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(54) Title: A 2-F LUOROBENZOATE SALT AND A 2, 6-DIF LUOROBENZOATE SALT OF N-{5-CHLORO-2- [((2S) -3-[1-(4-CHLOROBENZYL)PIPERIDIN-4- YL] AMINO } - 2 - HYDROXY- 2 -ME T HYLPR OPYL) OXY] - 4 - HYDROXY-PHENYL } ACETAMIDE

(57) Abstract: The invention provides a 2-fluorobenzoate salt and a 2,6-difluorobenzoate salt of N-[5-chloro-2-[(2S)-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl]acetamide or a solvate and polymorphic forms thereof, pharmaceutical compositions containing the salts or solvates and use thereof in therapy.

WO 2008/100202 A1

A 2-fluorobenzoate salt and a 2,6-difluorobenzoate salt of N-{5-chloro-2-[(2S)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide

FIELD OF THE INVENTION

5 The present invention relates to a 2-fluorobenzoate salt and a 2,6-difluorobenzoate salt of N-{5-chloro-2-[(2S)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide and polymorphic forms thereof, to pharmaceutical compositions containing said salts. The present invention further relates to processes for the preparation of said salts and polymorphic forms. The invention also
10 related to the use of salts and polymorphic forms in the treatment in therapy.

BACKGROUND OF THE INVENTION

15 Chemokine Receptor 1 (CCR1) is highly expressed in tissues affected in different autoimmune, inflammatory, proliferative, hyper proliferative and immunologically mediated diseases, e.g. asthma, chronic obstructive pulmonary disease, multiple sclerosis and rheumatoid arthritis. Therefore, inhibiting CCR1-mediated events with the salt of the invention, e.g. by cell activation and migration, is expected to be effective in the treatment
20 of such conditions.

In the manufacture of pharmaceutical compositions, it is important that the active compound is in a form in which it can be conveniently handled and processed in order to obtain a commercially-viable manufacturing process. In this connection, the chemical
25 stability and the physical stability of the active compound are important factors. The active compound, and compositions containing it, must be capable of being effectively stored over appreciable periods of time, without exhibiting any significant change in the physico-chemical characteristics (e.g. chemical composition, density, hygroscopicity and solubility) of the active compound.

30

Furthermore, if the active compound is to be incorporated into a composition for pulmonary administration, e.g., via a dry powder inhaler such as the Turbuhaler® device, it is desirable if the active compound can be readily micronised to yield a powder with

good flow properties and comprising a high fine crystalline particle fraction (i.e. a fraction in which the active compound particles have a mass median aerodynamic diameter of less than 10 µm (micrometer)). Such a fraction is capable of being carried deep into the lungs leading to faster and increased absorption of the active compound.

5

Patent application PCT/SE2006/000918 generally discloses piperidinyl derivatives and, in particular, the compound *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide and pharmaceutically acceptable salts or solvates thereof. These compounds have activity as CCR1 antagonists. Salts of said compound specifically disclosed in the application are the benzoate salt and the furoate salt.

10

Patent applications PCT/SE2006/000920 and PCT/SE2006/000921 disclose the benzoate and furoate salts of 4-({(*(2S)*-3-[2-(acetylamino)-5-hydroxyphenoxy]-2-hydroxy-2-methylpropyl}ammonio)-1-(4-chlorobenzyl)piperidine. However, the melting points for the benzoate salts of both polymorphs A and B of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide, are lower than those of 4-({(*(2S)*-3-[2-(acetylamino)-5-hydroxyphenoxy]-2-hydroxy-2-methylpropyl}ammonio)-1-(4-chlorobenzyl)piperidine. The melting points for the furoate salts of both polymorphs A and B of *N*-{5-Chloro-2-[[*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide are higher than those of 4-({(*(2S)*-3-[2-(acetylamino)-5-hydroxyphenoxy]-2-hydroxy-2-methylpropyl}ammonio)-1-(4-chlorobenzyl)piperidine. The low melting point of the benzoate salts has implications for its developability as an ingredient of a composition for pulmonary administration as the crystals may melt upon micronisation.

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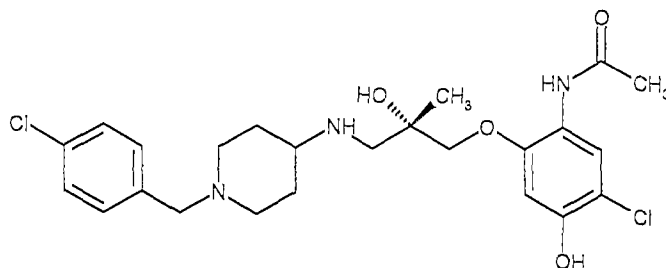
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It has now been found that substituted benzoic acid salts of the compound *N*-{5-chloro-2-[[*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide can be prepared, which have good physico-chemical properties, and which may be formulated in a dry powder composition for pulmonary administration.

