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(54) **Title**: SUBSTITUTED N-[1-CYANO-2-(PHENYL)ETHYL]PIPERIDIN-2-YLCARBOXMIDE COMPOUNDS 761

(57) **Abstract**: The present invention provides a compound: (S)-*N*-((S)-1-Cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethyl)piperidine-2- carboxamide; (S)-*N*-((S)-1-Cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethyl)piperidine-2-carboxamide; (S)-*N*-((S)-1-Cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethyl)piperidine-2-carboxamide; 4'-((S)-2-Cyano-2-((S)-piperidine-2-carboxamido)ethyl)biphenyl-4-yl methanesulfonate; or, (S)-N-((S)-1-Cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethyl)piperidine-2-carboxamide; or a pharmaceutically acceptable salt thereof; a process for its preparation, pharmaceutical compositions containing it and its use in therapy.

SUBSTITUTED N-[1-CYANO-2-(PHENYL)ETHYL]PIPERIDIN-2-YLCARBOXAMIDE COMPOUNDS 761

The present invention relates to peptidyl nitriles, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

WO2004/110988 discloses nitrile derivatives as inhibitors of DPPI.

Dipeptidyl peptidase I (DPPI; EC 3.4.14.1), also known as cathepsin C, is a lysosomal cysteine protease belonging to the papain family having a molecular weight of 200 kDa. DPPI was first discovered by Gutman and Fruton in 1948 (*J Biol Chem*, **174**, 851–858); however, the cDNA of the human enzyme was first described in 1995 (Paris et al. 1995, *FEBS Lett*, **369**, 326–330). DPPI is the only member of the papain family that is functional as a tetramer, consisting of four identical subunits. Each subunit is composed of an N-terminal fragment, a heavy chain and a light chain (Dolenc et al. 1995, *J Biol Chem*, **270**, 21626–21631).

DPPI is constitutively expressed in many tissues with highest levels in lung, kidney, liver and spleen. DPPI catalyses the removal of dipeptides from the N-terminal end of polypeptide substrates with broad specificity. Recent data suggest that besides being an important enzyme in lysosomal protein degradation, DPPI also functions as a key enzyme in the activation of granule serine proteases in cytotoxic T lymphocytes and natural killer cells (granzymes A and B), mast cells (chymase and tryptase) and neutrophils (cathepsin G and elastase).

Mast cells are found in many tissues but are present in greater numbers along the epithelial linings of the body, such as the skin, respiratory tract and gastrointestinal tract. In humans, two types of mast cells have been identified. The T-type, which expresses only tryptase, and the MC-type, which expresses both tryptase and chymase. In humans, the T-type mast cells are located primarily in alveolar tissue and intestinal mucosa while the TC-type cells predominate in skin and conjunctiva. Tryptase and chymase appear to be important mediators of allergic diseases, being involved in processes of inflammation, bronchoconstriction and mucus secretion.

Neutrophils play a critical role in host defence against invading pathogens. Neutrophils are produced in the bone marrow and are fully mature when released into the circulation to take up their role as the first line of cellular defence. Pro-inflammatory mediators and chemotactic attractants activate neutrophils and draw them to the site of

infection, where they act to engulf bacteria by phagocytosis, assaulting them with an arsenal of anti-bacterial compounds that use both oxidative and non-oxidative methods of attack. The powerful serine protease, neutrophil elastase, is one of those anti-bacterial compounds that are clearly involved in destroying bacteria. Neutrophil elastase is released into the phagolysome surrounding the microorganism, which it proceeds to destroy. Neutrophil elastase is able to attack the outer membrane protein, OmpA, in gram-negative bacteria, helping to directly kill the pathogen by degrading its membrane, as well as enabling other anti-bacterial compounds to gain access to the pathogen. In addition, neutrophil elastase may help process other anti-bacterial compounds, converting them from inactive pro-peptides into their active states, such as for cathelicidin.

Yet neutrophil elastase can also cause problems for its host. It is one of the most destructive enzymes in the body, with the capability of degrading extracellular matrix proteins (including collagens, proteoglycan, fibronectin, platelet receptors, complement receptor, thrombomodulin, lung surfactant and cadherins) and key plasma proteins (including coagulation and complement factors, immunoglobulin, several proteases and protease inhibitors). Under physiological conditions, endogenous protease inhibitors, such as α1-antitrypsin, tightly regulate the activity of neutrophil elastase. However, at inflammatory sites, neutrophil elastase is able to evade regulation, and once unregulated it can induce the release of pro-inflammatory cytokines, such as interleukin-6 and interleukin-8, leading to acute lung injury. It can even impair host defence against infection by degrading phagocyte surface receptors and opsonins. Its negative role is illustrated by its involvement in the tissue destruction and inflammation that characterise numerous diseases, including hereditary emphysema, chronic obstructive pulmonary disease, cystic fibrosis, adult respiratory distress syndrome, ischemic-reperfusion injury and rheumatoid arthritis.

There is strong evidence associating tryptase and chymase with a number of mast cell mediated allergic, immunological and inflammatory diseases. The fact that neutrophil elastase, cathepsin G and proteinease 3 also seem to play significant roles in these types of diseases point to DPPI being a valid therapeutic target due to its central role in activating these proteases (Adkison et al. **2002**, *J Clin Invest*, *109*, 363-271; Pham et al. **2004**, *J Immunol, 173*, 7277-7281).

In accordance with the present invention, there is provided a compound:

(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethyl)piperidine-2-carboxamide;
(*S*)-*N*-((*S*)-1-Cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethyl)piperidine-2-carboxamide;
(*S*)-*N*-((*S*)-1-Cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethyl)piperidine-2-carboxamide;
4'-((*S*)-2-Cyano-2-((*S*)-piperidine-2-carboxamido)ethyl)biphenyl-4-yl methanesulfonate; or,
(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethyl)piperidine-2-carboxamide;
or a pharmaceutically acceptable salt thereof.

A pharmaceutically acceptable salt is, for example, an acid addition salt such as a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

A compound of the invention or a pharmaceutically acceptable salt thereof may exist in solvated, for example hydrated, as well as unsolvated forms, and the present invention encompasses all such solvated forms.

Compounds of the invention are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of the invention and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of the invention and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as inhibitors of dipeptidyl peptidase I activity, and thus may 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 disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications

of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. 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 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;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; 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;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. 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;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. 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,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

Thus, the present invention provides a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

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

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

In particular, the compounds of the invention (including pharmaceutically acceptable salts) may be used in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}, chronic obstructive pulmonary disease (COPD) or allergic rhinitis.

The invention also provides a method of treating, or reducing the risk of, an obstructive airways disease or condition (e.g. asthma or COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of the invention and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compound of the invention or a pharmaceutically acceptable salt therof (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations 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 will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined 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 formulations, for example, formulations in the inhaler device known as the Turbuhaler®; 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 a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); or by rectal administration in the form of suppositories.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention (that is, compounds of the invention and pharmaceutically acceptable salts thereof) 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 micrometres (μm), and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be 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.

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

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

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 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.

