Title: COMBINATION OF A BENZOXAZINONE AND A FURTHER AGENT FOR TREATING RESPIRATORY DISEASES

Abstract: The invention provides a pharmaceutical product, kit or composition comprising a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yi)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof, and a second active ingredient selected from: a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist; an antioxidant; a CCR1 antagonist; a chemokine antagonist (not CCR1); a corticosteroid; a CRTh2 antagonist; a DPI antagonist; an Histone Deacetylase Inducer; an IKK2 inhibitor; a COX inhibitor; a lipoxygenase inhibitor; a leukotriene receptor antagonist; an MPO inhibitor; a muscarinic antagonist; a p38 inhibitor; a PDE inhibitor; a PPARy agonist; a protease inhibitor; a Statin; a thromboxane antagonist; a vasodilator; or, an ENAC blocker (Epithelial Sodium-channel blocker); and its use in the treatment of respiratory disease (for example chronic obstructive pulmonary disease (COPD) or asthma).
COMBINATION OF A BENZOXAZINONE AND A FURTHER AGENT FOR TREATING RESPIRATORY DISEASES

The present invention relates to a combination of two or more pharmaceutically active substances for use in the treatment of respiratory diseases (for example chronic obstructive pulmonary disease (COPD) or asthma) wherein one of the pharmaceutically active substances is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof.

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

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

COPD is a term which refers to a large group of lung diseases which can interfere with normal breathing. Current clinical guidelines define COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to
noxious particles and gases. The most important contributory source of such particles and
gases, at least in the western world, is tobacco smoke. COPD patients have a variety of
symptoms, including cough, shortness of breath, and excessive production of sputum; such
symptoms arise from dysfunction of a number of cellular compartments, including
neutrophils, macrophages, and epithelial cells. The two most important conditions covered
by COPD are chronic bronchitis and emphysema.

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

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

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

A further class of therapeutic agent used in the treatment of respiratory diseases are bronchodilators. Bronchodilators may be used to alleviate symptoms of respiratory diseases by relaxing the bronchial smooth muscles, reducing airway obstruction, reducing lung hyperinflation and decreasing shortness of breath. Types of bronchodilators in clinical use include β₂ adrenoceptor agonists, muscarinic receptor antagonists and methylxanthines. Bronchodilators are prescribed mainly for symptomatic relief and they are not considered to alter the natural history of respiratory diseases.

N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide and its trifluoroacetate salt, hemi-fumaric acid salt, benzenesulfonic acid salt, hydrochloric acid salt, hydrobromic acid salt, methanesulfonic acid salt, benzensulfonic acid salt, p-toluencesulfonic acid salt, maleic acid salt, citric acid salt, 1-hydroxy-2-naphthoic acid salt, benzoic acid salt, (R)-(−)-mandelic acid salt and L-(+)-tartaric acid salt are β2 adrenoceptor agonists and are disclosed in PCT/SE2009/050749 (published as WO2009/154557). The compound and its salts show at least a 5-fold selectivity of β2 adrenoceptor agonism over adrenergic α1D, adrenergic β1 and dopamine D2 activities.

Combination products comprising a β₂ adrenoceptor agonist and a corticosteroid are available. One such product is a combination of budesonide and formoterol fumarate (marketed by AstraZeneca under the tradename Symbicort ®), which has proven to be effective in controlling asthma and COPD, and improving quality of life in many patients.

In view of the complexity of respiratory diseases such as asthma and COPD, it is unlikely that any one mediator can satisfactorily treat a respiratory disease alone. Moreover, whilst combination treatments using a β₂ adrenoceptor agonist and a corticosteroid deliver significant patient benefits, there remains a medical need for new therapies against
respiratory diseases such as asthma and COPD, in particular for therapies with disease modifying potential.

Accordingly, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a salt thereof, and a second active ingredient selected from: a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist; an antioxidant; a CCR1 antagonist; a chemokine antagonist (not CCR1); a corticosteroid; a CRTh2 antagonist; a DPI antagonist; an Histone Deacetylase Inducer; an IKK2 inhibitor; a COX inhibitor; a lipoxygenase inhibitor; a leukotriene receptor antagonist; an MPO inhibitor; a muscarinic antagonist; a p38 inhibitor; a PDE inhibitor; a PPARy agonist; a protease inhibitor; a Statin; a thromboxane antagonist; a vasodilator; or, an ENAC blocker (Epithelial Sodium-channel blocker).

The pharmaceutical product of the present invention comprises a first active ingredient and a second active ingredient, and it may comprise a third active ingredient. The third active
ingredient can be chosen from the list of second active ingredients but would normally have a different mechanism of action. So, for example, the second active ingredient might be a muscarinic antagonist and the third active ingredient might be: a non-steroidal glucocorticosteroid receptor agonist, corticosteroid, a CCR1 antagonist or a PDE4 inhibitor.

The first active ingredient, which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a salt thereof, may be in the form of a solvate (such as a hydrate).

In another aspect of the invention a suitable salt of N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide is, for example, a hydrochloride, hydrobromide, trifluoroacetate, sulphate, sulfonate, phosphate, acetate, fumarate (such as a hemi-fumaric acid salt), maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate, /?-toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, olate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulphonate or naphthalene-1-(sulfonic acid)-5-sulphonate), edisylate (ethane-1,2-disulphonate or ethane-1-(sulfonic acid)-2-sulphonate), isethionate (2-hydroxyethylsulphonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, R-mandelate, S-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulphonate), camsylate (such as (1S)-(+)10-camphor-sulphonate), formate, glutamate, glutarate, glycolate, hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulphonate), pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate), palmitate or l-hydroxy-2-naphthoate.

In a further aspect the present invention provides a pharmaceutical product wherein the first active ingredient is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-
In one particular aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a salt thereof, and a second active ingredient selected from a:

- 5HT antagonist;
- adenosine antagonist;
- adenosine receptor agonist;
- anti-allergic;
- anti-asthmatic;
- antibiotic;
- anti-inflammatory;
- antioxidant;
- anti-viral;
- beta-2 adrenoceptor agonist;
- beta-2 adrenoceptor inverse agonist;
- C5a antagonist;
- chemokine antagonist;
- COX inhibitor;
- CSF-1 receptor kinase inhibitor;
- ENaC Inhibitor;
- glucocorticoid receptor agonist;
- guanylate cyclase inhibitor;
- histamine/leukotriene antagonist;
- histone deacetylase inducer;
- IKK2 inhibitor;
- immunosuppressant;
- Ion channel modulator;
- JAK inhibitor;
leukotriene antagonist;
lipoxygenase inhibitor;
MAP kinase inhibitor;
MEK inhibitor;
MPO inhibitor;
mucus clearance promoter;
mucus production inhibitor;
muscarinic antagonist;
muscarinic antagonist/beta-2 adrenoceptor agonist;
muscarinic antagonist/PDE inhibitor;
NO donor;
p38 inhibitor;
PDE inhibitor;
PDE5 inhibitor;
CRTh2 antagonist;
DPI antagonist;
phospholipase inhibitor;
PI3 kinase inhibitor;
PPARgamma agonist;
protease inhibitor;
RARgamma inhibitor;
selectin inhibitor;
sirtuin activator;
statin;
Syk inhibitor;
Th2 Cytokine Inhibitor;
thromboxane antagonist;
TLR agonist;
vasodilator; or,
VIP agonist.

A 5HT antagonist is, for example, PRX08066.
An adenosine antagonist is, for example, CVT6883 or EPI-12323.

An adenosine receptor agonist is, for example, regadenoson (CVT3146) (Adenosine, 2-[4-[([methylamino]carbonyl]-1H-pyrazol-1-yl]-).

An anti-allergic is, for example, tranilast (Benzoic acid, 2-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propen-1-yl]amino]-).

An anti-asthmatic is, for example, VAK694, PF-3893787, PF-3526299 or KPE-06001.

An antibiotic is, for example, telithromycin (2H-Oxacyclotetradecino[4,3-d]oxazole-2,6,8,14(IH,7H,9H)-tetrone, 4-ethyloctahydro-1-methoxy-3a,7,9,11,13,15-hexamethyl-1-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl)-10-[[3,4,6-trideoxy-3-(dimethylamino)l-beta-D-xylo-hexopyranosyl]oxy]-, (3aS,4R,7R,9R,10R,11R,13R,15R,15aR)-), levofloxacin (7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-l-piperazinyl)-7-oxo-, (3S)-), erythromycin (Erythromycin) or azithromycin (1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-.alpha-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)l-beta-D-xylo-hexopyranosyl]oxy]-, [2R-\(\text{2R}^*, 3S^*, 4R^*, 5R^*, 8R^*, 10R^*, 1\) 1R*,12S*,13S*,14R*])-).

An anti-inflammatory is, for example, PS9481 15 or PF-37 15455.

An antioxidant is, for example, niacin (3-Pyridinecarboxylic acid), N-acetylcysteine amide (Propanamide, 2-(acetylamino)-3-mercapto-, (2R)-), N-acetylcysteine, N-acetyl cysteine ethyl ester (L-Cysteine, N-acetyl- ethyl ester), N-acetyl cysteine choline ester (Ethanaminium, 2-[(2R)-2-(acetylamino)-3-mercapto-1-oxopropoxy]-N,N,N-trimethyl-), N-acetyl cysteine choline ester hydrochloride (Ethanaminium, 2-[(2R)-2-(acetylamino)-3-mercapto-1-oxopropoxy]-N,N,N-trimethyl-, chloride (1:1)), mannitol (D-Mannitol), erdosteine (Acetic acid, 2-[(2-oxo-2-[(tetrahydro-2-oxo-3-thienyl)amino]ethyl]thio]-) or allopurinol (4H-Pyrazolo[3,4-d]pyrimidin-4-one, 1,5-dihydro-).
An anti-viral is, for example, pleconaril (1,2,4-Oxadiazole, 3-[3,5-dimethyl-4-[3-(3-methyl-5-isoxazolyl)propoxy]phenyl]-5-(trifluoromethyl)-).