30

DETAILED DESCRIPTION OF THE INVENTION

The structure of *N*-{5-Chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide is shown below:



In one embodiment of the invention, there is provided the 2-fluorobenzoate salt of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (hereinafter referred to as “the 2-fluorobenzoate salt”) and the 2,6-difluorobenzoate salt of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (hereinafter referred to as “the 2,6-difluorobenzoate salt”).

10

The invention also provides solvates (including hydrates) as well as cocrystals of the 2-fluorobenzoate and 2,6- difluorobenzoate salts. In one embodiment the 2-fluorobenzoate and 2,6- difluorobenzoate salts are anhydrous. In another embodiment the 2-fluorobenzoate and 2,6- difluorobenzoate salts are in non-solvated form.

15

In an embodiment of the invention, the 2-fluorobenzoate and 2,6- difluorobenzoate salts or solvates thereof have crystalline properties and are preferably at least 50% crystalline, more preferably at least 60% crystalline, still more preferably at least 70% crystalline and most preferably at least 80% crystalline. Crystallinity can be estimated by conventional X-ray diffractometry techniques.

20

In another embodiment of the invention, the 2-fluorobenzoate and 2,6- difluorobenzoate salts or solvates thereof are from 50%, 60%, 70%, 80% or 90% to 95%, 96%, 97%, 98%, 99% or 100% crystalline.

25

Without being bound to any particular theory, the 2-fluorobenzoate and 2,6-difluorobenzoate salts are believed to be polymorphic. One embodiment of the invention relates to polymorphic forms of said salts.

In another embodiment one polymorph of the 2-fluorobenzoate (hereinafter referred to as Form A, 2-fluorobenzoate 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) 5.6, 9.2 and 11.2, or

(2) 5.6, 10.4 and 12.4, or

(3) 9.2, 10.4, 11.2, 12.4, 14.2 and 15.0 or

(4) 5.6, 10.4, 12.7, 13.6, 14.2, 15.0, 17.5 and 18.8 or

(5) 5.6, 9.2, 11.2, 12.4, 12.7, 13.6, 14.2, 15.0, 16.8, 17.7 and 19.1 or

(6) 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 18.8, 19.1 and 19.5 or

(7) 5.6, 9.2, 10.4, 12.4, 13.6, 14.2, 15.0, 16.8, 17.5, 18.8, 19.5 and 20.6 or

(8) 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 17.5, 17.7, 19.1, 19.5, 21.0, 22.6 and 25.2 or

(9) 5.6, 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 16.6, 16.8, 17.5, 18.8, 19.1, 19.5, 20.5, 21.0, and 22.6

One embodiment relates to Form A, 2-fluorobenzoate salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks:

12.7, 14.2, 16.6, 18.8 and 19.1.

In yet another embodiment one polymorph of the 2,6-difluorobenzoate (hereinafter referred to as Form A, 2,6-difluorobenzoate 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) 5.6, 9.1 and 11.2, or
- (2) 5.6, 10.3 and 12.6, or
- (3) 9.1, 10.3, 11.2, 12.3, 14.9 and 16.7 or
- (4) 5.6, 10.3, 12.6, 13.5, 14.2, 14.9, 17.4 and 19.0 or
- 5 (5) 5.6, 9.1, 11.2, 12.6, 13.5, 14.2, 16.7, 18.4, 18.7, 19.0 and 20.8 or
- (6) 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.7 and 19.0 or
- (7) 5.6, 9.1, 10.3, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 19.5 and 20.3 or
- (8) 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 18.7, 19.0, 20.3, 21.0 and 22.6
or
- 10 (9) 5.6, 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 16.7, 17.4, 18.7, 19.0, 19.5, 20.3, 20.8, and 23.4

One embodiment relates to Form A, 2,6-difluorobenzoate salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks:
12.6, 14.2, 18.4, 16.7, 17.4 and 23.4.

15

Both Forms A may be prepared substantially free of other physical forms by a process comprising the following steps:

- (i) contacting a heated solution at a temperature range of from 40 to 80°C (e.g. 60 °C) of
20 *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide dissolved in a suitable solvent or mixture of solvents (e.g. an organic solvent such as a polar solvent, including but not restricted to alcohols (e.g. methanol), cyanides (e.g. acetonitrile), acetone and ethyl acetate), with
- (ii) a heated solution at a temperature range of from 40 to 80°C (e.g. 60 °C) of 2-
25 fluorobenzoic acid or 2,6-difluorobenzoic acid dissolved in a suitable solvent or mixture of solvents (e.g. an organic solvent such as a polar solvent, including but not restricted to alcohols (e.g. methanol), cyanides (e.g. acetonitrile), acetone and ethyl acetate), to obtain a mixture,
- (iii) allowing the mixture to cool to ambient temperature (e.g. 20°C) to yield a precipitate
30 of Form A of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or Form A of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate, and

(iv) separating the precipitate from the mixture.