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 formulations of the compound of the invention may be filled into hard gelatine capsules.

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 carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention (that is, compounds of the invention and pharmaceutically acceptable salts thereof) may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation 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.

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 the following agents: 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 COX-2 inhibitors (such as meloxicam, celecoxib,

rofecoxib, valdecoxib, lumarocoxib, 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 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 pentoxyfylline.

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 CCR1, 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 CX_3CR1 for the C-X_3-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.

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-3-1s 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.

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 PDE4D, or an inhibitor of PDE5.

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 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.

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 agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

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, pirenzepine or telenzepine.

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

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.

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).

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.

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.

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.

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 pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

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 comP 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 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 peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptiline 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 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 biphosphonate such 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) 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 IKK), or a kinase involved in cell cycle regulation (such as a cylin 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, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGFβ); (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) 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; (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS; or (xxviii) a glucocorticoid receptor agonist.

In a further aspect the present invention provides a combination (for example for the treatment of COPD, asthma or allergic rhinitis) of a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined and one or more agents independently selected from:

- a non-steroidal glucocorticoid receptor (GR-receptor) agonist;
- a selective β_2 adrenoceptor agonist (such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol or indacaterol);
- a phosphodiesterase inhibitor (such as a PDE4 inhibitor);
- a protease inhibitor (such as a neutrophil elastase or matrix metalloprotease MMP-12 inhibitor);
- a glucocorticoid;
- an anticholinergic agent;
- a modulator of chemokine receptor function (such as a CCR1 receptor antagonist); and
- an inhibitor of kinase function (such as the kinases p38 or IKK).

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined, and a preparation of a second active ingredient which is

- a non-steroidal glucocorticoid receptor (GR-receptor) agonist;
- a selective β_2 adrenoceptor agonist;
- a phosphodiesterase inhibitor;
- a protease inhibitor;
- a glucocorticoid;
- an anticholinergic agent;
- a modulator of chemokine receptor function; or
- an inhibitor of kinase function;

for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a compound of the invention or a pharmaceutically acceptable salt thereof as hereinbefore defined, and a preparation of a second active ingredient which is

- a non-steroidal glucocorticoid receptor (GR-receptor) agonist;
- a selective β_2 adrenoceptor agonist;
- a phosphodiesterase inhibitor;
- a protease inhibitor;
- a glucocorticoid;
- an anticholinergic agent;
- a modulator of chemokine receptor function; or
- an inhibitor of kinase function;

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

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 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 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);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), 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, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-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-erbb2 antibody trastuzumab, or the anti-erbb1 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 αvβ3 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.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR spectra were recorded on Bruker Avance 600 (600 MHz), a Bruker DRX 500 (500 MHz) or a Varian UnityInova 500 MHz, 400 MHz or 300 MHz instrument. Either the central peaks of chloroform-*d* ($CDCl_3$; δ_H 7.27 ppm), dimethylsulfoxide-d_6 (d_6-DMSO; δ_H 2.50 ppm) or methanol-d_4 (CD_3OD; δ_H 3.31 ppm), or an internal standard of tetramethylsilane (TMS; δ_H 0.00 ppm) were used as references;

(ii) Mass spectra were recorded on an Agilent MSD (+ve and –ve APCI and/or electrospray (e.g. in multimode)) following analytical HPLC. Where values for m/z are given, generally only ions which indicate the parent mass are reported, and the mass ions quoted are the positive or negative mass ions: $[M]^+$, $[M+H]^+$, $[M-H]^-$, $[M+H\text{-}BOC]^+$ or $[M+2H\text{-}BOC]^+$;

(iii) the title and sub-title compounds of the examples and preparations were named using the IUPAC name program Struct=Name 9.0.7 from CambridgeSoft Corporation.

(iv) unless stated otherwise, reverse phase HPLC was conducted using a SunFire® reverse phase silica column, available from Waters Corp.;

(v) Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received. All operations were carried out at ambient temperature, *i.e.* in the range 17 to 28°C and, where appropriate, under an atmosphere of an inert gas such as nitrogen;

(vi) Analytical HPLC was carried out using either a Waters XBridge™ C8 3.5 μm column eluting with a gradient of acetonitrile in either 0.1% aqueous trifluoroacetic acid, 0.1% aqueous formic acid, 0.1% aqueous ammonium acetate or 0.1% aqueous ammonia; a Waters XBridge™ C18 3.5 μm column with a gradient of acetonitrile in 0.1% aqueous ammonia; a Waters Symmetry™ C18 3.5 μm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid; a Waters Sunfire™ C8 3.5 μm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid; or a Phenomenex Gemini™ C18 3 μm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid. UV spectra of the eluted peaks were measured using a diode array on an Agilent 1100® system, or equivalent;

(vii) the following abbreviations are used:

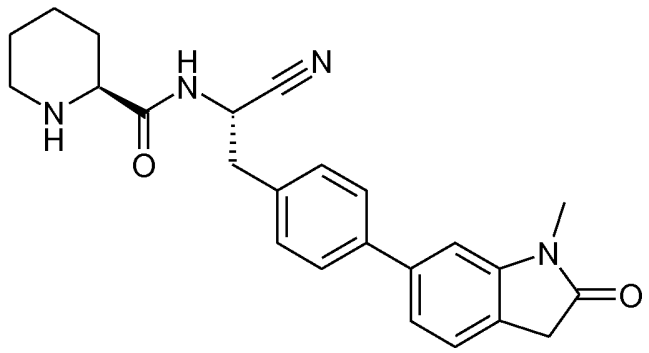
AIBN	2,2'-Azobisisobutyronitrile
Burgess reagent	Methyl (carboxysulfamoyl)triethyl ammonium hydroxide inner salt
CbzCl	Benzyloxycarbonylchloride
d	Day(s)
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
g	Gram(s)
h	Hour(s)
HATU	2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HM-N	Argonaut Isolute ® diatomaceous earth cartridge
HPLC	High performance liquid chromatography
Hunig's Base	Diisopropylethylamine (DIPEA)

LCMS	Liquid chromatography- mass spectroscopy
min	Minute(s)
mL	Millilitre(s)
n-BuLi	*n*-Butyllithium
NMP	1-Methylpyrrolidin-2-one
RPHPLC	Reverse phase high performance liquid chromatography
RT	Room temperature
SCX	Strong cation exchange resin
TBAF	Tetrabutylammonium fluoride
TBTU	2-(1H-Benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	tetrahydrofuran

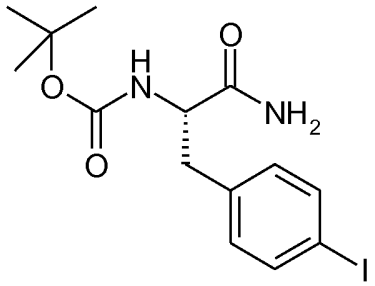
Examples

Example 1

(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethyl)piperidine-2-carboxamide