A beta-2 adrenoceptor agonist is, for example, terbutaline (1,3-Benzenediol, 5-[2-[(1,l-dimethylethyl)amino]-l-hydroxyethyl]-), salmeterol (e.g. as xinafoate) (2-Naphthalencarboxylic acid, 1-hydroxy-, compd. with 4-hydroxy-.alpha.1-[[6-(4-phenylbutoxy)hexyl]amino][methyl]-1,3-benzenedimethanol (1:1)), salmeterol (1,3-Benzenedimethanol, 4-hydroxy-.alpha.1-[[6-(4-phenylbutoxy)hexyl]amino][methyl]-), salbutamol (albuterol) (1,3-Benzene dimethanol, .alpha.1-[[(1,l-dimethylethyl)amino][methyl]-4-hydroxy-), procaterol (2(lH)-Quinolinone, 8-hydroxy-5-[(IR,2S)-l-hydroxy-2-[(l-methylethyl)amino]butyl]-, rel-), pirbuterol (2,6-Pyridinedimethanol, .alpha.6-[(l,l-dimethylethyl)amino][methyl]-3-hydroxy-), PF-610355, orciprenaline (metaproterenol) (1,3-Benzenediol, 5-[(l-hydroxy-2-[(l-methylethyl)amino][ethyl]-), milveterol (GSK 59797; TD3327) (Formamide, N-2-hydroxy-5-[(IR)-l-hydroxy-2-[(2-4-[(2R)-2-hydroxy-2-phenylethyl]amino][phenyl][ethyl]amino][ethyl][phenyl]-), levosalbutamol (levalbuterol) (1,3-Benzene dimethanol, .alpha.1-[[1,1-dimethylethyl)amino][methyl]-4-hydroxy-, (alpha.1R)-), LAS100977, isoprenaline (isoproterenol) (1,2-Benzene dial, 4-[(l-hydroxy-2-[(l-methylethyl)amino][ethyl]-), indacaterol (QAB-149) (2(lH)-Quinolinone, 5-[(IR)-2-[(5,6-diethyl-2,3-dihydro-lH-inden-2-yl)amino]-l-hydroxyethyl]-8-hydroxy-), GSK 59802, GSK 642444 (3-(4-6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy)-butyl]-benzenesulfonamide; compound with 3-phenyl-acrylic acid), formoterol (e.g. as fumarate) (Formamide, N-2-hydroxy-5-[(lR)-l-hydroxy-2-[(IR)-2-(4-methoxyphenyl)-l-methylethyl]amino][ethyl][phenyl]-, rel-), (2E)-2-butenedioate (2:1) (salt) (9CI)), formoterol (Formamide, N-2-hydroxy-5-[(IR)-l-hydroxy-2-[[[(IR)-2-((4-methoxyphenyl)-l-methylethyl]amino][ethyl][phenyl]-, rel-), carmoterol (2(lH)-Quinolinone, 8-hydroxy-5-[(IR)-l-hydroxy-2-[[[(IR)-2-(4-methoxyphenyl)-l-methylethyl]amino][ethyl]-), bitolterol (e.g. as mesylate) (Benzoic acid, 4-methyl-, 1,1-[[4-2-[l,1-dimethylethyl]amino]-l-hydroxyethyl]-1,2-phenylene] ester, methanesulfonate (1:1)), bitolterol (Benzoic acid, 4-methyl-, 1,1-[[4-2-[l,1-dimethylethyl]amino]-l-hydroxyethyl]-1,2-phenylene] ester), BI1744CL (8-2-3-[(3-4-Chloro-phenyl)-5-methyl-1,2,4]triazol-1-yl]-1,1-dimethyl-propylamino)-l-hydroxy-ethyl)-6-hydroxy-4H-
benzo[1,4]oxazin-3-one; Hydrochloride; Di-hydrate), bedoradrine (MN 221) (Acetamide, N,N-dimethyl-2-[[((7S)-5,6,7,8-tetrahydro-7-[[[(2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-2-naphthalenyl]oxy]-), bambuterol (e.g. as hydrochloride) (Carbamic acid, N,N-dimethyl-, 3-[[[(dimethylamino)carbonyl]oxy]-5-[2-[(1l,1-dimethylethyl)amino]-1-hydroxyethyl]phenyl ester, hydrochloride (1:1)), bambuterol (Carbamic acid, N,N-dimethyl-, C,C'-[5-[2-[(l,l-dimethylethyl)amino]-l-hydroxyethyl]-1,3-phenylene] ester), ASF1020, arformoterol (e.g. as tartrate) (Formamide, N-[2-hydroxy-5-[(IR)-l-hydroxy-2-[[[(IR)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanediol (1:1) (salt)) or arformoterol (Formamide, N-[2-hydroxy-5-[(IR)-l-hydroxy-2-[[[(IR)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]phenyl]-).

A beta-2 adrenoceptor inverse agonist is, for example, nadolol (INV002) (2,3-Naphthalenediol, 5-[(l,l-dimethylethyl)amino]-2-hydroxypropoxy]-l,2,3,4-tetrahydro-).

A C5a antagonist is, for example, MP435 (W5401 1).

A chemokine antagonist is, for example, PS-031291 (Pyrrolidine-1,2-dicarboxylic acid 2-[(4-chloro-benzyl)-methyl-amide] 1-[[4-trifluoromethyl-phenyl]-amide]), CCX-354, vicriviroc (Methanone, (4,6-dimethyl-5-pyrimidinyl)[4-[(3S)-4-[[IR]-2-methoxy-l-[(trifluoromethyl)phenyl]ethyl]-3-methyl-1-piperazine]-4-methyl-1-piperidiny], maraviroc (Cyclohexanecarboxamide, 4,4-difluoro-N-[(IS)-3-[(3-exo)-3-[3-methyl-5-(l-methylethyl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-), CCX-282, FX125L, SCH527123 (PS291822) or GSK656933 (SB656933) (N-(2-bromophenyl)-N'-[(4-cyano-1H-1,2,3-benzotriazol-7-yl)urea).

A COX inhibitor is, for example, piroxicam (2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide), meloxicam (2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide), indomethacin (IH-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-), ibuprofen (Benzeneacetic acid, alpha.-methyl-4-(2-methylpropyl)-), etodolac (Pyran[3,4-b]indole-
1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro-), nimesulide (Methanesulfonamide, N-(4-nitro-2-phenoxyphenyl)-), diclofenac sodium (Benzeneacetic acid, 2-{(2,6-dichlorophenyl)amino}-, sodium salt (1:1)), diclofenac (Benzeneacetic acid, 2-{(2,6-dichlorophenyl)amino}-), valdecoxib (Benzenesulfonamide, 4-(5-methyl-3-phenyl-4-isoxazolyl)-), parecoxib (Propanamide, N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonil]-), lumiracoxib (Benzeneacetic acid, 2-{(2-chloro-6-fluorophenyl)amino}-5-methyl-), etoricoxib (2,3'-Bipyridine, 5-chloro-6'-methyl-3-[4-methylsulfonyl]-), cimicoxib (UR-8880) (Benzenesulfonamide, 4-[(2-(4-ethoxyphenyl)-4-methyl-1H-pyrrol-1-yl)-].

A CSF-1 receptor kinase inhibitor is, for example, JNJ283 12141.

An ENaC Inhibitor is, for example, triamterene (2,4,7-Pteridinetriamine, 6-phenyl-), P-552-02 (N-(3,5-Diamino-6-chloro-pyrazine-2-carbonyl)-N’-{4-[4-(2,3-dihydroxypropoxy)-phenyl]-butyl}-guanidine), GS941 1 (P680), benzamil (2-Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(phenylmethyl)amino]methyl]-) or amiloride (2-Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro-).

A glucocorticoid receptor agonist is, for example, triamcinolone acetonide (Pregna-1,4-diene-3,20-dione, 9-fluoro-1,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (11.beta., 16.alpha.-)), QAE397, prednisone (Pregna-1,4-diene-3,11,21-trione, 17,21-dihydroxy-), mometasone furoate (Pregna-1,4-diene-3,20-dione, 9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-l 1-hydroxy-16-methyl-, (11.beta., 16.alpha.-)), loteprednol etabonate (Androsta-1,4-diene-17-carboxylic acid, 17-[(ethoxycarbonyl)oxy]-l 1-hydroxy-3-<sub>α</sub>-, chloromethyl ester, (1), fluticasone propionate (Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-l 1-hydroxy-16-methyl-3-oxo-17-l-oxopropoxy)-, S-(fluoromethyl) ester, (6.alpha., 11.beta., 16.alpha., 17.alpha.-)), fluticasone furoate (Androsta-1,4-diene-17-carbothioic acid, 6,9-difuoro-17-[(2-furanylcarbonyl)oxy]-l 1-hydroxy-16-methyl-3-oxo-, 5-(fluoromethyl) ester, (6.alpha., 11.beta., 16.alpha., 17.alpha.-)), flunisolide (Pregna-1,4-diene-3,20-dione, 9,16-difluoro-11,21-dihydroxy-16,17-[l -
methylethylidene)bis(oxy)|, (6.alpha.,11.beta.,16.alpha.-), dexamethasone cipecilate
(Pregna-1,4-diene-3,20-dione, 21-[((cyclohexylcarbonyl)oxy]-17-
[(cyclopropylcarbonyl)oxy]-9-fluoro-1-hydroxy-16-methyl-, (11.beta.,16.alpha.-),
desisobutryl ciclesonide (Pregna-1,4-diene-3,20-dione, 16,17-[(R)-
cyclohexymethylene]bis(oxy)]-1-1,21-dihydroxy-, (11.beta.,16.alpha.-),
clobetasol propionate (Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11.beta.,16.alpha.-), ciclesonide (Pregna-1,4-diene-3,20-dione, 16,17-
[(R)-cyclohexymethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-,
(11.beta.,16.alpha.-), butixocort propionate (Pregn-4-ene-3,20-dione, 11-hydroxy-17-(1-
oxobutoxy)-21-[(l-oxopropyl)thio]-, (11.beta.-), budesonide (Pregna-1,4-diene-3,20-dione, 16,17-[butyldenebis(oxy)]-1-1,21-dihydroxy-, (11.beta.,16.alpha.-),
beclomethasone dipropionate (Pregna-1,4-diene-3,20-dione, 9-chloro-l-1-hydroxy-16-
methyl-17,21-bis(l-oxopropoxy)-, (11.beta.,16.beta.-), alclometasone dipropionate
(Pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-,
(7.alpha.,11.beta.,16.alpha.-), GSK870086, PF-251802 or PF-4171327.

