.5 mg, 0.11 mmol) in 2-butanol (0.5 ml) were mixed and seeded with some crystals of Form B. The mixture was set aside in a closed vial at ambient temperature for 3 days. The precipitate obtained was washed with 2-butanol and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid. The salt contained traces of 2-butanol.

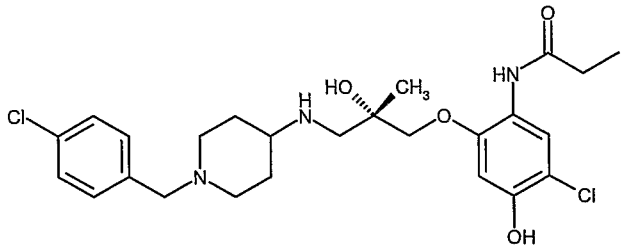
The identity and stoichiometry, base to acid, of 1:1 were confirmed by NMR.

The furoate Form B salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089):

(1) 6.7, 11.0 and 13.4, or
(2) 6.7, 10.4, 11.0 and 13.4, or
(3) 6.7, 10.4, 12.4, 13.4 and 13.7, or
(4) 6.7, 10.4, 13.4 and 20.9, or
(5) 6.7, 10.4, 11.0, 12.4, 13.4, 13.7, 15.6, 16.0 and 17.6, or
(6) 6.7, 10.4, 11.0, 12.4, 13.4, 13.7, 15.6, 16.0, 16.1, 17.6, 18.0, 18.6, 18.9, 20.1, 20.9 and 23.4.

Example 2

***N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide di-trifluoroacetate.**



(i) *N*-(2-Hydroxy-4-methoxyphenyl)propanamide

To an ice-cooled solution of 2-hydroxy-4-methoxyaniline.HCl (600 mg, 3.4 mmol) and triethylamine (3 eq) in dichloromethane (25 mL) propionic anhydride (1.1 eq) was added dropwise. The solution was left at ambient temperature for 5 h. The reaction was quenched with water, the layers separated and the organic phase extracted with 1N NaOH (aq) (3 x 25 mL). The pH of the aqueous phase was adjusted with concentrated HCl to 5 and extracted with dichloromethane (3 x 25 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and removed *in vacuo*, providing the subtitled compound as a brown solid (555 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$- d_6) δ 7.04 (b), 6.83 (d, J = 8.4, 1H), 6.58 (d, J = 2.8, 1H), 6.43 (dd, J_1 = 8.4, J_2 = 2.8, 1H), 3.77 (s, 3H), 2.49 (q, J = 7.6, 2H), 1.29 (t, J = 7.5, 3H); APCI-MS: m/z 196 [MH^+].

(ii) *N*-(5-Chloro-2-hydroxy-4-methoxyphenyl)propanamide

To an ice-cooled solution of N-(2-hydroxy-4-methoxyphenyl)propanamide (500 mg, 2.6 mmol) and dimethylformamide hydrogen chloride (1 eq) in DMF (5 mL), MCPBA (70%, 1 eq) was added in small portions. The reaction was stirred for an additional 5 minutes, afterwhich it was quenched with 1M $NaHCO_3$ (aq) (50 mL). The aquous phase was washed with ethyl acetate (50 mL). The organic phase was washed with water (3 x 25 mL), dried and removed *in vacuo*, providing the subtitled compound as a purple solid (408 mg, 71%).

^{1}H NMR (300 MHz, acetone-d_6) δ 9.68 (b, 1H), 9.12 (b, 1H), 7.37 (s, 1H), 6.62 (s, 1H), 3.83 (s, 3H), 2.49 (q, J = 7.7, 2H), 1.18 (t, J = 7.5, 3H); APCI-MS: m/z 229 [M^+].

(iii) *N*-(5-Chloro-4-methoxy-2-{[(2*S*)-methyloxiran-2-yl]methoxy}phenyl)propanamide

A suspension of *N*-(5-Chloro-2-hydroxy-4-methoxyphenyl)propanamide (202 mg, 0.88 mmol), [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (1 eq) and cesium carbonate (1.2 eq) in DMF (4 mL) was stirred at room temperature for 4 h. The mixture was separated over water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with water (2 x 30 mL), dried and removed *in vacuo*, providing the subtitled compound as an off-white solid (249 mg, 95%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.80 (b, 1H), 6.61 (s, 1H), 4.14 (m, 1H), 3.98 (m, 1H), 3.85 (s, 3H), 2.94 (m, 1H), 2.79 (m, 1H), 2.42 (q, J = 7.6, 2H), 1.47 (s, 3H), 1.25 (t, J = 7.5, 3H); APCI-MS: m/z 299 [MH^+].