One embodiment relates to a process for the preparation of Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt: comprising the steps of;

- 5 (i) contacting a solution at a temperature range of from 40 to 80°C of *N*-{5-chloro-2-
[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-
4-hydroxyphenyl}acetamide dissolved in an organic solvent, with
- (ii) a solution at a temperature range of from 40 to 80°C of 2-fluorobenzoic acid or 2,6-
difluorobenzoic acid dissolved in an organic solvent, to obtain a mixture,
- 10 (iii) allowing the mixture to cool to ambient temperature to yield a precipitate of Form A
of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-
methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or
Form A of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-
hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate, and
- 15 (iv) separating the precipitate from the mixture.

In another embodiment the organic solvent used in steps (i) and/or (ii) is acetonitrile.

Where reference is made in this specification to Forms A being substantially free of other
20 physical forms (or substantially pure), this means that at least 90% by weight, e.g. 90, 91,
92, 93, 94, 95, 96, 97, 98, 99 or 100 %w, of either the 2-fluorobenzoate salt or the 2,6-
difluorobenzoate salt is present in that physical form.

The term 'compounds of the invention' as used in this specification, means the 2-
25 fluorobenzoate salt and 2,6- difluorobenzoate salt, or solvates thereof, as well as the Form
A, 2-fluorobenzoate and the Form A, 2,6-difluorobenzoate salt in any degree of
crystallinity.

Medical use

30 The compounds of the invention are useful as modulators of CCR1 or MIP-1 α chemokine
receptor activity. *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-
hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide ditrifluoroacetate has an IC₅₀
of below 5 nM in the Human CCR1 binding assay as described in PCT/SE2006/000918,

and may be administered to a mammal, including man, for the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases.

- 5 A compound of the invention, can be used in the treatment of:
1. respiratory tract: 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
10 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;
15 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
20 fever); nasal polyposis; acute viral infection including the common cold, and infection due
to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
 2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis,
both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar
spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease;
25 seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis,
reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-
related arthropathies and bone disorders such as tuberculosis, including Potts' disease and
Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout,
calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and
30 synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome;
systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed
connective tissue disease, and undifferentiated connective tissue disease; inflammatory
myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile

arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection,

5 hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, 10 osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

15 4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous 20 eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; 25 iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; 30 eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer;
5 acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
- 10 10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain,
15 pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura,
20 eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;
12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;
- 25 13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and
30 complications of varicose veins;
14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as

Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,
15. gastrointestinal tract: Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminate colitis,
5 irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Combination therapies

10 The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutical composition or composition comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

15 In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below;

20 non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective
25 COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumiracoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular
30 therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline.

In addition the invention relates to a combination of a compound of the invention, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, with a modulator of chemokine receptor function such as an antagonist of CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the invention, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene

compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

5 The present invention further relates to the combination of a compound of the invention, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄, selected from the group consisting of the phenothiazin-3-ols such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

10

The present invention still further relates to the combination of a compound of the invention, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE₄ inhibitor an inhibitor of the isoform PDE_{4D}, or an inhibitor of PDE₅.

15

The present invention still further relates to the combination of a compound of the invention, and an endothelin antagonist such as Tezosentan, Bosentan, Enrasentan, and Sixtasentan.

20 The present invention still further relates to the combination of a compound of the invention, and an angiotensin II antagonist such as Azilzartan, Losartan, Valsartan, Candesartan, and Telmisartan.

25 The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a dual antagonists for both angiotensin II and endothelin A receptors (DARAs) such as disclosed in WO2000001389 and WO2001044239.

30 The present invention further relates to the combination of a compound of the invention, and an adenosine A_{2a} agonist such as CGS-21680 and/or an adenosine A₃ agonist such as IB-MECA and/or an adenosine A_{2b} antagonist.

The present invention further relates to the combination of a compound of the invention, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or
5 parenterally.

The present invention still further relates to the combination of a compound of the invention, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

10

The present invention further relates to the combination of a compound of the invention, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic
15 agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

20

The present invention further relates to the combination of a compound of the invention, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirzepine or telenzepine.

25

The present invention still further relates to the combination of a compound of the invention, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

30

The present invention further relates to the combination of a compound of the invention, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

5

The present invention further relates to the combination of a compound of the invention, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

10

The present invention further relates to the combination of a compound of the invention, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

15

The present invention still further relates to the combination of a compound of the invention, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

20

The present invention further relates to the combination of a compound of the invention, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

25

30

The present invention still further relates to the combination of a compound of the invention, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2

receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

5 The present invention further relates to the combination of a compound of the invention, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a COMT inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of
10 neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, and an agent for the treatment of acute or chronic pain, such as a centrally or
15 peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention,
20 together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a bisphosphonate such
25 as alendronate.