A guanylate cyclase inhibitor is, for example, riociguat (Bay632521) (Carbamic acid, N-
[4,6-diamino-2-[l-[(2-fluorophenyl)methyl]-lH-pyrazolo[3,4-b]pyridin-3-yl]-5-
pyrimidinyl]-N-methyl-, methyl ester).

A histamine/leukotriene antagonist is, for example, azelastine (l(2H)-Phthalazinone, 4-[(4-
chlorophenyl)methyl]-2-(hexahydro-1-methyl-lH-azepin-4-yl)-).

A histone deacetylase inducer is, for example, theophylline (IH-Purine-2,6-dione, 3,9-
dihydro-1,3-dimethyl-) or aminophylline (theophylline + 1,2-ethandiamine) (IH-Purine-
2,6-dione, 3,9-dihydro-1,3-dimethyl-, compd. with 1,2-ethanediame (2:1)).

An IKK2 inhibitor is, for example, IMD2560 (N-(3,5-Bis-trifluoromethyl-phenyl)-5-
chloro-2-hydroxy-benzamide) or IMD1041.

An immunosuppressant is, for example, tacrolimus (15,19-Epoxy-3H-pyrido[2,1-
c][1,4]oxazacyclotricosine-1, 7,20,21(4H,23H)-tetrone,
5,6,8,1 1,12,13, 14,15, 16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(lE)-2-[(IR,3R,4R)-4-hydroxy-3-methoxy-cyclohexyl]-l-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propen-1-yl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-).

An ion channel modulator is, for example, senicapoc (ICA17043) (Benzeneacetamide, 4-fluoro-.alpha.- (4-fluorophenyl)-.alpha.- phenyl-) or andolast (diazolast; CR2039) (Benzamide, 4-(2H-tetrazol-5-yl)-N-[4-(2H-tetrazol-5-yl)phenyl]-).

A JAK inhibitor is, for example, INCB28050, VX509, R348 or CP-690550 (1-Piperidinepropanenitrile, 4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-.beta.-OCH3, (3R,4R)-).

A leukotriene antagonist is, for example, zileuton (Urea, N-(1-benzo[b]thien-2-ylethyl)-N-hydroxy-), zafirlukast (Carbamic acid, N-[3-[[2-methoxy-4-[[[(2-methylphenyl)sulfonyl]amino]carbonyl]phenyl]methyl]-1-methyl-1H-indol-5-yl]-, cyclopentyl ester), pranlukast (Benzamide, N-[4-oxo-2-(2H-tetrazol-5-yl)-4H-l-benzopyran-8-yl]-4-(4-phenylbutoxy)-), montelukast (Cyclopropanecacetic acid, 1-[[[1R]-1-[3-[[lE]-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl][thio]methyl]-) or masilukast (ZD3523) (lH-Indole-5-carboxamide, 3-[[2-methoxy-4-[[[(2-methylphenyl)sulfonyl]amino]carbonyl]phenyl]methyl]-1-methyl-N-[(2R)-4,4,4-trifluoro-2-methylbutyl]-).

A lipoxygenase inhibitor is, for example, TA270 (4-Hydroxy-l-methyl-3-octyloxy-7-sinapinoylamino-2(IH)-quinolinone), settleuton (MK0633) (2H-l-Benzopyran-2-one, 4-(4-fluorophenyl)-7-[[5-[[lS]-1-hydroxy-1-(trifluoromethyl)propyl]-l,3,4-oxadiazol-2-yl]amino]methyl]-), PF-4191834, LDP977 (MLN977; PEP03) (Urea, N-[4-[[2S,5S]-5-[[4-fluorophenoxymethyl]tetrahydro-2-furany]-3-butyln-1-yl]-N-hydroxy-), clafirinast; (RBx7796), GSK2190915 (AM803), GSK2190914 (AM103) or licofelone (1H-Pyrrolizine-5-acetic acid, 6-(4-chlorophenyl)-2,3-dihydro-2,2-dimethyl-7-phenyl-).
A MAP kinase inhibitor is, for example, CEP 1347 (KT7515) (9,12-Epoxy-1H-
diindolo[1,2,3-fg:3′,2′,l′-kl]pyrrolo[3,4-i][1,6]benzodiaocine-10-carboxylic acid, 5,16-
bis[(ethylthio)methyl]-2,3 ,9,10,1,12-hexahydro- 10-hydroxy-9-methyl- 1-oxo-, methyl ester, (9S,10R,12R)-) or GLPG0259.

A MEK inhibitor is, for example, RDEAI 19 (Cyclopropane-sulfonamide, N-[3,4-difluoro-
2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-l-[(2S)-2,3-dihydroxypropyl]-),
ARRY300 or ARRY162 (ARRY438162).

An MPO inhibitor is, for example, resveratrol (1,3-Benzenediol, 5-[(IE)-2-(4-
hydroxyphenyl)ethenyl]-) or piceatannol (1,2-Benzenediol, 4-[(IE)-2-(3,5-
dihydroxyphenyl)ethenyl]-).

A mucus clearance promoter is, for example, ambroxol (Cyclohexanol, 4-[(2-amino-3,5-
dibromophenyl)methyl][amino]-, trans-).

A mucus production inhibitor is, for example, lomucin (MSI 1995; Talniflumate) (3-
Pyridinecarboxylic acid, 2-[[3-(trifluoromethyl)phenyl][amino]-, 1,3-dihydro-3-oxo-1-
isobenzofuranyl ester), BIO 11006 or VR496.

A muscarinic antagonist is, for example, trospium chloride (ALKS27) (Spiro[8-
azoniabicyclo[3.2.1]octane-8, l′-pyrroldinium], 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-,
chloride (1:1), (1.alpha.,3.beta.,5.alpha.-)), tiotropium bromide (3-Oxa-9-
azoniatriaclyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-
bromide (1:1), (l.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.-), QAX028, QAT370, PTOOl,
oxitropium bromide (3-Oxa-9-azoniatriaclyclo[3.3.1.02,4]nonane, 9-ethyl-7-[(2S)-3-
hydroxy-l-oxo-2-phenylpropoxy]-9-methyl-, bromide (1:1),
(l.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.-), ipratropium bromide (8-
Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy- 1-oxo-2-phenylpropoxy)-8-methyl-8-(l-
methyl-ethyl)-, bromide (1:1), (3-endo,8-syn-)), GSK704838, GSK573719 (3-[(2-3-(5-
Cyclohexyloxycarbonyl-thiophen-2-yl)-ureido] -3-(4-hydroxy-phenyl)-propionylamino] -1-
(3-hydroxy-benzyl)-1-methyl-piperidinium), GSK1 160724 (TD4208), glycopyrronium
bromide (racemate) (Pyrrolidinium, 3-[(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-l,l-dimethyl-, bromide (1:1)), glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide): R,R- See below, R,R- glycopyrronium bromide (Pyrrolidinium, 3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetyl]oxy]-1,1-dimethyl-, bromide (1:1), (3R)-rel-), R,S-glycopyrronium bromide (Pyrrolidinium, 3-[(2R)-2-cyclopentyl-2-hydroxy-2-phenylacetyl]oxy]-l,l-dimethyl-, bromide (1:1), (3S)-rel-), S,S-glycopyrronium chloride (Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, chloride, [S-(R*,R*)]- (9CI)), dexpirronium, darotropium bromide (8-Azoniabicyclo[3.2.1]octane, 3-(2-cyano-2,2-diphenylethyl)-8,8-dimethyl-, bromide (1:1), (3-endo)-), BEA2180BR (Hydroxy-di-thiophen-2-yl-acetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-6-en-3-yl ester; hydrobromide) or aclidinium bromide (l-Azoniabicyclo[2.2.2]octane, 3-[(2-hydroxy-2,2-di-2-thienylacetyl]oxy]-l-(3-phenoxypropyl)-, bromide (1:1), (3R)-).

A muscarinic antagonist/beta-2 adrenoceptor agonist is, for example, GSK961081 (TD5959).

A muscarinic antagonist/PDE inhibitor is, for example, UCB 101333-3 (N,2-dicyclopropyl-6-(hexahydro-1H-azepin-1-yl)-5-methyl-4-pyrimidinamine).

A NO donor is, for example, N30-201 (S-nitrosoglutathione).

A p38 inhibitor is, for example, TA5493, SCI0323 (2-[(5-[[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-6-methoxy-1-methyl-IH-indol-3-yl]-N,N-dimethyl-2-oxo-acetamide), PS540446, PH797804 (3-[3-Bromo-4-(2,4-difluoro-benzylxylo)-6-methyl-2-oxo-2H-pyridin-1-yl]-4,N-dimethyl-benzamide), losmapimod (GSK856553; GW856553) (3-Pyridinecarboxamide, 6-[5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl]-N-(2,2-dimethylpropyl)-), KC-706 (2-(5-tert-Butyl-2-m-tolyl-2H-pyrazol-3-yl)-2-hydroxyimino-N-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-acetamide), GSK681323, GSK610677, BMS582949, BIBW2948BS or ARRY-797.