(iv) *N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide di-trifluoroacetate

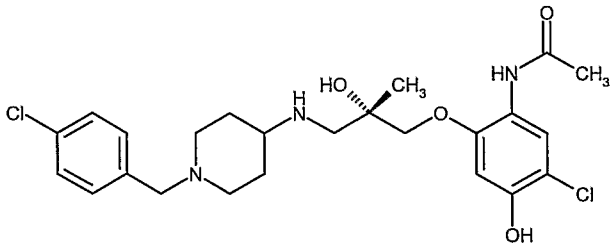
To a solution of 1-(4-chlorobenzyl)-piperidin-4-yl amine (50 mg, 0.2 mmol) and *N*-(5-chloro-4-methoxy-2-{[(2*S*)-methyloxiran-2-yl]methoxy}phenyl)propanamide (1 eq) in acetonitrile (5 mL), lithium perchlorate (10 eq) was added. The reaction mixture was refluxed for 18h. The reaction mixture was poured over a MEGA BE-SCX column (Bond Elut®, 5 g, 20 mL). The column was first washed with methanol (3 x 10 mL) and subsequently with a mixture of ammonia/methanol (1/20, 3 x 10 mL). The basic layers were pooled and the solvent removed *in vacuo*, providing *N*-{5-chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-methoxyphenyl} propaneamide as a light brown oil (100 mg, 86%), which was redissolved in dichlormethane (4 mL). The solution was cooled to 0 °C and 1M BBr_3 in dichloromethane (1 mL) added dropwise. The reaction was stirred for 18h, afterwhich it was quenched with methanol. The solvent was removed *in vacuo* and the residue purified by reverse phase prep. HPLC, using acetonitrile and water containing 0.1% TFA in gradient as mobile phase. Pooled fractions were freeze-dried to give the titled product as an amorphous white solid (38 mg, 39%).

^{1}H NMR (300 MHz, acetone-d_6) δ 8.66 (broad), 8.09 (3, 1H), 7.60 (d, J =8.4, 4H), 7.47 (d, J = 8.4, 4H), 6.78 (s, 1H), 4.41 (s, 2H), 4.10-3.93 (m, 2H), 3.70-3.65 (m, 4H), 3.44-2.39

(m, 1H), 3.20 (m, 2H), 2.52-2.37 (m, 6H), 1.38 (s, 3H), 1.10 (t, *J*=7.5, 3H); APCI-MS: m/z 510 [MH^+].

Example 3

***N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide di-trifluoroacetate.**

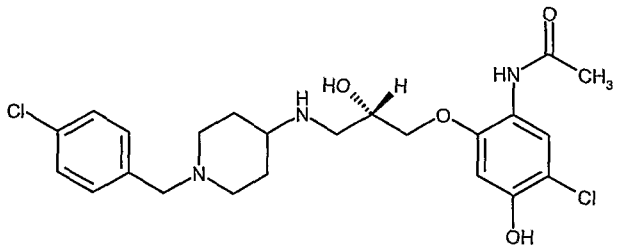


Synthesis analogous to that described for example 2 but wherein 2-hydroxy-4-methoxyaniline.HCl is reacted with acetic anhydride (1.1 eq).

^{1}H NMR (300 MHz, acetone-d_6) δ 8.77 (s, 1H), 8.06 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 6.79 (s, 1H), 4.43 (s, 2H), 4.08 (d, *J* = 9.9 Hz, 1H), 3.94 (d, *J* = 9.9 Hz, 1H), 3.79-3.61 (m, 3H), 3.68 (d, *J* = 12.5 Hz, 1H), 3.42 (d, *J* = 12.7 Hz, 1H), 3.32-3.13 (m, 2H), 2.63-2.48 (m, 2H), 2.49-2.29 (m, 2H), 2.08 (s, 3H), 1.38 (s, 3H); APCI-MS: m/z 496 [MH^+].

Example 4

***N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl}acetamide di-trifluoroacetate.**

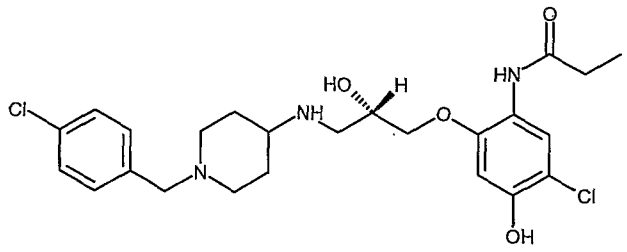


Synthesis analogous to that described for example 3 but wherein *N*-(5-chloro-2-hydroxy-4-methoxyphenyl)acetamide is reacted with S-(+)-glycidyl nosylate (1 eq)

^{1}H NMR (300 MHz, acetone-d_6) δ 8.64 (broad, NH), 8.21 (s, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 9.0 Hz, 2H), 6.74 (s, 1H), 4.41-4.35 (m, 3H), 4.13-4.01 (m, 2H), 3.69-3.40 (m, 5H), 3.14 (m, 2H), 2.55-2.47 (m, 2H), 2.31 (m, 2H), 2.09 (s, 3H); APCI-MS: m/z 482 [MH$^+$].