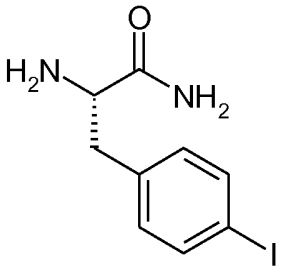
(i) (*S*)-*tert*-Butyl 1-amino-3-(4-iodophenyl)-1-oxopropan-2-ylcarbamate



(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-iodophenyl)propanoic acid (35.1 g) was dissolved in DMF (200 mL) and to the resulting solution was added *N*-ethylmorpholine (17.0 mL) followed by TBTU (28.8 g). The mixture was stirred at room temperature for 0.5h and then cooled to 0°C. 0.880 Ammonia (11.1 mL) was added and the mixture was allowed to warm to room temperature. The mixture was allowed to stir at room temperature for 16h and was then poured into water and the resulting precipitate removed by filtration. The solid was dried in vacuo to give the sub-titled compound (34.2 g).

m/e (APCI+) 290 $[M+2H-BOC]^+$

(ii) (*S*)-2-Amino-3-(4-iodophenyl)propanamide

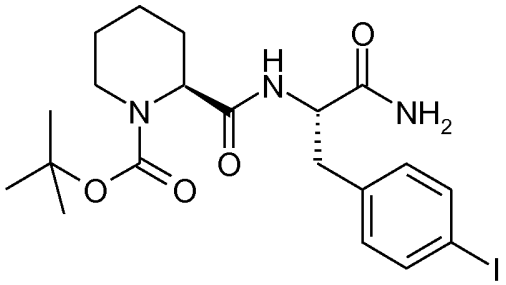


(*S*)-*tert*-Butyl 1-amino-3-(4-iodophenyl)-1-oxopropan-2-ylcarbamate (Example 1, step (i), 2.41 g) was stirred in dichloromethane (125 mL) and to the suspension was added trifluoroacetic acid (8 mL). The mixture was stirred for 2h and then concentrated to ~12 mL *in vacuo*. The residue was stirred for 2 days, dissolved in ethyl acetate / dichloromethane and washed with water containing an excess of sodium bicarbonate. The organic layer was dried and evaporated to the sub-titled compound (1.52 g).

^{1}H NMR (399.824 MHz, $CDCl_3$) δ 7.61 (d, 2H), 7.26 (s, 1H), 7.03 (d, 2H), 6.40 (s, 1H), 3.55 (s, 1H), 3.09 (dd, 1H), 2.71 (dd, 1H), 1.81 (s, 2H).

m/e (APCI+) 291 $[M+H]^+$

(iii) (*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4-iodophenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate

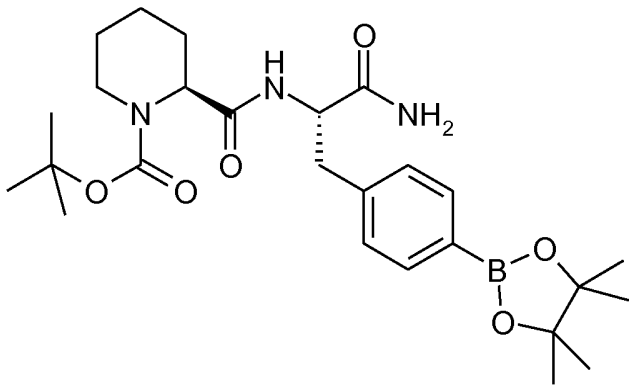


(*S*)-2-Amino-3-(4-iodophenyl)propanamide (Example 1, step (ii), 2 g), (2*S*)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (2.4 g) and di*iso*propylethylamine (3 mL) were dissolved in DMF (10 mL) and to the solution was added 2-(1-*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.3 g). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with diethyl ether (200 mL) then washed with water (250 mL) and brine (4x 250 mL). The organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Crude product was purified by flash silica chromatography eluting with ethyl acetate to give the sub-titled compound (2.88 g) as an oil.

^{1}H NMR (299.946 MHz, $CDCl_3$) δ 7.63 (dd, 2H), 6.98 (dd, 2H), 6.49 (d, 1H), 6.18 - 6.04 (m, 1H), 5.48 (s, 1H), 4.77 - 4.62 (m, 2H), 3.90 - 3.78 (m, 1H), 3.15 - 3.00 (m, 2H), 2.43 - 2.31 (m, 1H), 2.24 - 2.14 (m, 1H), 1.68 - 1.43 (m, 14H).

m/e (APCI+) 401 $[M+H\text{-}BOC]^+$

(iv) (*S*)-*tert*-Butyl 2-((*S*)-1-amino-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ylcarbamoyl)piperidine-1-carboxylate

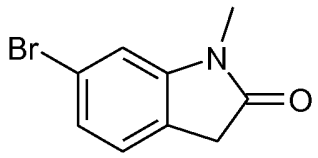


1,1'-Bis(diphenylphosphino)ferrocene (0.097 g) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.141 g) were stirred in dry dimethylsulfoxide (5 mL) under nitrogen for 10 minutes. Potassium acetate (1.016 g), (*S*)-*tert*-butyl 2-((*S*)-1-amino-3-(4-iodophenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (iii), 1.73 g) dissolved in dry DMSO (5 mL) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.165 g) were added and the reaction was heated at 80°C overnight. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The extracts were washed with brine, then dried and evaporated. The crude material was purified by flash silica chromatography, eluting with ethyl acetate to give the subtitled compound as a colourless foam (1.28 g).

^{1}H NMR (399.824 MHz, $CDCl_3$) δ 7.75 (d, 2H), 7.24 (d, 2H), 6.48 - 6.39 (m, 1H), 5.30 - 5.23 (m, 1H), 4.72 (q, 1H), 4.67 - 4.62 (m, 1H), 3.22 - 3.14 (m, 1H), 3.13 - 3.06 (m, 1H), 2.48 - 2.36 (m, 1H), 2.25 - 2.18 (m, 1H), 1.53 - 1.45 (m, 4H), 1.42 (s, 9H), 1.33 (s, 12H).

m/e (APCI+) 402 $[M+2H-BOC]^+$

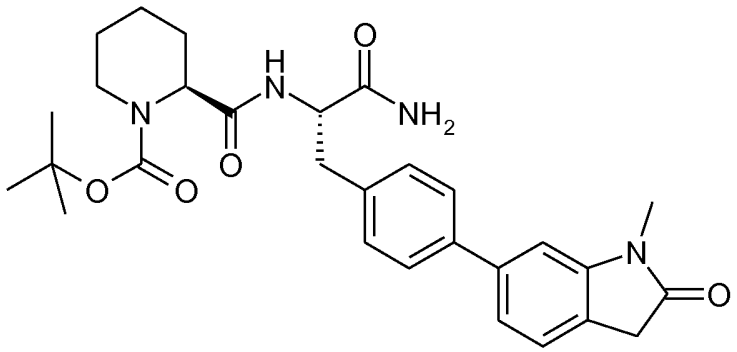
(v) 6-Bromo-1-methylindolin-2-one



Sodium hydride (113 mg) in xylenes (5 mL) was heated to near reflux under nitrogen. 6-Bromoindolin-2-one (500 mg) was then slowly added and the mixture was refluxed for 90 mins. Dimethyl sulfate (0.225 mL) was added and the mixture heated for a further 2 h. The reaction was cooled, diluted with ethyl acetate and washed with water (x3) the organic layer was dried using sodium sulphate and concentrated *in vacuo*. The orange residue was purified by flash chromatography eluting with 15-25% ethyl acetate in *iso*hexane to give the sub-titled compound (90 mg) as a solid.