A PDE inhibitor is, for example, RPL554 (VMX554), tetomilast (OPC6535) (2-Pyridinecarboxylic acid, 6-[2-(3,4-diethoxyphenyl)-4-thiazoly])-), roflumilast
(Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-), pentoxifylline (1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-), oglemilast (GRC3886) (1-Dibenzofurancarboxamide, N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-8-[(methylsulfonyl)amino]-), Ibudilast (KC404) (1-Propanone, 2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-), GSK256066 (5-[4-Amino-1-(3-cyclopentoxy-4-methoxy-phenyl)-cyclohexylethyl]-pyrimidin-2-ylamine), ELB353 (AWD12353) (N-(3,5-Dichloro-pyridin-4-yl)-2-[l-(4-fluoro-benzyl)-IH-pyrrolo[2,3-b]pyridin-3-yl]-2-oxo-acetamide) or apremilast (CC-10004) (Acetamide, N-[2-[(IS)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-IH-isoindol-4-yl]).

A PDE5 inhibitor is, for example, vardenafil (Imidazo[5,1-f][1,2,4]triazin-4(1H)-one, 2-[2-ethoxy-5-[(4-ethyl-l-piperazinyl)sulfonyl]phenyl]-5-methyl-7-propyl-), udenafil (Benzenesulfonamide, 3-(6,7-dihydro-l-methyl-7-oxo-3-propyl-lH-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(l-methyl-2-pyrrolidinyl)ethyl]-4-propoxy-), tadalafil (Pyrazino[1'1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(l,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-), sildenafil (7H-Pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-[(4-methyl-l-piperazinyl)sulfonyl]phenyl]-1,6-dihydro-1-methyl-3-propyl-), PF-489791, mirodenafil (4H-Pyrrolo[3,2-d]pyrimidin-4-one, 5-ethyl-3,5-dihydro-2-[5-[(4-2-hydroxyethyl)-l-piperazinyl]sulfonyl]-2-propropoxyphenyl]-7-propyl-), MEM1414 (R1533), lodenafil (7H-Pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-[(4-2-hydroxyethyl)-1-piperazinyl]sulfonyl]phenyl]-1,6-dihydro-l-methyl-3-propyl-) or avanafil (5-Pyrimidincarboxamide, 4-[(3-chloro-4-methoxyphenyl)methyl]amino]-2-[2S)-2-(hydroxymethyl)-l-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-).

A CRTh2 antagonist is, for example, SOA002, QAV680, ODC9101 (OC000459) (5-Fluoro-l-(4-methanesulfonyl-benzenesulfonyl)-2 -methyl-IH-indol-3-yl]-acetic acid), OC499, MLN6095 (SAR398171), AP768, AMG853, AM211, ADC3680 or ACT129968 ([3-(2,3-Dihydro-indole-1-carbonyl)-l,2,3,4-tetrahydro-carbazol-9-yl]-acetic acid).

A DPI antagonist is, for example, SAR389644 or laropiprant (L888839; MK-0524) (Cyclopent[b]indole-3-acetic acid, 4-[(4-chlorophenyl)methyl]-7-fluoro-1,2,3,4-tetrahydro-
A phospholipase inhibitor is, for example, giripladib (PLA695) (Benzoic acid, 4-[3-[5-chloro-1-(diphenylmethyl)-2-[[2-(trifluoromethyl)phenyl]methyl] sulfonyl]amino]ethyl]-1H-indol-3-yl]propyl) hydrochloride (NM702; NT702; INDI702) (3(2H)-Pyridazinone, 4-bromo-6-[3-(4-chlorophenyl)propoxy]-5-[(3-pyridinylmethyl)amino]- hydrochloride (1:1)) or GRC-4039.

A PI3 kinase inhibitor is, for example, CAL101.

A PPARgamma agonist is, for example, rosiglitazone (2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-), rivoglitazone (2,4-Thiazolidinedione, 5-[[4-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)ethoxy]phenyl]methyl]-), pioglitazone (2,4-Thiazolidinedione, 5-[[4-2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-), lobeglitazone (2,4-Thiazolidinedione, 5-[[4-2-[(6-(4-methoxyphenoxy)-4-pyrimidinyl)methylamino]ethoxy]phenyl]methyl]-) or balaglitazone (2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazoliny]methoxy]phenyl]methyl]-).

A protease inhibitor is, for example, JNJ1031 1795 (RWJ355871) (Phosphonic acid, P-[2-3-[[methyl][1-(2-naphthalenyl)carbonyl]-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoetyl]-), JNJ18054478, V-85546 (ASH 1793), Ilomastat (Butanediamide, N4-hydroxy-N 1-[(1S)-1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoetyl]-2-(2-methylpropyl)-, (2R)-), doxycycline (2-Naphthacencarboxamide, 4-(dimethylamino)- 1,4,4a,5,5a,6,11.12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)-), EXT100 or Bay719678.

A RARgamma inhibitor is, for example, palovarotene (R667; Ro667; RO3300067) (Benzoic acid, 4-[(1E)-2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(IH-pyrazol-1-ylmethyl)-2-naphthalenyl] ethenyl]-).

A selectin inhibitor is, for example, bimosiamose (TBC1269) ([1,l'-Biphenyl]-3-acetic
A sirtuin activator is, for example, GSK2245840 (SIRT2104).

A statin is, for example, simvastatin (Butanoic acid, 2,2-dimethyl-, (lS,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-l-naphthalenyl ester), rosvuastatin (6-Heptenoic acid, 7-[4-(4-fluorophenyl)-6-[(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-, (3R,5S,6E)-), pravastatin (1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-6,8a-beta, delta,.6-trihydroxy-2-methyl-8-[2(S)-2-methyl-1-oxobutoxy]-, (beta.R, delta.R, IS,2S,6S,8aR)), lovastatin (Butanoic acid, 2-methyl-, (lS,3R,7S,8S,8aR)-l,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-l-naphthalenyl ester, (2S)- or atorvastatin (1H-Pyrrole-l-heptanoic acid, 2-(4-fluorophenyl)-.beta., delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-{(phenylamino)carbonyl}-, (beta.R, delta.R)).

A Syk inhibitor is, for example, tamatinib (R788; R406) (2H-Pyrido[3,2-b]-l,4-oxazin-3(4H)-one, 6-[(5-fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl)amino]-2,2-dimethyl-4-[(phosphonoxy)methyl]-) or R343 (2-{3-[4-(2,2-Difluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamino)-5-fluoro-pyrimidin-2-ylamino}-phenoxy}-N-methyl-acetamide).

A Th2 Cytokine Inhibitor is, for example, suplatast tosylate (Sulfonium, [3-[4-(3-ethoxy-2-hydroxypropoxy)phenyl]amino]-3-oxopropyl]dimethyl-, 4-methylbenzenesulfonate (1:1)) or suplatast (Sulfonium, [3-[4-(3-ethoxy-2-hydroxypropoxy)phenyl]amino]-3-oxopropyl]dimethyl-).

A thromboxane antagonist is, for example, seratrodast (Benzenoheptanoic acid, .zeta.-2,4,5-trimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)- or ramatroban (9H-Carbazole-9-propanoic acid, 3-[(4-fluorophenyl)sulfonyl]amino]-l,2,3,4-tetrahydro-, (3R)-).

A TLR agonist is, for example, AVE0675.
A vasodilator is, for example, BMS-346567 (PS-433540), LABCGRP, daglutril (lH-1-Benazepine-1-acetic acid, 3-[[[1-[(2R)-2-(ethoxycarbonyl)-4-phenylbutyl]cyclopentyl]carbonylamino]-2,3,4,5-tetrahydro-2-oxo- (3S)-], bosentan (Benzenesulfonamide, 4-[[1,1-dimethylethyl]-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)]2,2'-bipyrimidin]-4-yl]-), sitaxsentan sodium (3-Thiophenesulfonamide, N-(4-chloro-3-methyl-5-isoxazolyl)-2-[2-(6-methyl-1,3-benzodioxol-5-yl)acetyl]-, sodium salt (1:1)), fondosantan potassium (2H-1,2-Benzothiazine-3-carboxylic acid, 4-(7-ethyl-1,3-benzodioxol-5-yl)-2-[2-(trifluoromethyl)phenyl]-, 1,1-dioxide, potassium salt (1:1)), darusentan (Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-. (alpha.S)-), clazosantan (2-Pyridinesulfonamide, N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(2H-tetrazol-5-yl)-4-pyridinyl]-4-pyrimidinyl]-5-methyl-), avosentan (2-Pyridinesulfonamide, N-[6-methoxy-5-(2-methoxyphenoxy)-2-(4-pyridinyl)-4-pyrimidinyl]-5-methyl-), atrasentan (3-Pyrroloidinecarboxylic acid, 4-[[1,3-benzodioxol-5-yl]-l-[2-(dibutylamo)-2-oxoethyl]-2-(4-methoxyphenyl)-, (2R,3R,4S)-], ambrisentan (BSF-302146) (Benzenepropanoic acid, .alpha.-[(4,6-dimethoxy-2-pyrimidinyl)oxy]-.beta.-methoxy-.beta.-phenyl-. (alpha.S)-), treprostinil (Acetic acid, 2-[[[[R,2R,3aS,9aS]-2,3,3a,4,9,9a-hexahydro-2-hydroxy-l-[{(3S)-3-hydroxyoctyl]}IH-benz[f]inden-5-yl]oxy]-), Iloprost (Pentanoic acid, 5-[[3aS,4R,5R,6aS]-hexahydro-5-hydroxy-4-[(IE,3S)-3-hydroxy-4-methyl-1-octen-6-yn-1-yl]-2(IH)-pentalenylidene]-, (5E)-), fasudil (Isoquinoline, 5-[(hexahydro-IH-1,4-diazepin-1-yl)sulfonfonyl]- or sodium ferulate (2-Propenoic acid, 3-(4-hydroxy-3-methoxyphenyl)-, sodium salt (1:1)).

A VIP agonist is, for example, RG7103 (R7103).

The first and second active ingredients can be administered simultaneously (either in a single pharmaceutical preparation (that is, the active ingredients are in admixture) or via separate preparations), or sequentially or separately via separate pharmaceutical preparations.