Example 5

***N*-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxylpropyl)oxy]-4-hydroxyphenyl} propaneamide di-trifluoroacetate.**



Synthesis analogous to that described for example 2 but wherein *N*-(5-chloro-2-hydroxy-4-methoxyphenyl)acetamide is reacted with S-(+)-glycidyl nosylate (1 eq)

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (broad), 9.78 (broad), 9.79 (broad), 9.00 (broad), 8.88 (broad), 7.79 (m, 1H), 7.62-7.50 (m, 4H), 6.63 (s, 1H), 5.98 (broad), 4.29 (m, 2H), 4.16 (m, 1H), 3.95-3.88 (m, 2H), 341-2.97 (m, 7H), 2.35-2.22 (m, 4H), 1.82-1.75 (m, 2H), 1.07 (m, 3H); APCI-MS: m/z 496 [MH$^+$].

Human CCR1 binding assay

Membranes

HEK293 cells, from ECACC, stably expressing recombinant human CCR1 (HEK-CCR1) were used to prepare cell membranes containing CCR1. The membranes were stored at -70°C. The concentration of membranes of each batch was adjusted to 10% specific binding of 33 pM [^{125}I] MIP-1α.

Binding assay

100 µL of HEK-CCR1 membranes diluted in assay buffer pH 7.4 (137 mM NaCl (Merck, Cat No 1.06404), 5.7 mM Glucose (Sigma, Cat No G5400), 2.7 mM KCl (Sigma, Cat No P-9333), 0.36 mM NaH_2PO_4 x H_2O (Merck, Cat No 1.06346), 10 mM HEPES (Sigma, Cat No H3375), 0.1% (w/v) Gelatine (Sigma, Cat No G2625)) with the addition of 17500 units/L Bacitracin (Sigma, Cat No B1025) were added to each well of the 96 well filter plate (0.45 µm opaque Millipore cat no MHVB N4550). 12 µL of compound in assay buffer, containing 10% DMSO, was added to give final compound concentrations of $1x10^{-5.5}$-$1x10^{-9.5}$ M. 12 µl cold human recombinant MIP-1α (270-LD-050, R&D Systems, Oxford, UK), 10 nM final concentration in assay buffer supplemented with 10% DMSO, was included in certain wells (without compound) as non-specific binding control (NSB). 12 µl assay buffer with 10% DMSO was added to certain wells (without compound) to detect maximal binding (B0).

12 µL [^{125}I] MIP-1α, diluted in assay buffer to a final concentration in the wells of 33 pM, was added to all wells. The plates with lid were then incubated for 1.5 hrs at room temperature. After incubation the wells were emptied by vacuum filtration (MultiScreen Resist Vacuum Manifold system, Millipore) and washed once with 200 µl assay buffer. After the wash, all wells received an addition of 50 µL of scintillation fluid (OptiPhase "Supermix", Wallac Oy, Turko, Finland). Bound [^{125}I] MIP-1α was measured using a Wallac Trilux 1450 MicroBeta counter. Window settings: Low 5-High 1020, 1-minute counting/well.

Calculation of percent displacement and IC_{50}

The following equation was used to calculate percent displacement.

Percent displacement = 1- ((cpm test – cpm NSB) / (cpm B0- cpm NSB)) where:

cpm test = average cpm in duplicate wells with membranes and compound and [^{125}I] MIP-1α cpm;

NSB = average cpm in the wells with membranes and MIP-1α and [^{125}I] MIP-1α (non-specific binding) cpm;

B0 = average cpm in wells with membranes and assay buffer and [^{125}I] MIP-1α (maximum binding).

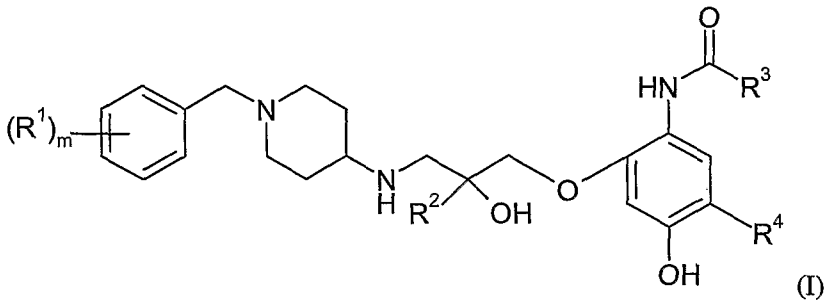
The molar concentration of compound producing 50% displacement (IC_{50}) was derived using the Excel-based program XLfit (version 2.0.9) to fit data to a 4-parameter logistics function.