The present invention still further relates to the combination of a compound of the invention, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v)
30 adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or inhibitors of kappaB kinases,

such as IKK1, IKK2 or IKK3), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, 5 sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) 10 elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) 15 inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical 20 oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as 25 adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- 30 (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or idoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin,

leuporelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erb2 antibody trastuzumab, or the anti-erb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or

(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected

immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies. For example, for the treatment of airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma, the compounds of the invention can be combined with one or more agents for the treatment of such a condition. Where such a combination is to be administered by inhalation, then the one or more agents is selected from the list comprising:

- a PDE4 inhibitor including an inhibitor of the isoform PDE4D;
- a selective β .sub2. adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol or indacaterol;
- a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine;
- a steroid (such as budesonide);
- an inhibitor of p38 kinase function;
- an inhibitor of matrix metalloproteases, most preferably targeting MMP-2, -9 or MMP-12; or,
- an inhibitor of neutrophil serine proteases, most preferably neutrophil elastase or proteinase 3.

In another embodiment of the invention where such a combination is for the treatment of airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma, the compounds of the invention, can be administered by inhalation or by the oral route and the other agent can be administered by inhalation or by the oral route. The compounds of the invention and the other agent, may be administered together. They may be administered sequentially. Or they may be administered separately.

Thus, the present invention provides *N*-{5-chloro-2-[[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-

hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt for use in therapy.

In one aspect, the present invention provides *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt for use in treatment of airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma.

In a further aspect, the present invention provides the use of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, in the manufacture of a medicament for treatment of airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma.

In a further aspect, the present invention provides the use of Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt, in the manufacture of a medicament for treatment of airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma.

The invention also provides a method of treating an airway disease, respiratory disease and/or an inflammatory disease such as for example chronic obstructive pulmonary disease and asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, Form A, 2-

fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt or a pharmaceutical composition comprising said compounds.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the mode of administration, the treatment desired and the disorder indicated but may typically be in the range from 0.001 mg/kg to 30 mg/kg.

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.

Pharmaceutical composition

The present invention also provides a pharmaceutical composition comprising *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The compounds of the invention may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the compounds of the invention (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical compositions are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition may comprise from 0.01 to 100 %w (per cent by weight), more preferably from 0.01 to 80 %w, still more preferably from 0.05 to 70 %w, and even more preferably from 0.05 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate or solvates thereof, Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder compositions, for example, compositions in the inhaler device known as the Turbuhaler[®] device (Model 0, 1, 2, or 3) or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

In an embodiment of the invention, the 2-fluorobenzoate salt or 2,6-difluorobenzoate salt of the invention is administered by inhalation. In a further embodiment, the 2-fluorobenzoate salt or 2,6-difluorobenzoate salt of the invention is administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

When administered via inhalation the dose of the compounds of the invention may 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.

- 5 Dry powder compositions and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 µm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic
10 acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol.
15 Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

20

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® device (Model 0, 1, 2, or 3) in which a dosing unit meters the desired dose which is then inhaled
25 by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato
30 starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be

coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

- 5 For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid compositions of the compound of the invention may be filled into hard gelatine capsules.

10

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or
15 carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

20

The invention therefore further relates to combination therapies wherein the compounds of the invention or a pharmaceutical composition comprising said compounds is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

25

Detailed description of the drawings

Figure 1. X-ray powder diffraction pattern of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate (Form A, 2-fluorobenzoate salt).

30

Figure 2. X-ray powder diffraction pattern of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate (Form A, 2,6-difluorobenzoate salt).

Examples

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

5

General Methods

¹H NMR spectra were recorded at 298K on a Varian Unity *Inova* 400 MHz (software : VNMR 6.1C and VNMRJ 1.1D; probe: Nalorac 5mm DG400-5AT) or a Varian *Mercury*-VX 300 MHz (software: VNMR 6.1C; probe: Varian 5mm AutoSW PFG) instrument. The central peaks of acetone-*d*₆ or dimethylsulphoxide (DMSO)-*d*₆ were used as internal references.

The following method was used for LC/MS analysis:

MS Instrument:	Agilent 1100 series, equipped with APCI interface
15 LC instrument:	Agilent 1100 series, equipped with UV-detector VWD, autosampler ALS, binary pump and degasser
LC-column:	Chromolith Speed ROD, RP-C18, ø 4.6 x 50 mm
Eluant:	Solvent A: water + 0.1% trifluoroacetic acid (TFA); Solvent B: acetonitrile + 0.1% TFA
20 Conditions	LC: flow 2.5 ml/minute; 5 to 95% B in gradient; run time 3.6 minutes; UV 220 nm MS: positive detection; capillary voltage 3 kV

Example 1

25 **Preparation of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate (1:1 salt), Form A, 2-fluorobenzoate salt**