In further aspects of the invention:
A non-steroidal glucocorticoid receptor (GR) agonist is, for example, a compound disclosed in WO 2006/046916.

An antioxidant is, for example, Allopurinol, Erdosteine, Mannitol, N-acetyl cysteine choline ester, N-acetyl cysteine ethyl ester, N-Acetylcysteine, N-Acetylcysteine amide or Niacin.

A CCR1 antagonist is, for example, a compound disclosed in WO2001/062728 or WO2001/098273, or a pharmaceutically acceptable salt thereof (such as a hydrochloride, trifluoroacetate, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt); BX471 ((2R)-1-[2-[[aminocarbonyl]amino]-4-chlorophenoxy]acetyl]-4-[(4-fluorophenyl)methyl]-2-methylpiperazine monohydrochloride) or CCX634.

Also, a CCR1 antagonist is, for example, a compound disclosed in WO2001/062728 or WO2001/098273 [such as N-(2-[(2S)-3-{[(3R)-l-[4-chlorophenyl]methyl]-3-pyrrolidinyl] amino}-2-hydroxypropoxy]-4-fluorophenyl)acetic acid, N-(2-{(2S)-3-[(3S)-1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl] amino}-2-hydroxypropoxy)-4-fluorophenyl)acetamide, N-(2-{(2S)-3-[(4-chlorobenzyl)-4-piperidinyl]amino}-2-hydroxypropoxy)-4-hydroxyphenyl)acetamide, (2-[[2S]-3-[[2R,5S]-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl] amino]-2-hydroxy-2-methylpropyloxy]-4-fluorophenyl)acetic acid, (2-[[2S]-3-[[3S,4R]-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl] amino]-2-hydroxy-2-methylpropyloxy]-4-fluorophenyl)acetic acid, (2-[[2S]-3-[[2R,4S,5S]-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl] amino]-2-hydroxy-2-methylpropyloxy]-4-fluorophenyl)acetic acid, (2-[[2S]-3-[[2R,4S,5S]-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl] amino]-2-hydroxy-2-methylpropyloxy]-4-fluorophenyl)acetic acid, Methyl (2-[[2S]-3-[[1-(4-chlorobenzyl)piperidin-4-yl] amino]-2-hydroxypropyloxy]-4-fluorophenyl)propanoate, N-[2-((2S)-3-[[1-(4-chlorobenzyl)-4-
piperidinyl)amino]-2-hydroxypropoxy)-4-chlorophenyl acetamide, N-[2-((2S)-3-[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy)-4-fluorophenyl] acetamide, N-[5-chloro-2-((2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy)-4-hydroxyphenyl] acetamide, N-[5-chloro-2-((2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy)-4-hydroxyphenyl] propaneamide, (2-[[2S]-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxy-2-methylpropoxy]oxy)-4-fluorophenyl)methanesulfonic acid, N-5-chloro-(2-((2S)-3-1-[(4-chlorobenzyl)-4-piperidinyl] amino]-2-hydroxypropoxy)-N'-(cyclopropyl)urea, N-(2-((2S)-3-1-[(4-chlorobenzyl)-4-piperidinyl] amino]-2-hydroxypropoxy)-N'-cyclopropyl-urea, (2S)-l-(2-ethylphenoxy)-3[(l-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)benzaldehyde, 2-((2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)-N-cyclopropylbenzamide, Methyl 2-((2S)-3-1-[(4-chlorobenzyl)-4-piperidinyl]amino]-2-hydroxypropoxy)-4-fluorobenzoate, N-2-((2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy)oxy)-2-hydroxy-2-methylpropoxy)benzaldehyde, 2-((2S)-3-[(1-[4-chlorobenzyl]-4-piperidinyl)amino]-2-hydroxypropoxy)-N-cyclopropylbenzamide, Methyl 2-((2S)-3-1-[(4-chlorobenzyl)-4-piperidinyl]amino]-2-hydroxypropoxy)-4-fluorobenzoate, N-2-((2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy)oxy)-4-hydroxy-N-methylbenzamide, 2-((2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy)oxy)-4-hydroxy-N-methylbenzamide, 4-fluoro-2-((2S)-3-(5-fluorophenyl)oxy)-4-chlorophenylacetamide, 4-fluoro-2-((2S)-3-(5-fluorophenyl)oxy)-4-chlorophenylacetamide,

N-(2-[(2S)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]oxy]benzenesulfonic acid, (hemi)fumarate, benzoate, furoate or succinate salt); BX471 ((2R)-l-[[2-
[(aminocarbonyl)amino]-4-chlorophenoxy]acetyl]-4-[(4-fluorophenyl)methyl]-2-methylpiperazine monohydrochloride); or CCX634.

Also, a CCR1 antagonist is, for example, N-forderby-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl] acetamide (see WO 2003/051839), or, 2-{2-Chloro-5-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy]-2-methylpropanoic acid (see PCT publication no. WO 2008/010765), or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

A chemokine antagonist (other than a CCR1 antagonist), for example, 656933 (N-(2-bromophenyl)-N*-(4-cyano-1H-1,2,3-benzotriazol-7-yl)urea), 766994 (4-((1(2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl)methyl)amino)carbonyl]amino)carbonyl]methyl)benzamide), CCX-282, CCX-915, Cyanovirin N, E-921, INCB-003284, INCB-9471, Maraviroc, MLN-3701, MLN-3897, T-487 (N-{1-[3-(4-ethoxyphenyl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl]ethyl}-N-(pyridin-3-ylmethyl)-2-[4-(trifluoromethoxy)phenyl]acetamide) or Vicriviroc.

A corticosteroid is, for example, Alclometasone dipropionate, Amelometasone, Beclomethasone dipropionate, Budesonide, Butixocort propionate, Ciclesonide, Clobetasol propionate, Desisobutyrylciclesonide, Etiprednol dicloacetate, Fluocinolone acetonide, Fluticasone Furoate, Fluticasone propionate, Loteprednol etabonate (topical) or Mometasone furoate.

A CRTh2 antagonist is, for example, a compound from WO 2004/106302 or WO 2005/018529.

A DPI antagonist is, for example, L888839 or MK0525.

An histone deacetylase inducer is, for example, ADC4022, Aminophylline, a Methylxanthine or Theophylline.
An IKK2 inhibitor is, for example, 2-\{2-(2-Methylamino-pyrimidin-4-yl)-1H-indole-5-carbonyl\}-amino}-3-(phenyl-pyridin-2-yl-amino)-propionic acid.

A COX inhibitor is, for example, Celecoxib, Diclofenac sodium, Etodolac, Ibuprofen, Indomethacin, Meloxicam, Nimesulide, OC1768, OC2125, OC2184, OC499, OCD9101, Parecoxib sodium, Piceatannol, Piroxicam, Rofecoxib or Valdecoxib.

A lipoxygenase inhibitor is, for example, Ajulemic acid, Darbufelone, Darbufelone mesilate, Dexibuprofen lysine (monohydrate), Etalocib sodium, Licofelone, Linazolast, Lonapalene, Masoprocol, MN-001, Tepoxalin, UCB-35440, Veliflapon, ZD-2138, ZD-4007 or Zileuton ((±)-1-(1-Benz(o)b)thien-2-ylethyl)-1-hydroxyurea.

A leukotriene receptor antagonist is, for example, Ablukast, Iralukast (CGP 457 15A), Montelukast, Montelukast sodium, Ontazolast, Pranlukast, Pranlukast hydrate (mono Na salt), Verlukast (MK-679) or Zafirlukast.

An MPO Inhibitor is, for example, a Hydroxamic acid derivative (N-(4-chloro-2-methyl-phenyl)-4-phenyl-4-[[[(4-propan-2-ylphenyl)sulfonylaminomethyl]piperidine-1-carboxamide), Piceatannol or Resveratrol.


In one aspect of the invention a muscarinic antagonist is Aclidinium bromide, Glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide), Oxitropium bromide, Pirenzepine, telenzepine or Tiotropium bromide.

In another aspect of the invention a muscarinic antagonist is Glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide) or Tiotropium bromide.

In yet another aspect a muscarinic antagonist is (i?)-l-[2-(4-Fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin- 1-yl-propionyloxy)- 1-azonia-bicyclo[2.2.2]octane (see WO2008/075005); wherein the counter-ion is, for example, chloride, bromide, sulfate, methanesulfonate, benzenesulfonate (besylate), toluenesulfonate (tosylate), naphthalene-
bissulfonate (napadisylate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, fumarate or succinate).

A p38 Inhibitor is, for example, a compound from WO 2005/042502, 681323, 856553, AMG548 (2-[(2S)-2-amino-3-phenylpropyl]amino]-3-methyl-5-(2-naphthalenyl)-6-(4-pyridinyl)-4(3H)-pyrimidinone), Array-797, AZD6703, Doramapimod, KC-706, PH 797804, R1503, SC-80036, SCI0469, VX702 or VX745 (5-(2,6-dichlorophenyl)-2-(phenylthio)-6H-pyrimido[1,6-b]pyridazin-6-one).