m/e (APCI+) 227 $[M+H]^+$

(vi) (*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate

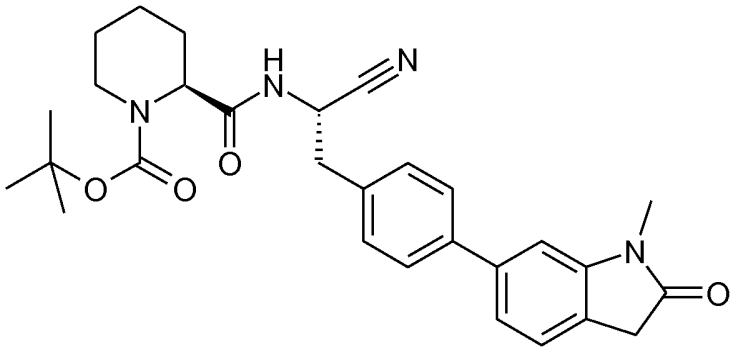


(*S*)-*tert*-Butyl 2-((*S*)-1-amino-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (iv), 200 mg) was dissolved in acetonitrile (15 mL) and treated with aqueous 2M potassium carbonate (0.6 mL), 1,1 *bis*(di-*tert*-butylphosphino)ferrocene palladium dichloride (24 mg) and 6-bromo-1-methylindolin-2-one (Example 1, step (v), 90 mg) with stirring under nitrogen. The reaction

was heated to 80°C for 4h. The reaction mixture was diluted with dichloromethane (30 mL) and dried with magnesium sulfate before being passed through an isolute HM-N cartridge, washed through with dichloromethane. The organic extracts were concentrated *in vacuo* and purified by flash silica chromatography eluting with ethyl acetate to give the sub-titled compound (200 mg).

m/e (APCI+) 421 $[M+2H\text{-}BOC]^+$

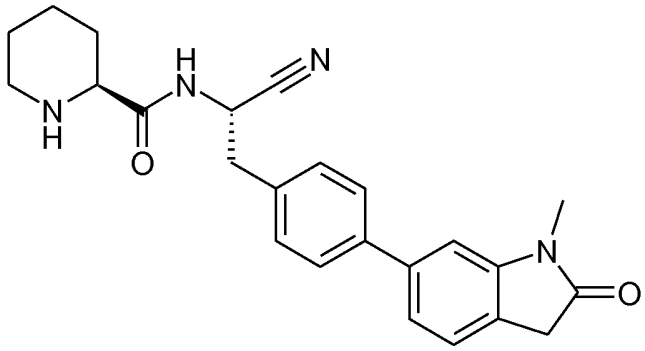
(vii) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate



Triethylamine (0.348 mL) in dichloromethane (5 mL) was cooled to 0°C with stirring under nitrogen. A solution of Burgess' reagent (229 mg) in dichloromethane (5 mL) was added dropwise and stirred for 15 minutes and the reaction allowed to warm to room temperature. A solution of (*S*)-*tert*-butyl 2-((*S*)-1-amino-3-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (vi), 200 mg) was added and the mixture stirred for 18h. Silica was added to the reaction mixture and it was concentrated *in vacuo*. The silica was dry loaded and purified by flash silica chromatography eluting with 1:1 ethyl acetate / *iso*hexane to give the sub-titled compound as an oil (90 mg).

m/e (APCI+) 403 $[M+2H\text{-}BOC]^+$

(viii) (*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethyl)piperidine-2-carboxamide (Example 1)



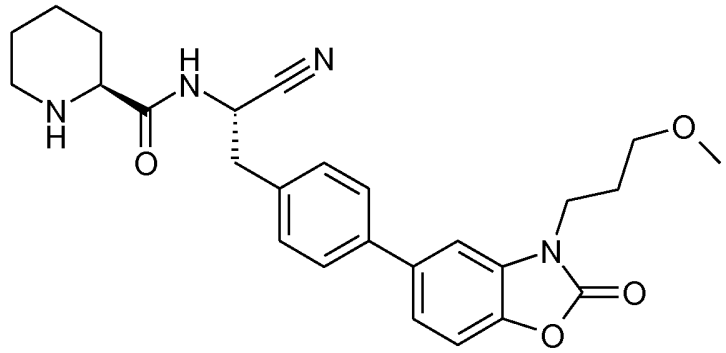
(*S*)-*tert*-butyl 2-((*S*)-1-cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate (Example 1, step (vii), 90 mg) was dissolved in formic acid (3.4 mL) and stirred at 45°C for 1 h. The reaction was concentrated *in vacuo* and the residue was purified by preparative HPLC eluting with dichloromethane 2% 2M ammonia in MeOH to give the titled compound as a solid (50 mg).

^{1}H NMR (399.824 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.59 (d, 2H), 7.37 (d, 2H), 7.30 (d, 1H), 7.24 (dd, 1H), 6.99 (d, 1H), 5.18 (dd, 1H), 3.56 (s, 2H), 3.33 (dd, 1H), 3.26 (s, 3H), 3.16 (d, 2H), 2.96 (dd, 1H), 2.73 - 2.66 (m, 2H), 1.89 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.42 (m, 2H).

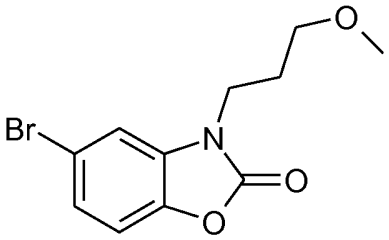
m/e (MultiMode+) 403 $[M+H]^+$

Example 2

(*S*)-*N*-((*S*)-1-Cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethyl)piperidine-2-carboxamide



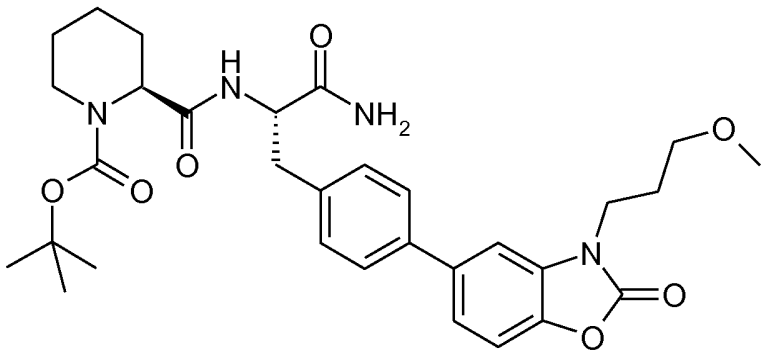
(i) 5-Bromo-3-(3-methoxypropyl)benzo[d]oxazol-2(3*H*)-one