Hot solutions (60 °C) of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (99 mg, 0.2 mmol), which may be prepared by processes described in patent application PCT/SE2006/000918, or by processes analogous to those disclosed in WO 01/98273, in acetonitrile (2 ml) and 2-fluorobenzoic acid (60 mg, 0.4 mmol) in acetonitrile (2 ml) were mixed. The resulting mixture was left to cool down from 60 °C to ambient temperature

(20°C) in a closed vial. The solution was then filtered and subsequently seeded with *N*-{5-chloro-2-[(*2S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide benzoate, polymorph B (described in patent application PCT/SE2006/000918). A white precipitate was formed without
5 turbidity. After standing at ambient temperature overnight the precipitate obtained was filtered, washed with acetonitrile (3 x 1 ml) and dried *in vacuo* at 60°C overnight to give the titled salt as an off-white solid (89 mg, 70%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 7.76-7.72 (m, 2H), 7.51-7.45 (m, 1H), 7.37-7.35 (m, 2H), 7.30-7.28 (m, 2H), 7.22-7.16 (m, 2H), 6.65 (s, 1H), 3.823.77 (m, 2H),
10 3.42 (s, 2H), 2.93-2.74 (m, 5H), 1.99 (s, 3H), 1.97-1.86 (m, 4H), 1.43-1.40 (m, 2H), 1.23 (s, 3H); APCI-MS: *m/z* 496 [MH⁺]; density 1.349 g/cm³.

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

Example 2

15 **Preparation of *N*-{5-chloro-2-[(*2S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate (1:1 salt), Form A, 2,6-difluorobenzoate salt**

The 2,6-difluorobenzoate salt was prepared in a similar fashion and scale as described for Example 1, to give the titled salt as an off-white solid (89 mg; 68%).

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 7.76 (s, 1H), 7.39-7.37 (m, 2H), 7.31-7.22 (m, 3H), 7.00-6.95 (m, 2H), 6.67 (s, 1H), 3.85-3.79 (m, 2H), 3.46 (s, 2H), 3.14-2.81 (m, 5H), 1.96 (s, 3H), 1.99-1.93 (m, 4H), 1.63-1.53 (m, 2H), 1.30 (s, 3H); APCI-MS: *m/z* 496 [MH⁺]; density 1.385 g/cm³.

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

Example 3

X-Ray Powder Diffraction Analyses

General Procedures

30 X-ray powder diffraction (XRPD) analyses may be performed on samples prepared according to standard methods (see for example Giacovazzo *et al.*, eds., Fundamentals of Crystallography, Oxford University Press (1992); Jenkins & Snyder, eds., Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York (1996); Bunn, ed.,

Chemical Crystallography, Clarendon Press, London (1948); and Klug & Alexander eds., X-ray Diffraction Procedures, John Wiley & Sons, New York (1974)).

X-ray powder diffraction patterns of the Forms A salt described in Examples 1 and 2 above
5 (in anhydrous form) were obtained as described below:

A Bragg-Brentano para-focusing powder X-ray diffractometer using monochromatic $\text{CuK}\alpha$ radiation (45 kV and 40 mA) was used for the analyses. The primary optics contained
10 soller slits and an automatic divergence slit. Flat samples were prepared on zero background plates that were rotated during the measurements. The secondary optics contained soller slits, an automatic anti scatter slit, a receiving slit and a monochromator. The diffracted signal was detected with a proportional xenon-filled detector. Diffraction patterns were collected between $2^\circ \leq 2\theta$ (theta) $\leq 40^\circ$ in a continuous scan mode with a step size of $0.016^\circ 2\theta$ at a rate of $4^\circ 2\theta$ per minute. Raw data were stored electronically.

15 Evaluation was performed on raw or smoothed diffraction patterns.

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

The results obtained are shown in figure 1 and figure 2.

Form A, 2-fluorobenzoate salt exhibits at least the following characteristic X-ray powder diffraction (XRPD) peaks (expressed in degrees 2θ) (the margin of error being consistent
25 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):

- 30 (1) 5.6, 9.2 and 11.2, or
(2) 5.6, 10.4 and 12.4, or
(3) 9.2, 10.4, 11.2, 12.4, 14.2 and 15.0 or
(4) 5.6, 10.4, 12.7, 13.6, 14.2, 15.0, 17.5 and 18.8 or

- (5) 5.6, 9.2, 11.2, 12.4, 12.7, 13.6, 14.2, 15.0, 16.8, 17.7 and 19.1 or
(6) 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 18.8, 19.1 and 19.5 or
(7) 5.6, 9.2, 10.4, 12.4, 13.6, 14.2, 15.0, 16.8, 17.5, 18.8, 19.5 and 20.6 or
(8) 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 15.0, 16.6, 17.5, 17.7, 19.1, 19.5, 21.0, 22.6 and 25.2
5 or
(9) 5.6, 9.2, 10.4, 11.2, 12.4, 13.6, 14.2, 16.6, 16.8, 17.5, 18.8, 19.1, 19.5, 20.5, 21.0, and
22.6

Form A, 2,6-difluorobenzoate salt exhibits at least the following characteristic X-ray
10 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):