A PDE Inhibitor: such as a PDE4 inhibitor is, for example, 256066, Arofylline (3-(4-chlorophenyl)-3,7-dihydro-1-propyl-1H-Purine-2,6-dione), AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-1-[(4-fluorophenyl)methyl]-5-hydroxy-a-oxo-1H-indole-3-acetamide), BAY 19-8004 (Bayer), CDC-801 (Calgene), Celgene compound ((R)R-β-(3,4-dimethoxyphenyl)-1,3-dihydro-1-oxo-2H-isooindole-2-propanamide), Cilomilast (cis-4-cyano-4-(3-cyclopentylxoy)-4-methoxyphenyl]-cyclohexanecarboxylic acid), a compound in WO2006098353 from Kyowa Hakko Kogyo Co. Ltd. Japan, 2-(3,5-dichloro-4-pyridinyl)-1-(7-methoxyspiro[1,3-benzodioxole-2,1’-cyclopentan]-4-yl)ethanone (CAS number 185406-34-2), Compound from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-methyl[benzoyl]amino)cyclohexyl]-)pyridinecarboxamide), Compound from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-hydroxyethyl)]benzoyl]amino)cyclohexyl]-3-pyridinecarboxamide, CT2820, GPD-1116, Ibudilast, IC 485, KF 31334, KW-4490 (Kyowa Hakko Kogyo), Lirimilast (2-(2,4-dichlorobenzoyl)-6-[(methylsulfonyl)oxy]-3-benzo furanyl]-urea), Merck Compound (N-cyclopropyl-1,4-dihydro-4-oxo-1-[3-(3-pyridylmethlythynyl)phenyl]-) 1,8-naphthyridine-3-carboxamide), Oglemilast (N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-8-[(methylsulfonyl)amino]-l-dibenzofurancarboxamide), ON06126, ORG 20241 (4-(3,4-dimethoxyphenyl)-N-hydroxy-2-thiazolecarboximidamide), PD 189659/PD 168787 (Parke-Davis), Pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-) 1H-purine-2,6-dione), Pfizer compound (5-fluoro-N-[4-[(2-hydroxy-4-methyl benzoyl)amino]cyclohexyl]-2-(thian-4-yloxy)pyridine-3-carboxamide, Pfizer UK
500,001, Piclamilast (3-(cyclopentyloxy)-N-(3,5-dichloro-4-pyridinyl)-4-methoxy-
benzamide), PLX-369 (WO 2006026754), Roflumilast (3-(cyclopropylmethoxy)-N-(3,5-
dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide), SCH 351591 (N-(3,5-dichloro-l-
oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinolinecarboxamide), SelectID(TM) 
CC-10004 (Calgene), T-440 (Tanabe), Tetomilast (6-[2-(3,4-diethoxyphenyl)-4-thiazolyl]-
2-pyridinecarboxylic acid), Tofimilast (9-cyclopentyl-7-ethyl-6,9-dihydro-3-(2-thienyl)-
5H-pyrazolo[3,4-c]1,2,4-triazolo[4,3-a]pyridine), TPI 1100, UCB 101333-3 (N,2-
dicyclopropyl-6-(hexahydro-1H-azepin-1-yl)-5-methyl-4-pyrimidinamine), V-11294A 
(Napp), VM554/VM565 (Vernalis), or Zardaverine (6-[4-(difluoromethoxy)-3-
methoxyphenyl]-3(2H)-pyridazinone).

A PDE5 Inhibitor is, for example, Gamma-glutamyl[s-(2-iodobenzyl)cysteinyl]glycine, 
Tadalafil, Vardenafil, sildenafil, 4-phenyl-methylamino-6-chloro-2-(1-imidazolyl)-
quinazoline, 4-phenyl-methylamino-6-chloro-2-(3-pyridyl)-quinazoline, 1,3-dimethyl-6-(2-
propoxy-5-methanesulphonamidophenyl)-1,5-dihydropyrazolo [3,4-d]pyrimidin-4-one or 
l-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one.

A PPARy agonist is, for example, Pioglitazone, Pioglitazone hydrochloride, Rosiglitazone 
Maleate, Rosiglitazone Maleate ((-)-enantiomer, free base), Rosiglitazone 
maleate/Metformin hydrochloride or Tesaglitizar.

A Protease Inhibitor is, for example, Alpha l-antitrypsin proteinase Inhibitor, EPI-HNE4, 
UT-77, ZD-0892 or a compound from WO 2006/004532, WO 2005/026123, WO 
2002/0744767 or WO 22002/074751; or a TACE Inhibitor (for example DPC-333, Sch-
709156 or Doxyeyeline).

A Statin is, for example, Atorvastatin, Lovastatin, Pravastatin, Rosuvastatin or Simvastatin.

A Thromboxane Antagonist is, for example, Ramatroban or Seratrodast.

A Vasodilator is, for example, A-306552, Ambrisentan, Avosentan, BMS-248360, BMS-
346567, BMS-465149, BMS-509701, Bosentan, BSF-302146 (Ambrisentan), Calcitonin
Gene-related Peptide, Daglutril, Darusentan, Fandosentan potassium, Fasudil, Iloprost, KC-12615 (Daglutril), KC-12792 2AB (Daglutril), Liposomal treprostinil, PS-433540, Sitaxsentan sodium, Sodium Ferulate, TBC-11241 (Sitaxsentan), TBC-3214 (N-(2-acetyl-4,6-dimethylphenyl)-3-[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-2-thiophencarboxamide), TBC-3711, Trapidil, Treprostinil diethanolamine or Treprostinil sodium.

An ENAC (Epithelial Sodium-channel blocker) is, for example, Amiloride, Benzamil, Triamterene, 552-02, PSA14984, PSA25569, PSA23682 or AER002.

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

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

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient selected from:

a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;
a CCR1 antagonist;
a chemokine antagonist (not CCR1);
a corticosteroid;
an IKK2 inhibitor;
a muscarinic antagonist;
a p38 inhibitor; or,
a PDE inhibitor.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(l-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient which is a non-steroidal Glucocorticoid Receptor (GR) Agonist for example, a compound disclosed in WO 2006/046916.

In yet another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(l-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient which is a CCR1 antagonist, for example, a compound disclosed in WO2001/062728 or WO2001/098273 [such as N-(2{{(2S)-3[{(3R)-1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}] amino}-2-hydroxypropoxy} -4-fluorophenyl)acetamide, N-(2{{(2S)-3[{(3S)-1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}] amino}-2-hydroxypropoxy} -4-fluorophenyl)acetamide, N-(2-{{(2S)-3-[(4-chlorobenzyl)-4-piperidinyl] amino}-2-hydroxypropoxy} -4-hydroxyphenyl)acetamide, (2-{{(2S)-3-[(2R,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(3S,4R)-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(3R,4R)-1-(4-chlorobenzyl)-3-methylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4R,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, Methyl (2-{{(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2R,4R,5R)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy }-4-fluorophenyl)acetic acid, (2-{{(2S)-3-[(2S,4S,5S)-1-(4-chlorobenzyl)-2,5-dimethylpiperidin-4-yl]a...
(hemi)fumarate, benzoate, furoate or succinate salt)); BX471 ((2R)-1-[[2-[(aminocarbonyl)amino]-4-chlorophenoxy]acetyl]-4-[(4-fluorophenyl)methyl]-2-methylpiperazine monohydrochloride); or CCX634.

In another aspect a CCR1 antagonist is \( N\{2-((25)-3-\{1-(4-chlorobenzyl)piperidin-4-yl)amino\}-2-hydroxy-2-methylpropyl\}oxy\}-4-hydroxyphenyl \) acetamide, or, 2-\{2-Chloro-5-\{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl\}oxy\}-4-\{(methylamino)carbonyl\}phenoxy\} -2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt). For example \( N\{2-((25)-3-\{1-(4-chlorobenzyl)piperidin-4-yl\}amino\}-2-hydroxy-2-methylpropyl\}oxy\} -4-hydroxyphenyl \) acetamide as a benzoate salt, or, 2-\{2-Chloro-5-\{[(2S)-3-(5-chloro-1H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl\}oxy\}-4-\{(methylamino)carbonyl\}phenoxy\} -2-methylpropanoic acid as the free acid.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient which is a chemokine antagonist (not CCR1), for example, 656933 \{N-(2-bromophenyl)-N'-(4-cyano-1H,2,3-benzotriazol-7-yl)urea\}, 766994 \{4-\{\{\{([2R]-4-(3,4-dichlorobenzyl)morpholin-2-yl)amino\}carbonyl\}-amino\}methyl\}benzamide), CCX-282, CCX-915, Cyanovirin N, E-921, INCB-003284, INCB-9471, Maraviroc, MLN-3701, MLN-3897, T-487 \{N-[1-[3-(4-ethoxyphenyl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl]ethyl]-N-(pyridin-3-ylmethyl)-2-[4-(trifluoromethoxy)phenyl] acetamide\} or Vicriviroc.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a corticosteroid, for example,
Alclometasone dipropionate, Amelometasone, Beclomethasone dipropionate, Budesonide, Butixocort propionate, Ciclesonide, Clobetasol propionate, Desisobutyrylciclesonide, Etiprednol dicloacetate, Fluocinolone acetonide, Fluticasone Furoate, Fluticasone propionate, Loteprednol etabonate (topical) or Mometasone furoate.

In one embodiment of the present invention the corticosteroid is selected from budesonide, fluticasone propionate, fluticasone fruoate mometasone furoate, beclomethasone propionate or butixocort propionate ester.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a corticosteroid, for example, Budesonide, Fluticasone Furoate or Fluticasone propionate.