A mixture of 5-bromobenzo[d]oxazol-2(3*H*)-one (1.1 g), 3-methoxypropyl methanesulfonate (1.297 g) and potassium carbonate (2.131 g) in acetonitrile (25 mL) was heated at 70°C for 16h. Water was added and the mixture was extracted with ethyl acetate (3 times). The combined organic layers were dried with magnesium sulfate, evaporated and purified by flash silica chromatography eluting with *iso*hexane - acetone (5:1) to give the sub-titled compound as an oil (1.5 g).

m/e (APCI+) 286/288 $[M+H]^+$

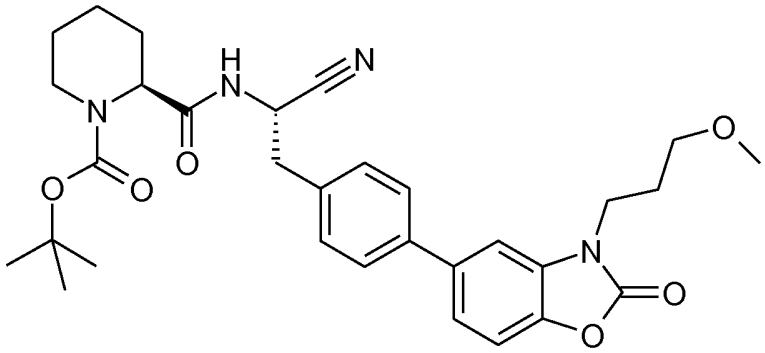
(ii) (*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate



(S)-*tert*-Butyl 2-((*S*)-1-amino-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (iv), 400 mg), 1,1 *bis*(di-*tert*-butylphosphino)ferrocene palladium dichloride (14 mg), aqueous potassium carbonate solution (2M, 1.197 mL) in acetonitrile (30 mL) under a nitrogen atmosphere, was treated with 5-bromo-3-(3-methoxypropyl)benzo[d]oxazol-2(3*H*)-one (Example 2, step (i), 228 mg). The reaction mixture was heated at 80°C for 3h, then concentrated to dryness and the residue purified by chromatography on silica using ethyl acetate as eluant to give the sub-titled compound (450 mg) as a foam.

m/e (APCI+) 481 $[M+2H\text{-}BOC]^+$

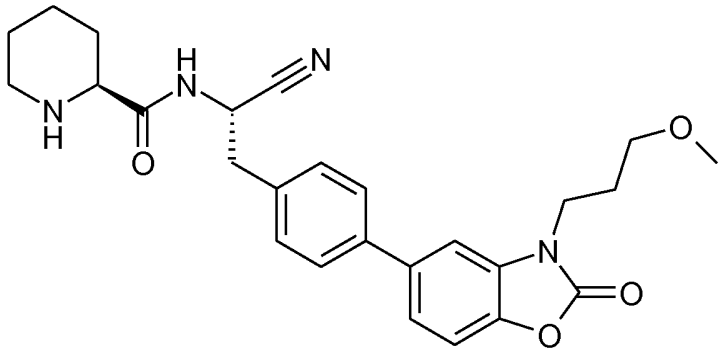
(iii) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate



Triethylamine (0.702 mL) in dichloromethane (5 mL) was stired under nitrogen and cooled to 0°C before the dropwise addition of Burgess' reagent (462 mg) in dichloromethane (5 mL). The mixture was stired for 15 mins and allowed to warm to room temperature. A solution of (*S*)-*tert*-butyl 2-((*S*)-1-amino-3-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 2, step (ii), 450 mg) in dichloromethane (5mL) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was absorbed onto silica which was dry loaded and purified by flash silica chromatography eluting with 1:1 ethyl acetate / *iso*hexane to give the sub-titled compound (380 mg).

m/e (APCI-) 561 $[M-H]^-$

(iv) (*S*)-*N*-((*S*)-1-Cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethyl)piperidine-2-carboxamide (Example 2)



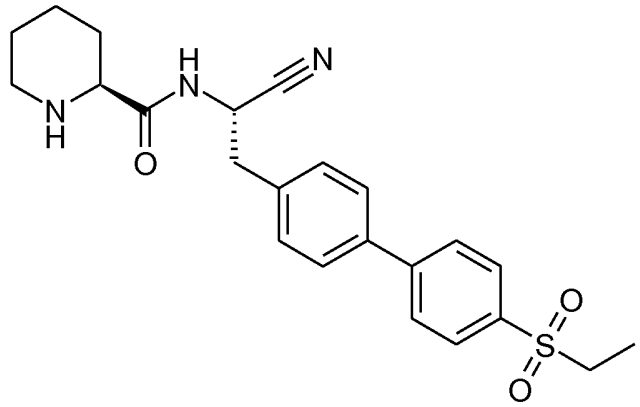
(*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate (Example 2, step (iii), 300 mg) was dissolved in formic acid (0.8 mL) and stirred for 4 h at room temperature. The reaction was concentrated *in vacuo* and purified by flash silica chromatography eluting with 98:2 dichloromethane / 2N ammonia in MeOH to give the titled compound as a solid (160 mg).

^{1}H NMR (399.824 MHz, $CDCl_3$) δ 7.56 (dt, 2H), 7.41 (d, 1H), 7.37 (d, 2H), 7.30 (dd, 1H), 7.22 (d, 1H), 5.20 (sextet, 1H), 3.98 (t, 2H), 3.44 (t, 2H), 3.32 (s, 1H) 3.15 (d, 2H), 2.92 (d, 1H), 2.68 (dd, 1H), 2.07 (quintet, 2H), 1.91 - 1.29 (m, 9H).

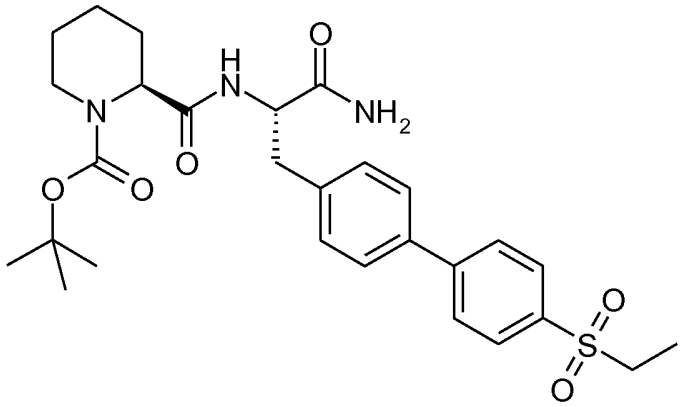
m/e (MultiMode+) 463 $[M+H]^+$

Example 3

(*S*)-*N*-((*S*)-1-Cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethyl)piperidine-2-carboxamide