- 15 (1) 5.6, 9.1 and 11.2, or
(2) 5.6, 10.3 and 12.6, or
(3) 9.1, 10.3, 11.2, 12.3, 14.9 and 16.7 or
(4) 5.6, 10.3, 12.6, 13.5, 14.2, 14.9, 17.4 and 19.0 or
20 (5) 5.6, 9.1, 11.2, 12.6, 13.5, 14.2, 16.7, 18.4, 18.7, 19.0 and 20.8 or
(6) 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.7 and 19.0 or
(7) 5.6, 9.1, 10.3, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 19.5 and 20.3 or
(8) 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 14.9, 16.7, 17.4, 18.4, 18.7, 19.0, 20.3, 21.0 and 22.6
or
25 (9) 5.6, 9.1, 10.3, 11.2, 12.3, 13.5, 14.2, 16.7, 17.4, 18.7, 19.0, 19.5, 20.3, 20.8, and 23.4

Example 4

Differential Scanning Calorimetry (DSC)

Using standard methods, for example those described in Höhne, G. W. H. et al (1996),
30 Differential Scanning Calorimetry, Springer, Berlin, the calorimetric response of a test
sample to increasing temperature was investigated using a Q1000 Modulated Temperature
Differential Scanning Calorimeter (MTDSC) in "heat only" mode with a ramp rate of 5°C

per minute. Approximately 2 to 5 mg of test sample was placed in aluminium cups with lids (no crimping) under a nitrogen atmosphere.

It is well known that the DSC onset and peak temperatures may vary due to the purity of the sample and instrumental parameters, especially the temperature scan rate. A person skilled in the art can use routine optimization/calibration to set up instrumental parameters for a differential scanning calorimeter so that data comparable to the data presented here can be collected.

The melting temperature for a typical sample of the anhydrous Form A, 2-fluorobenzoate salt (example 1) was found to be $138^{\circ}\text{C} \pm 2^{\circ}\text{C}$ (onset).

The melting temperature for a typical sample of the anhydrous Form A, 2,6-difluorobenzoate salt (example 2) was found to be $140^{\circ}\text{C} \pm 2^{\circ}\text{C}$ (onset).

Example 5

Hygroscopicity Determination

The weight change of a test sample at room temperature (25°C) and at 80% relative humidity (RH) were investigated by recording adsorption-desorption isotherms using a symmetric vapor-sorption analyser SGA-100 (VTI Corporation) using different methods, the main features being: a single sorption/desorption cycle from 0 to 90% RH in 10% RH steps with a dm/dt trigger value of 0.002%, (dm/dt = change in mass with time - when the balance stability is within this value the next step is automatically started, however, if those conditions are not achieved there is a default maximum time for each step of 6 hours). Approximately 2 to 10 mg of the test sample was placed in a sample holder and exposed to different relative humidities.

<u>Test Sample</u>	<u>Water Uptake (% w/w) at 80% RH</u>
Anhydrous Form A, 2-fluorobenzoate salt	< 0.7
Anhydrous Form A, 2,6-difluorobenzoate salt	< 0.7

CLAIMS

1. A 2-fluorobenzoate salt of *N*-{5-chloro-2-(((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide or a solvate thereof.
5
2. A 2,6-difluorobenzoate salt of *N*-{5-chloro-2-(((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide or a solvate thereof.
10
3. The compound according to claim 1 or 2, which is anhydrous.
4. The compound according to claim 1 or 3, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):
15 12.7, 14.2, 16.6, 18.8 and 19.1.
5. The substantially pure compound according to claim 4 having an X-ray powder diffraction pattern substantially the same as that shown in figure 1.
- 20 6. The compound according to claim 2 or 3, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):
12.6, 14.2, 18.4, 16.7, 17.4 and 23.4.
7. The substantially pure compound according to claim 6 having an X-ray powder
25 diffraction pattern substantially the same as that shown in figure 2.
8. A pharmaceutical composition comprising the compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 30 9. The compound according to any one of claims 1 to 7 or the pharmaceutical composition according to claim 8 in combination with a dry powder inhaler.
10. The compound according to any one of claims 1 to 7 for use in therapy.

11. Use of the compound according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor 1 (CCR1) activity is beneficial.

5

12. Use of the compound according to any one of claims 1 to 7 in the manufacture of a medicament for treatment of airway disease, respiratory disease and/or an inflammatory disease.

10

13. Use of the compound according to any one of claims 1 to 7 in the manufacture of a medicament for treatment of asthma.

14. Use of the compound according to any one of claims 1 to 7 in the manufacture of a medicament for treatment of chronic obstructive pulmonary disease.

15

15. A method of treating a airway disease, respiratory disease and/or an inflammatory disease such as chronic obstructive pulmonary disease and asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of the compound according to any one of claims 1 to 7 or the pharmaceutical composition according to claim 8.