In one embodiment of the present invention the corticosteroid is budesonide. Budesonide and its preparation is described, for example, in Arzneimittel-Forschung (1979), 29 (11), 1687-1690, DE 2,323,215 and US 3,929,768. Presently available formulations of budesonide are marketed under the tradename 'Entocort ®'.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is an IKK2 inhibitor, for example, 2-{[2-(2-Methylamino-pyrimidin-4-yl)-1H-indole-5-carbonyl]-amino }-3-(phenyl-pyridin-2-yl-amino)-propionic acid.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is an IKK2 inhibitor, for example, 2-{[2-(2-Methylamino-pyrimidin-4-yl)-1H-indole-5-carbonyl]-amino }-3-(phenyl-pyridin-2-yl-amino)-propionic acid.
yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a muscarinic antagonist, for example, Acclidinium bromide, Glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide), Oxitropium bromide, Pirenzepine, telenzepine, Tiotropium bromide, 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide (see WO 01/041 18), 3(R)-l-phenethyl-3-[(9H-xanthene-9-carbonyloxy)-l-azoniabicyclo[2.2.2]octane bromide or (3R)-3-[(2S)-2-cyclopentyl-2-hydroxy-2-thien-2-ylacetoxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]actone bromide (see WO 01/041 18); or a quaternary ammonium salt (such as [2-((S)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5 -ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl] dimethyl-(3-phenoxy-propyl)-ammonium salt, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl] dimethyl-(2-phenoxyethoxy-ethyl)-ammonium salt, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-((3,4-dichloro-benzyl)-oxy)-ethyl]- dimethyl-ammonium salt, [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-[2-((4-Chloro-benzyl)-oxy)-ethyl]- dimethyl-ammonium salt, (i?)-l-2-[4-(4-Fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane, (R)-3-(l-Phenyl-cycloheptanecarbonyloxy)-1-(pyrazin-2-ylcarbamoymethyl)-1-azonia-bicyclo[2.2.2]octane, (R)-3-(l-Phenyl-cycloheptanecarbonyloxy)-1-azonia-bicyclo[2.2.2]octane, (R)-3-[(3,5-Fluoro-phenyl)-cycloheptanecarbonyloxy]-1-azonia-bicyclo[2.2.2]octane, (i?)-3-[l-(3-Fluoro-phenyl)-cycloheptanecarbonyloxy]-1-azonia-bicyclo[2.2.2]octane, (i?)-3-[(2-Methyl-pyridin-4-ylcarbamoymethyl)-methyl]-1-azonia-bicyclo[2.2.2]octane; wherein the counter-ion is, for example, chloride, bromide, sulfate, methanesulfonate, benzenesulfonate (besylate),
toluenesulfonate (tosylate), napthalenebissulfonate (napadisylate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, fumarate or succinate).

In a further aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1 -methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is Oxitropium bromide or Tiotropium bromide.

In one aspect of the invention the muscarinic receptor antagonist is a long acting muscarinic receptor antagonist, that is a muscarinic receptor antagonist with activity that persists for more than 12 hours. Examples of long acting muscarinic receptor antagonists include tiotropium bromide.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1 -methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is Tiotropium bromide.

In yet another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1 -methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the
hemi-fumaric acid salt), and a second active ingredient is Glycopyrrolate (such as R,R-, R,S-, S,R-, or S,S-glycopyrronium bromide).

In a further aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is (i?)-l-[2-(4-Fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin-1-yl-propionyloxy)-l-azonia-bicyclo[2.2.2]octane; wherein the counter-ion is, for example, chloride, bromide, sulfate, methanesulfonate, benzenesulfonate (besylate), toluenesulfonate (tosylate), naphthalenebissulfonate (napadisylate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, fumarate or succinate.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a p38 inhibitor, for example, a compound from WO 2005/042502, 681323, 856553, AMG548 (2-[(2S)-2-amino-3-phenylpropyl]amino]-3-methyl-5-(2-naphthalenyl)-6-(4-pyridinyl)-4(3H)-pyrimidinone), Array-797, AZD6703, Doramapimod, KC-706, PH 797804, R1503, SC-80036, SCI0469, 6-chloro-5-[(25’,5i?)]-4-[(4-fluorophenyl)methyl]-2,5-domethyl-l-piperazinyl[carbonyl]-N,N,l-trimethyl-a-oxo-l H-indole-3-acetamide, VX702 or VX745 (5-(2,6-dichlorophenyl)-2-(phenylthio)-6H-pyrimido[ 1,6-b]pyridazin-6-one).

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a PDE Inhibitor: such as a PDE4 inhibitor (for example, 256066, Arofylline (3-(4-chlorophenyl)-3,7-dihydro-1-propyl-1H-...
Purine-2,6-dione), AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-1-[(4-fluorophenyl)methyl]-5-hydroxy-α-oxo-IH-indole-3-acetamide), BAY19-8004 (Bayer), CDC-801 (Calgene), Celgene compound ((PR)-P-(3,4-dimethoxyphenyl)-1,3-dihydro-l-oxo-2H-isooindole-2-propanamide), Cilomilast (cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-cyclohexanecarboxylic acid), a compound in WO2006098353 from Kyowa Hakko Kogyo Co. Ltd. Japan, 2-(3,5-dichloro-4-pyridinyl)-1-(7-methoxyspiro[l,3-benzodioxole-2',1'-cyclopentan]-4-yl)ethanone (CAS number 185406-34-2), Compound from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-methylbenzoyl)amino]cyclohexyl]-3-pyridinecarboxamide), Compound from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-(hydroxymethyl)benzoyl]amino]cyclohexyl]-3-pyridinecarboxamide), CT2820, GPD-14456, Ibudilast, IC 485, KF 31334, KW-4490 (Kyowa Hakko Kogyo), Lirimilast (2-(2,4-dichlorobenzoyl)-6-[(methylsulfonyl)oxy]-3-benzofuranyl)-urea), Merck Compound (N-cyclopropyl-1,4-dihydro-4-oxo-1-[3-(3-pyridinylethynyl)phenyl]-) 1,8-naphthyridine-3-carboxamide), Oglemilast (N-(3,5-dichloro-4-pyridinyl)-4-(difuoromethoxy)-8-[(methylsulfonyl)amino]-l-dibenzofuran carboxamide), ON06126, ORG 20241 (4-(3,4-dimethoxyphenyl)-N-hydroxy-2-thiazolecarboximidamide), PD189659/PD168787 (Parke-Davis), Pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl) )1H-purine-2,6-dione), Pfizer compound (5-fluoro-N-[4-[(2-hydroxy-4-methylbenzoyl)amino]cyclohexyl]-2-(thiacyl-oxy)pyridine-3-carboxamide), Pfizer UK 500,001, Piclamilast (3-(cyclopentylxylo)-N-(3,5-dichloro-4-pyridinyl)-4-methoxy benzamide), PLX-369 (WO 2006026754), Roflumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide), SCH 351591 (N-(3,5-dichloro-1-oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinolinecarboxamide), SelCID(TM) CC-10004 (Calgene), T-440 (Tanabe), Tetomilast (6-2-(3,4-dithoxyphenyl)-4-thiazolyl]-2-pyridinecarboxylic acid), Tofimilast (9-cyclopentyl-7-ethyl-6,9-dihydro-3-(2-thienyl)-5H-pyrazolo[3,4-c]-1,2,4-thiazolo[4,3-alpyridine), TPI 1100, UCB 101333-3 (N,2-dicyclopentyl-6-(hexahydro-1H-azepin-1-yl)-5-methyl-4-pyrimidinamine), V-11294A (Napp), VM554/VM565 (Vernalis), or Zardaverine (6-[4-(difluoromethoxy)-3-methoxyphenyl]-3(2H)-pyridazinone); or a PDE5 Inhibitor, for example, Gamma-glutamyl[s-(2-iodobenzyl)cysteinyl]glycine, Tadalafil, Vardenafil, sildenafil, 4-phenyl-methylamino-6-chloro-2-(l-imidazolyl)-quinazoline, 4-phenyl-methylamino-6-chloro-2-
(3-pyridyl)-quinazoline, 1,3-dimethyl-6-(2-propoxy-5-methanesulphonylamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one or 1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one.

In another aspect the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient is a PDE4 inhibitor, for example, 256066, Arofylline (3-(4-chlorophenyl)-3,7-dihydro-1-propyl-1H-Purine-2,6-dione), AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-1-[(4-fluorophenyl)methyl]-5-hydroxy-a-oxo-1H-indole-3-acetamide), BAY19-8004 (Bayer), CDC-801 (Calgene), Celgene compound ((PR)-P-(3,4-dimethoxyphenyl)-1,3-dihydro-1-oxo-2H-isouindole-2-propanamide), Cilomilast (cis-4-cyano-4-[3-(cyclopentyl)oxy]-4-methoxyphenyl]-cyclohexanecarboxylic acid), a compound in WO2006098353 from Kyowa Hakko Kogyo Co. Ltd. Japan, 2-(3,5-dichloro-4-pyridinyl)-1-(7-methoxyspiro[1,3-benzoxazole-2,1'-cyclopentan]-4-yl)ethanone (CAS number 185406-34-2)), Compound from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-methylbenzoyl)amino]cyclohexyl]-3-pyridinecarboxamide), Compounds from Pfizer (2-(3,4-difluorophenoxy)-5-fluoro-N-[cis-4-[(2-hydroxy-5-(hydroxymethyl)benzoyl)amino]cyclohexyl]-3-pyridinecarboxamide, CT2820, GPD-1 116, Ibidilast, IC 485, KF 31334, KW-4490 (Kyowa Hakko Kogyo), Lirimilast (1-(2,4-dichlorobenzoyl)-6-[(methylsulfonyl)oxy]-3-benzofuran-1-carboxamide), Merck Compound (N-cyclopropyl-1,4-dihydro-4-oxo-1-[3-(3-pyrindylethynyl)phenyl]-1,8-naphthyridine-3-carboxamide), Oglemilast (N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-8-[(methylsulfonyl)amino]-1-dibenzofurancarbocboximide), ON06 126, ORG 20241 (4-(3,4-dimethoxyphenyl)-N-hydroxy)-2-thiazolecarboximidamidine), PD189659/PD 168787 (Parke-Davis), Pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexy])-1H-purine-2,6-dione), Pfizer compound (5-fluoro-N-[4-[(2-hydroxy-4-methylbenzoyl)amino]cyclohexyl]-2-(thian-4-yloxy)pyridine-3-carboxamide, Pfizer UK 500,001, Piclamilast (3-(cyclopentyl)oxy)-N-(3,5-dichloro-4-pyridinyl)-4-methoxybenzamide), PLX-369 (WO 2006026754), Rofiumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide), SCH 351591 (N-(3,5-dichloro-1-...
oxido-4-pyridinyl)-8-methoxy-2-(trifluoromethyl)-5-quinolinecarboxamide), SelCID(TM)
CC-10004 (Calgene), T-440 (Tanabe), Tetomilast (6-[2-(3,4-dioxyphenyl)-4-thiazolyl]-
2-pyridinecarboxylic acid), Tofimilast (9-cyclopentyl-7-ethyl-6,9-dihydro-3-(2-thienyl)-
5H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine), TPI 1100, UCB 101333-3 (N,2-
dicyclopentyl-6-(hexahydro-1H-azepin-1-yl)-5-methyl-4-pyrimidinamine), V-11294A
(Napp), VM554/VM565 (Vernalis), or Zardaverine (6-[4-(difluoromethoxy)-3-
methoxyphenyl]-3(2H)-pyridazinone).