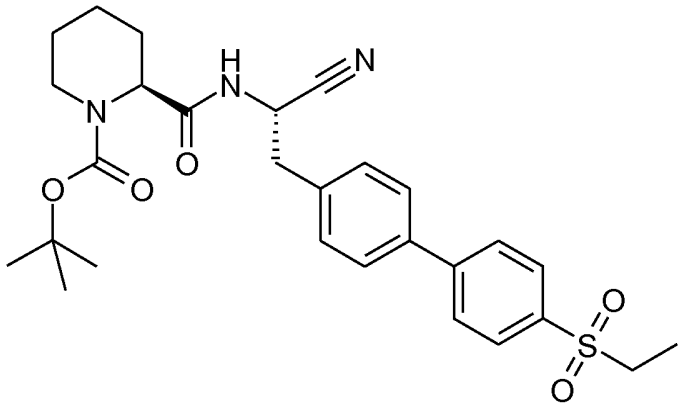
(i) (*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4'-(ethylsulfonyl)biphenyl-4-yl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate



(*S*)-*tert*-Butyl 2-((*S*)-1-amino-1-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (iv), 300 mg) and 1-bromo-4-(ethylsulfonyl)benzene (160 mg) were dissolved in acetonitrile (3.5 mL) and water (1.5 mL) and treated with potassium carbonate (250 mg) and 1,1 *bis*(di-*tert*-butylphosphino)ferrocene palladium dichloride (12 mg). The mixture was heated at 75°C under an atmosphere of nitrogen for 3 h. The reaction mixture was poured into water (75 mL) and extracted with ethyl acetate (3 x 25 mL). The organic extract was washed with brine (50 mL) dried over sodium sulfate and evaporated to afford the sub-titled compound (300 mg).

m/e (APCI+) 443 [M+H-BOC]

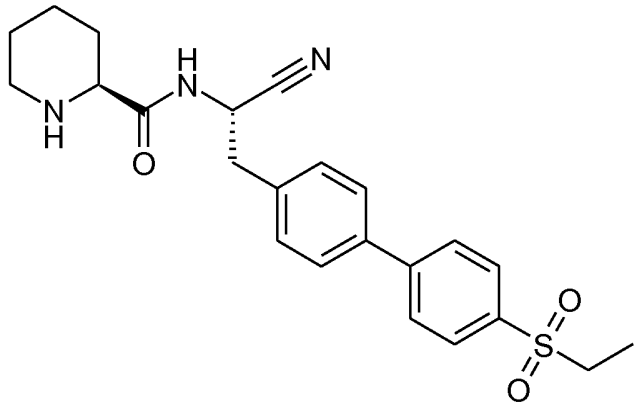
(ii) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethylcarbamoyl)piperidine-1-carboxylate



(*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4'-(ethylsulfonyl)biphenyl-4-yl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 3, step (i), 300 mg) in dichloromethane (10 mL) was treated with Burgess' reagent (315 mg) and stirred at room temperature overnight under an atmosphere of nitrogen. The mixture was poured into ethyl acetate (75 mL) and washed with water (3 x 25 mL), brine (25 mL) and dried over sodium sulfate. The residue from evaporation was purified by chromatography on silica eluting with ethyl acetate / hexane (1:2) to afford the sub-titled compound (280 mg).

m/e (APCI+) 426 $[M+2H-BOC]^+$

(iii) (*S*)-*N*-((*S*)-1-Cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethyl)piperidine-2-carboxamide (Example 3)



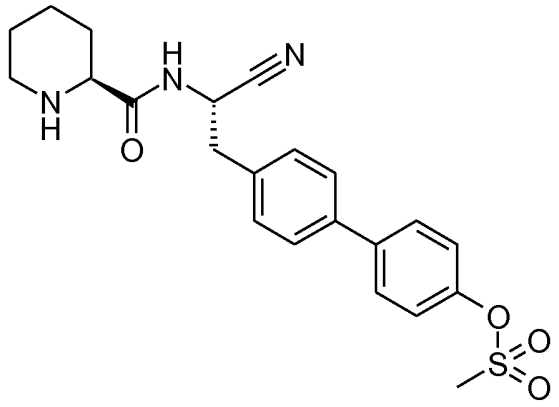
(*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethylcarbamoyl)piperidine-1-carboxylate (Example 3, step (ii), 280 mg) was dissolved in formic acid (5 mL) and stirred at room temperature for 3 h. The mixture was poured into saturated sodium bicarbonate solution (70 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (25 mL) dried over sodium sulfate and evaporated to a crude residue which recrystallised from *iso*propyl alcohol (3 mL) to afford the titled compound (62 mg).

^{1}H NMR (399.824 MHz, d_6-DMSO) δ 8.51 (d, 1H), 7.94 (s, 4H), 7.73 (d, 2H), 7.45 (d, 2H), 5.04 (q, 1H), 3.36 - 3.29 (m, 2H), 3.23 - 3.17 (m, 2H), 3.09 - 3.04 (m, 1H), 2.82 - 2.72 (m, 1H), 2.32 - 2.22 (m, 1H), 1.62 - 1.53 (m, 2H), 1.46 - 1.36 (m, 1H), 1.34 - 1.19 (m, 4H), 1.13 (t, 3H).

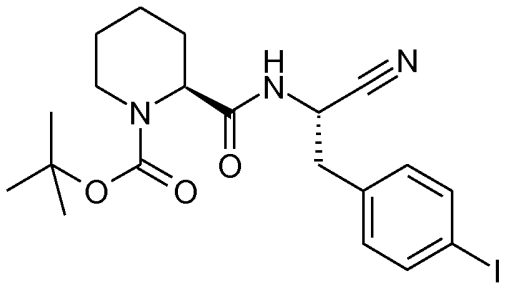
m/e (MultiMode+) 426 $[M+H]^+$

Example 4

4'-((*S*)-2-Cyano-2-((*S*)-piperidine-2-carboxamido)ethyl)biphenyl-4-yl methanesulfonate



(i) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4-iodophenyl)ethylcarbamoyl)piperidine-1-carboxylate

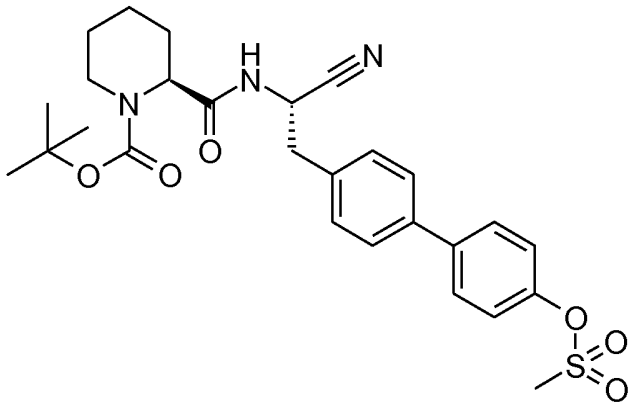


(*S*)-*tert*-Butyl 2-((*S*)-1-amino-3-(4-iodophenyl)-1-oxopropan-2-ylcarbamoyl)piperidine-1-carboxylate (Example 1, step (iii), 1.1 g) in dichloromethane (30 mL) was stirred with Burgess' reagent (0.680 g) for 18 h at room temperature. The reaction mixture was poured into water (25 mL) and separated. The organic extract was dried over magnesium sulfate and evaporated *in vacuo* to afford the sub-titled compound (1.030 g) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H), 7.01 (d, 2H), 5.18 - 5.07 (m, 1H), 4.70 - 4.64 (m, 1H), 4.00 - 3.81 (m, 1H), 3.13 - 2.98 (m, 2H), 2.47 - 2.36 (m, 1H), 2.24 - 2.14 (m, 1H), 1.66 - 1.29 (m, 15H).