20

16. A combination of the compound according to any one of claims 1 to 7 or the pharmaceutical composition according to claim 8, and one or more agents selected from the list comprising:

25

- a PDE4 inhibitor;
- a selective β .sub2. adrenoceptor agonist;
- a muscarinic receptor antagonist;
- a steroid;
- an inhibitor of p38 kinase function;
- an inhibitor of matrix metalloproteases; or,
- an inhibitor of neutrophil serine proteases.

30

17. A process for the preparation of Form A, 2-fluorobenzoate salt or Form A, 2,6-difluorobenzoate salt: comprising the steps of;

- (i) contacting a solution at a temperature range of from 40 to 80°C of *N*-{5-chloro-2-
[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-
4-hydroxyphenyl}acetamide dissolved in an organic solvent, with
5 4-hydroxyphenyl}acetamide dissolved in an organic solvent, with
- (ii) a solution at a temperature range of from 40 to 80°C of 2-fluorobenzoic acid or 2,6-difluorobenzoic acid dissolved in an organic solvent, to obtain a mixture,
- (iii) allowing the mixture to cool to ambient temperature to yield a precipitate of Form A
of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-
methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate or
10 Form A of *N*-{5-chloro-2-[[[(2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-
hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate, and
- (iv) separating the precipitate from the mixture.

Figure 1. X-ray powder diffraction pattern of *N*-{5-chloro-2-[(*2S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide 2-fluorobenzoate.

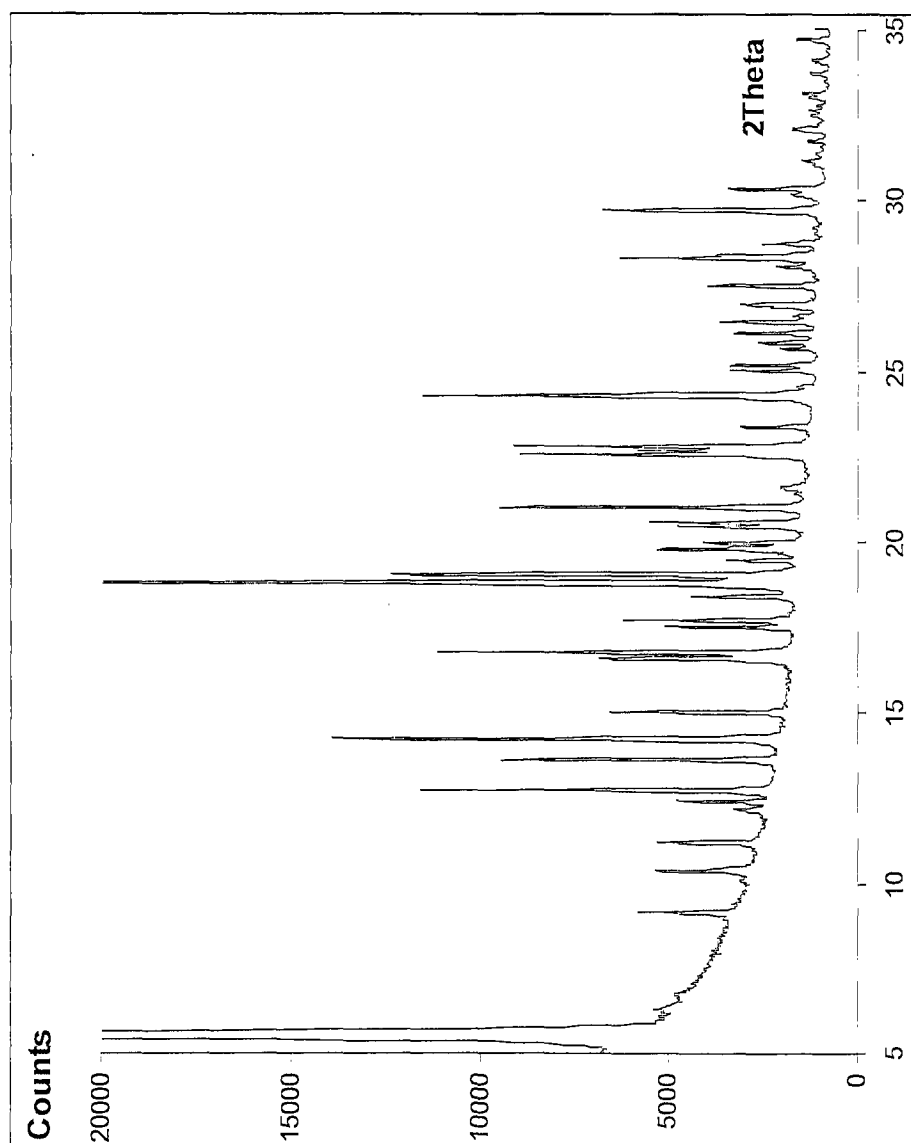
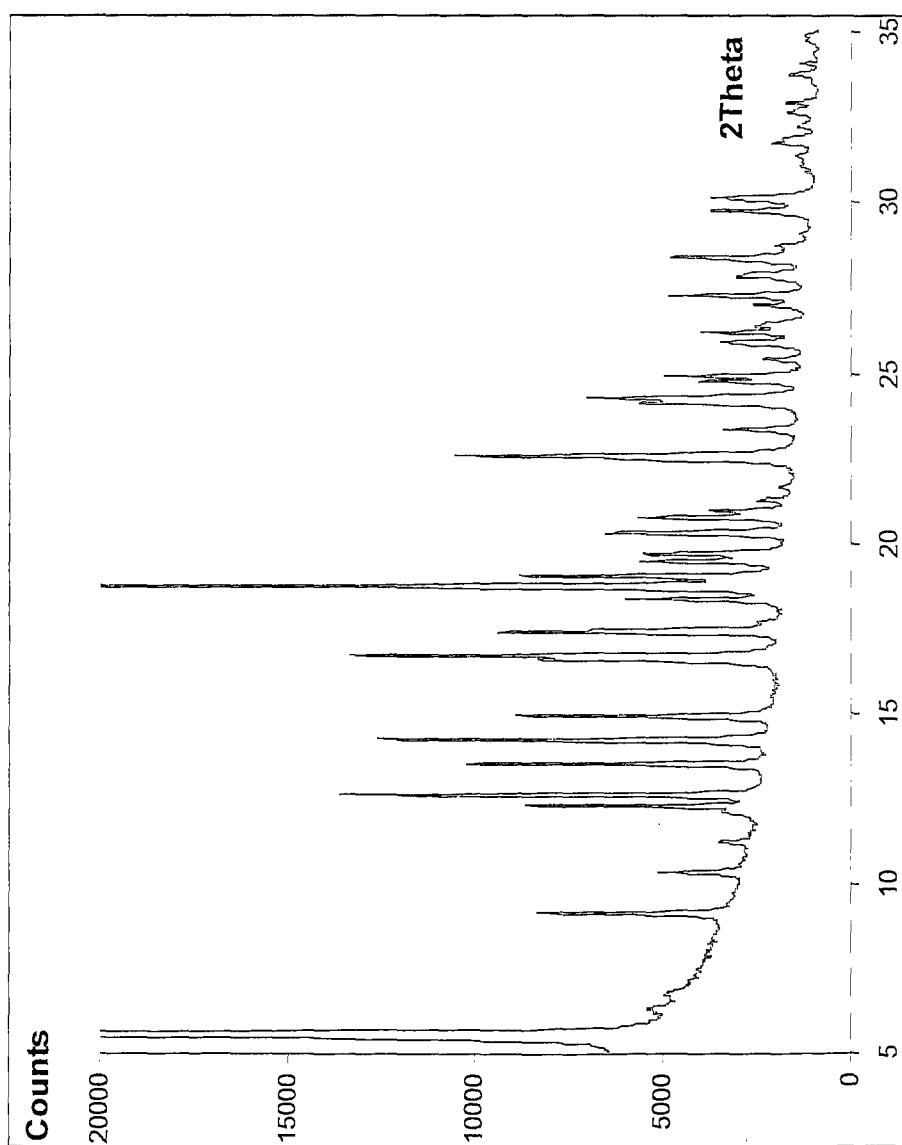