All compounds of the Examples 1 to 5 had IC_{50} values of less than 20 nM.

CLAIMS

1. A pharmaceutical product comprising, in combination,

(a) a first active ingredient which is a compound of general formula



(I)

wherein

m is 0, 1 or 2;

each R^1 independently represents halogen or cyano;

R^2 represents a hydrogen atom or methyl;

R^3 represents the group C_1-C_4 alkyl;

and

R^4 represents hydrogen or halogen;

or a pharmaceutically acceptable salt thereof; and

(b) a second active ingredient which is a β_2–agonist.

2. A composition according to claim 1, wherein R^1 is halogen.

3. A composition according to claim 1 or claim 2, wherein R^4 is hydrogen or chlorine.

4. A product according to claim 1 or claim 2, wherein R^4 is hydrogen.

5. A composition according to any preceding claim, wherein R^3 is methyl or ethyl.

6. A composition according to any preceding claim, wherein the first active ingredient is selected from
N-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl}acetamide,
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl} propaneamide, or
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide,
or a pharmaceutically acceptable salt thereof.

7. A product according to any preceding claim, wherein the first active ingredient is a salt selected from the benzoate, fuorate or hemi-fumarate salt of *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide.

8. A product according to any preceding claim, in which the second active ingredient is formoterol or indacaterol.

9. A product according to claim 11, in which the third active ingredient is formoterol.

10. A product according to claim 9, in which the second active ingredient is formoterol fumarate dihydrate.

11. A product according to any preceding claim, which is in a form suitable for administration by inhalation.

12. A product according to any preceding claim for use in therapy.

13. Use of a product according to any preceding claim, in the manufacture of a medicament for the treatment of a respiratory disease.

14. Use according to claim 13, wherein the respiratory disease is chronic obstructive pulmonary disease.

15. Use according to claim 13, wherein the respiratory disease is asthma.

16. A method of treating a respiratory disease, which method comprises simultaneously, sequentially or separately administering:
(a) a (therapeutically effective) dose of a first active ingredient which is a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof; and
(b) a (therapeutically effective) dose of a second active ingredient which is a β_2–agonist.

17. A kit comprising a preparation of a first active ingredient which is a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient which is a β_2–agonist and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

18. A kit according to claim 17, wherein the first active ingredient is selected from
N-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl}acetamide,

N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl} propaneamide, or
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide,
or a pharmaceutically acceptable salt thereof.

19. A kit according to claim 17 or claim 18, wherein the second active ingredient is formoterol.

20. A kit according to claim 19, wherein the second active ingredient is formoterol fumarate dihydrate.

21. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, and a second active ingredient which is a β_2–agonist.

22. A composition according to claim 21, wherein the first active ingredient is selected from
N-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide;
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl}acetamide,
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxypropyl)oxy]-4-hydroxyphenyl} propaneamide, or
N-{5-Chloro-2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl} propaneamide,
or a pharmaceutically acceptable salt thereof.

23. A composition according to claim 21 or claim 22, in which the third active ingredient is formoterol.

24. A composition according to claim 23, in which the third active ingredient is formoterol fumarate dihydrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000971

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.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 16 relates to a method of 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 fee, this Authority did not invite payment of any additional fee.

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.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000971

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, A61P

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03051839 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003)	1-24
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Y	US 3994974 A (MASUO MURAKAMI ET AL), 30 November 1976 (30.11.1976)	1-24
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Y	WO 0075114 A1 (NOVARTIS AG), 14 December 2000 (14.12.2000)	1-24
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Y	WO 03082292 A1 (GLAXO GROUP LIMITED), 9 October 2003 (09.10.2003)	1-24
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[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
13 December 2006	19 -12- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000971

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0198270 A2 (DUPONT PHARMACEUTICALS COMPANY), 27 December 2001 (27.12.2001) --	1-24
A	WO 2005010154 A2 (MERCK & CO., INC.), 3 February 2005 (03.02.2005) --	1-24
A	WO 02076933 A1 (GLAXO GROUP LIMITED), 3 October 2002 (03.10.2002) --	1-24

International patent classification (IPC)

A61K 31/4468 (2006.01)
A61K 31/167 (2006.01)
A61K 31/4375 (2006.01)
A61P 11/00 (2006.01)
A61P 11/06 (2006.01)
A61P 11/08 (2006.01)

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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.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

25/11/2006

International application No.
PCT/SE2006/000971

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