me (Multimode-) 482 $[M-H]^-$

(ii) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4'-(methylsulfonyloxy)biphenyl-4-yl)ethylcarbamoyl)piperidine-1-carboxylate

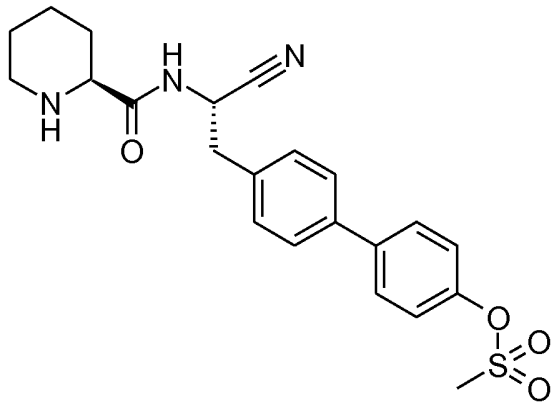


A stirred solution of (*S*)-*tert*-butyl 2-((*S*)-1-cyano-2-(4-iodophenyl)ethylcarbamoyl)piperidine-1-carboxylate (Example 4, step (i), 0.40 g), 4-(methylsulfonyloxy)phenylboronic acid (179 mg) and potassium acetate (244 mg) in a mixture of acetonitrile (10 mL) and water (10 mL) was degassed with nitrogen and treated with 1,1 *bis*(di-*tert*-butylphosphino)ferrocene palladium dichloride (54 mg). The resultant mixture was stirred at 85°C under nitrogen for 10 h. The reaction was diluted with water (100 mL), extracted with ethyl acetate (2 x 100 mL) and the organic extracts dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by chromatography on silica eluting with 40% ethyl acetate in *iso*hexane. Pure fractions were evaporated to dryness to afford the sub-titled compound (295 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2H), 7.53 (d, 2H), 7.39 - 7.32 (m, 4H), 5.24 - 5.15 (m, 1H), 4.69 (s, 1H), 4.04 - 3.84 (m, 1H), 3.25 - 3.08 (m, 5H), 2.51 - 2.37 (m, 1H), 2.26 - 2.16 (m, 1H), 1.66 - 1.29 (m, 15H).

m/e (Multimode-) 526 $[M-H]^-$

(iii) 4'-((*S*)-2-Cyano-2-((*S*)-piperidine-2-carboxamido)ethyl)biphenyl-4-yl methanesulfonate (Example 4)



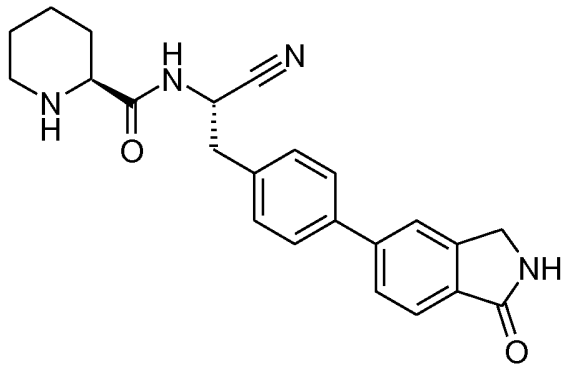
A solution of (*S*)-*tert*-butyl 2-((*S*)-1-cyano-2-(4'-(methylsulfonyloxy)biphenyl-4-yl)ethylcarbamoyl)piperidine-1-carboxylate (Example 4, step (ii), 0.29 g) in formic acid (4 mL) was stirred at 50°C for 20 min. The reaction was poured into ice / water (100 mL), basified to pH 9 with 0.880 ammonia and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, evaporated *in vacuo* and the residue purified by chromatography on silica eluting with 4% 2M methanolic ammonia in dichloromethane. Pure fractions were evaporated to dryness to afford the titled compound (188 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H), 7.55 (d, 2H), 7.39 - 7.33 (m, 5H), 5.20 (q, 1H), 3.26 (dd, 1H), 3.19 (s, 3H), 3.15 (d, 2H), 2.92 - 2.86 (m, 1H), 2.70 - 2.62 (m, 1H), 1.90 - 1.83 (m, 1H), 1.75 - 1.66 (m, 1H), 1.45 - 1.29 (m, 5H).

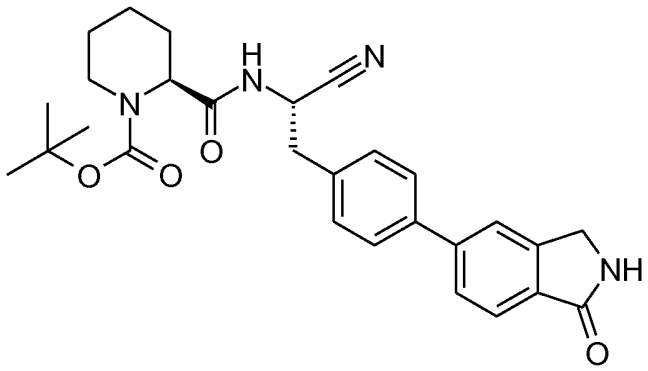
m/e (Multimode+) 428 $[M+H]^+$

Example 5

(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethyl)piperidine-2-carboxamide



(i) (*S*)-*tert*-Butyl 2-((*S*)-1-cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate



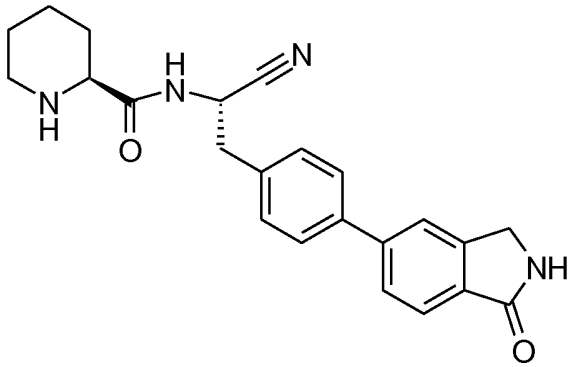
A stirred solution of (*S*)-*tert*-butyl 2-((*S*)-1-cyano-2-(4-iodophenyl)ethylcarbamoyl)piperidine-1-carboxylate (Example 4, step (i), 0.40 g), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (214 mg) and potassium acetate (244 mg) in a mixture of acetonitrile (10 mL) and water (10 mL) was degassed with nitrogen then treated with 1,1 *bis*(di-*tert*-butylphosphino)ferrocene palladium dichloride (54 mg). The resultant mixture was stirred at 85°C under nitrogen for 10 h. The reaction was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over magnesium sulfate, evaporated *in vacuo* and the residue purified by chromatography on silica eluting with ethyl acetate. Pure fractions were evaporated to dryness to afford the sub-titled compound (245 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 1H), 7.67 (d, 1H), 7.64 (s, 1H), 7.61 (d, 2H), 7.38 (d,