Figure 2. X-ray powder diffraction pattern of *N*-{5-chloro-2-[(*(2S)*-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide 2,6-difluorobenzoate.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/000118

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: C07D, 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.
A	WO 2007015667 A1 (ASTRAZENECA AB), 8 February 2007 (08.02.2007), page 2, line 9 - line 23, example 1,2,4,5 --	1-17
A	WO 2007015666 A1 (ASTRAZENECA AB), 8 February 2007 (08.02.2007), page 2, line 19 - line 23, example 1,2 --	1-17
A	WO 2007015664 A1 (ASTRAZENECA AB), 8 February 2007 (08.02.2007), page 7, line 13 - line 24, example 4,5 -- -----	1-17

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

1 April 2008

Date of mailing of the international search report

04 -04- 2008

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2008/000118

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.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 15 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2008/000118

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/SE2008/000118

International patent classification (IPC)

C07D 211/58 (2006.01)

A61K 31/4468 (2006.01)

A61K 9/72 (2006.01)

A61P 11/00 (2006.01)

A61P 11/06 (2006.01)

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- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.

The password is **UCZTZRYGYW**.

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/01/2008

International application No.

PCT/SE2008/000118

WO	2007015667	A1	08/02/2007	AR	055107 A	08/08/2007
				AU	2006276345 A	08/02/2007
				UY	29712 A	28/02/2007

WO	2007015666	A1	08/02/2007	AR	055365 A	22/08/2007
				AU	2006276344 A	08/02/2007
				UY	29714 A	28/02/2007

WO	2007015664	A1	08/02/2007	AU	2006276342 A	08/02/2007