2H), 6.44 (s, 1H), 5.28 - 5.17 (m, 1H), 4.73 (s, 1H), 4.52 (s, 2H), 4.06 - 3.86 (m, 1H), 3.24 - 3.11 (m, 2H), 2.55 - 2.41 (m, 1H), 2.28 - 2.15 (m, 1H), 1.66 - 1.57 (m, 1H), 1.54 - 1.30 (m, 14H).

m/e (Multimode-) 487 $[M-H]^-$

(ii) (*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethyl)piperidine-2-carboxamide (Example 5)



A solution of (*S*)-*tert*-butyl 2-((*S*)-1-cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethylcarbamoyl)piperidine-1-carboxylate (Example 5, step (i), 243 mg) in formic acid (4 mL) was stirred at 50°C for 20 min. The reaction mixture was poured into ice / water (100 mL), basified to pH 9 with 0.880 ammmonia and extracted with ethyl acetate (2 x 100 mL). The organics were dried over sodium sulfate, evaporated *in vacuo* and the residue purified by preparative HPLC on a Waters' SunFire column using methanol in aqueous 0.1% trifluoroacetic acid as eluent. The fractions containing the desired compound were concentrated *in vacuo* to remove the methanol and the aqueous residue basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (2 x 100mL). The organics were dried over sodium sulfate and evaporated *in vacuo* to give the titled compound (105 mg).

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.60 - 8.48 (m, 2H), 7.84 (s, 1H), 7.79 - 7.64 (m, 4H), 7.47 - 7.38 (m, 2H), 5.07 - 4.98 (m, 1H), 4.42 (s, 2H), 3.25 - 3.14 (m, 2H), 3.12 (s, 1H), 2.84 - 2.75 (m, 1H), 1.63 - 1.53 (m, 2H), 1.47 - 1.37 (m, 1H), 1.36 - 1.17 (m, 4H).

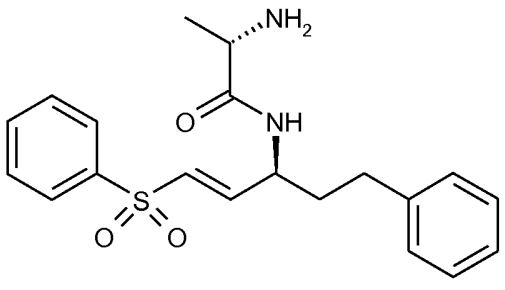
m/e (MultiMode+) 389 $[M+H]^+$

Pharmacological Analysis

Biological Assay

Fluorescence assay for recombinant human (rh) DPP1

The activity of DPP1 was determined by measuring the enzymatic release of aminomethyl coumarin (AMC) from the peptide substrate (H-Gly-Arg-AMC), which leads to an increase in fluorescence intensity at λex =350nm and λem =450nm. The assay was carried out in black 384 well plates in a final volume of 50µl at 22°C. The assay conditions contained the following: 25mM piperazine buffer pH5.0; 50mM NaCl, 5mM DTT; 0.01% (v/v) Triton X-100; 100µM H-Gly-Arg-AMC and rhDPP1 (~50pM). Potential inhibitors were made up in DMSO and then diluted in the assay to give a final concentration of not exceeding 1% (v/v) DMSO. A 10-point half-log dilution series of the inhibitors (highest concentration typically 10µM) was tested and the pIC_{50} determined using a 4-paramater logistic equation in a non-linear curve fitting routine. A standard DPP1 inhibitor (vinyl sulfone, see below) was used as a positive control in the assay. Routinely, inhibitors were pre-incubated with rhDPP1 for 30min prior to the addition of the peptide substrate to start the reaction for a further 60min at 22°C. After that the plates were immediately read in a fluorescence plate reader using the above emission and excitation wavelengths [modified from Kam, CM, Gotz, MG, Koot, G, McGuire, MJ, Thiele, DL, Hudig, D & Powers, JC (2004). Arch Biochem Biophys, 427, 123-134 & McGuire, MJ, Lipsky, PE & Thiele, DL (1992). Arch Biochem Biophys, 295, 280-288]. The results obtained are shown in Table 1 below.



vinyl sulfone

Table 1

Compound of Example	DPP1 activity, pIC_{50}
1	7.8
2	8.1
3	7.8
4	7.7
5	8.1

CLAIMS

1. A compound
(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-methyl-2-oxoindolin-6-yl)phenyl)ethyl)piperidine-2-carboxamide;
(*S*)-*N*-((*S*)-1-Cyano-2-(4-(3-(3-methoxypropyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)phenyl)ethyl)piperidine-2-carboxamide;
(*S*)-*N*-((*S*)-1-Cyano-2-(4'-(ethylsulfonyl)biphenyl-4-yl)ethyl)piperidine-2-carboxamide;
4'-((*S*)-2-Cyano-2-((*S*)-piperidine-2-carboxamido)ethyl)biphenyl-4-yl methanesulfonate; or,
(*S*)-*N*-((*S*)-1-Cyano-2-(4-(1-oxoisoindolin-5-yl)phenyl)ethyl)piperidine-2-carboxamide;
or a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of claim 1 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

4. A compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof for use in therapy.

5. A compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof for use in treating asthma, chronic obstructive pulmonary disease or allergic rhinitis.

6. Use of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating asthma, chronic obstructive pulmonary disease or allergic rhinitis.

7. A method of treating an obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

8. A combination of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and one or more agents independently selected from:

- a non-steroidal glucocorticoid receptor agonist;
- a selective β_2 adrenoceptor agonist;
- a phosphodiesterase inhibitor;
- a protease inhibitor;
- a glucocorticoid;
- an anticholinergic agent;
- a modulator of chemokine receptor function; and
- an inhibitor of kinase function.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/050964

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4402 A61K31/4439 C07D211/36 C07D401/12 C07D413/12
A61P11/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BONDEBJERG J ET AL: "Dipeptidyl nitriles as human dipeptidyl peptidase I inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD- DOI:10.1016/J.BMCL.2006.01.102, vol. 16, no. 13, 1 July 2006 (2006-07-01), pages 3614-3617, XP025107425 ISSN: 0960-894X [retrieved on 2006-07-01] page 3615; table 1; compounds 2, 7, 9 -----	1-8
A	WO 2005/021487 A1 (MERCK FROSST CANADA INC [CA]; BAYLY CHRISTOPHER [CA]; BLACK CAMERON [C) 10 March 2005 (2005-03-10) page 40 - page 79; claims 1-24; examples 4, 5, 12, 22 ----- -/--	1-8

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2010	23/08/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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X,P	WO 2009/074829 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; CAGE PETER ALAN [PT]; FU) 18 June 2009 (2009-06-18) the whole document	1-8
A	WO 2004/110988 A1 (COMBIO AS [DK]; BONDEBJERG JON [DK]; FUGLSANG HENRIK [DK]; NAERUM LARS) 23 December 2004 (2004-12-23) the whole document	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

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