In another aspect the present invention provides a pharmaceutical product comprising, in
combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-
3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(l-methyl-1H-pyrazol-4-
yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the
hemi-fumaric acid salt), and a second active ingredient is a PDE4 inhibitor, for example
AWD 12-281 (N-(3,5-dichloro-4-pyridinyl)-l-[4-fluorophenyl]methyl]-5-hydroxy-a-oxo-
IH-indole-3-acetamide) or roflumilast.

In another aspect the present invention provides a pharmaceutical product comprising, in
combination, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-
3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(l-methyl-1H-pyrazol-4-
yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the
hemi-fumaric acid salt), and a second active ingredient is roflumilast.

The first active ingredient and the second active ingredient of the pharmaceutical product
of the present invention may be administered simultaneously, sequentially or separately to
treat respiratory diseases. By simultaneously is meant that the active ingredients are in
admixture, or they could be in separate chambers of the same inhaler. By sequential it is
meant that the active ingredients are administered, in any order, one immediately after the
other. They still have the desired effect if they are administered separately, but when
administered in this manner they are generally administered less than 4 hours apart,
conveniently less than two hours apart, more conveniently less than 30 minutes apart and
most conveniently less than 10 minutes apart, for example less than 10 minutes but not one
immediately after the other.
The active ingredients of the present invention may be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. The active ingredients may be delivered to the lung and/or airways via oral administration in the form of a solution, suspension, aerosol or dry powder formulation. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from an adjuvant, carrier, binder, lubricant, diluent, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

In another embodiment the first and second active ingredients are administered via a single pharmaceutical composition (that is, the first and second active ingredients are in admixture). Therefore, the present invention further provides a pharmaceutical composition comprising, in admixture, a first active ingredient which is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof (such as the hemi-fumaric acid salt), and a second active ingredient as defined above. The pharmaceutical composition optionally further comprises a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions of the present invention can be prepared by mixing the first active ingredient with the second active ingredient and a pharmaceutically acceptable adjuvant, diluent or carrier. Therefore, in a further aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition, which comprises mixing the first and second active ingredients and a pharmaceutically acceptable adjuvant, diluent or carrier.

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

In one embodiment of the present invention, the first active ingredient is administered via inhalation. When administered via inhalation the dose of the first active ingredient (that is N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide in: salt form, solvate form, or, solvate of salt form) will generally be in the range of from 0.1 microgram (µg) to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 100 µg, 0.1 to 50 µg, 0.1 to 5 µg, 5 to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 100 µg, 5 to 50 µg, 5 to 10 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 100 µg, 10 to 50 µg, 10 to 5 µg, 50 to 1000 µg, 50 to 100 µg, 50 to 10 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 100 µg, 20 to 50 µg, 20 to 5 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 100 µg, 50 to 10 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In one embodiment of the present invention the second active ingredient is administered by inhalation. When administered via inhalation the dose of the second active ingredient will generally be in the range of from 0.1 microgram (µg) to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 100 µg, 0.1 to 50 µg, 0.1 to 5 µg, 5 to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 100 µg, 5 to 50 µg, 5 to 10 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 100 µg, 10 to 50 µg, 10 to 5 µg, 50 to 1000 µg, 50 to 100 µg, 50 to 10 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 100 µg, 20 to 50 µg, 20 to 5 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 100 µg, 50 to 10 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In another embodiment the present invention provides a pharmaceutical product wherein the molar ratio of first active ingredient to second active ingredient is from 1:1000 to 1000:1, such as from 1:100 to 100:1, for example from 1:50 to 50:1, for example 1:20 to 20:1.
In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient as defined above, and a second active ingredient as defined above, wherein each active ingredient is formulated for inhaled administration. In a further aspect of this embodiment, the pharmaceutical product is in the form of a pharmaceutical composition comprising the first and second active ingredients in admixture, and which composition is formulated for inhaled administration.

The active ingredients of the present invention are conveniently delivered via oral administration by inhalation to the lung and/or airways in the form of a solution, suspension, aerosol or dry powder (such as an agglomerated or ordered mixture) formulation. For example a metered dose inhaler device may be used to administer the active ingredients, dispersed in a suitable propellant and with or without an additional excipient such as ethanol, a surfactant, lubricant or stabilising agent. A suitable propellant includes a hydrocarbon, chlorofluorocarbon or a hydrofluoroalkane (e.g. heptafuoroalkane) propellant, or a mixture of any such propellants, for example in a pressurised metered dose inhaler (pMDI). Preferred propellants are P134a and P227, each of which may be used alone or in combination with other another propellant and/or surfactant and/or other excipient. A nebulised aqueous suspension or, preferably, solution may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulation. A suitable device for delivering a dry powder is Turbuhaler®.

The pharmaceutical product of the present invention can, for example, be administered: via an inhaler having the first and second active ingredients in separate chambers of the inhaler such that on administration the active ingredients mix in either the mouthpiece of the inhaler or the mouth of a patient or both (for simultaneous use); or, where the first and second active ingredients are in separate inhalers, via separate inhalers (for separate or sequential use); or the first and second active ingredients are in admixture in an inhaler when the inhaler is supplied to a patient (for simultaneous use).

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

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

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

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

The present invention further provides the use of a pharmaceutical product according to the invention in the manufacture of a medicament for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis (such as chronic obstructive pulmonary disease or asthma; for example chronic obstructive pulmonary disease).
The present invention still further provides a method of treating a respiratory disease which comprises simultaneously, sequentially or separately administering:
(a) a therapeutically effective dose of a first active ingredient as defined above; and,
(b) a therapeutically effective dose of a second active ingredient as defined above;
to a patient in need thereof.

In a further aspect the present invention provides the use of a pharmaceutical product, kit or composition as hereinbefore described for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis (such as chronic obstructive pulmonary disease or asthma; for example chronic obstructive pulmonary disease).

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly. Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

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 a combination of the invention, as hereinbefore defined, when inhaled, may be in the range from 0.05 micrograms per kilogram body weight (\(^g/kg\)) to 100 micrograms per kilogram body weight (\(^g/kg\)).

A combination of the invention, as hereinbefore defined, may be used on its own but will generally be administered in the form of a pharmaceutical composition in which a combination of the invention, as hereinbefore defined, 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 for example comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, and such as from 0.10 to 50 %w, of active ingredients, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a combination as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

**General Methods**

Unless stated otherwise, starting materials were commercially available; all solvents and commercial reagents were of laboratory grade and were used as received and 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. 'Microwave' heating refers to heating to constant temperature, using variable power microwave irradiation in a CEM Discover® microwave reactor. Hydrogenation reactions were carried out using a Buchi Peteric® system or a ThalesNano H-Cube® system, as detailed. Concentration of all solutions was carried out by evaporation under reduced pressure (*in vacuo*), *e.g.* using a Buchi Rotavapor® rotary evaporator.

Thin Layer Chromatography (TLC) was carried out using aluminium- or glass-backed plates coated with silica (particle size <63 μm; porosity 60 A; surface area -500 m²/g), with a fluorescent (UV 254) indicator. Following elution, the plates were visualized by either UV 254 irradiation, or development with a suitable indicator, such as iodine (pre-absorbed onto silica), an aqueous solution of potassium permanganate, or an aqueous solution of cerium (IV) ammonium nitrate. Examples of indicator preparations can be

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.

Medium pressure liquid chromatography (MPLC) on silica (particle size <63 μm; porosity 60 Å; surface area -500 m²/g) was carried out using pre-packed Biotage FLASH™ columns or equivalent, e.g. Thomson SINGLE StEPTM, Biotage Isolute™, Teledyne Isco RediSep™, or Silicycle UltraPure silica columns at recommended solvent flow rates and sample loadings. Fraction purity was determined by either TLC or analytical HPLC.

Preparative HPLC was carried out using either a Phenomenex Gemini™ C18 5 μm column, a Waters Sunfire™ C18 5 μm column, a Waters XBridge™ C8 5 μm column or a Waters X Terra™ 5 μm, unless otherwise detailed, using either acetonitrile in aqueous 0.1-0.2% trifluoroacetic acid, acetonitrile in aqueous 0.1-0.2% ammonium acetate, or acetonitrile in an aqueous 0.1-0.2% ammonia solution as eluent, as detailed. Fractions were collected following detection by UV spectroscopy at a wavelength such as 220 or 254 nm. Fraction purity was determined by either TLC or analytical HPLC.

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-δ (CDCl₃; δH 7.27 ppm), dimethylsulfoxide-^ (d₆-DMSO; δH 2.50 ppm) or methanol-^ (CD3OD; δH 3.31 ppm), or an internal standard of
tetramethylsilane (TMS; δ_H 0.00 ppm) were used as references. Mass spectra were recorded on an Agilent MSD (+ve and -ve APCI and/or electrospray (e.g. in multimode)) following analytical HPLC.

XRPD was carried out on PANalytical CubiX PRO machine in 0 - 0 configuration over the scan range 2° to 40° 20 with 100-second exposure per 0.02° increment. The X-rays were generated by a copper long-fine focus tube operated at 45kV and 40mA. The wavelength of the copper X-rays was 1.5418 Å. The Data was collected on zero background holders on which ~ 2mg of the compound was placed. The holder was made from a single crystal of silicon, which had been cut along a non-diffracting plane and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction.

DSC thermograms were measured using a TA Q1000 Differential Scanning Calorimeter, with aluminium pans and pierced lids. The sample weights varied between 0.3 to 5mg. The procedure was carried out under a flow of nitrogen gas (50ml/min) and the temperature studied from 25 to 300°C at a constant rate of temperature increase of 10°C per minute.

All other processes were carried out using standard laboratory techniques, e.g. as detailed in 'Experimental Organic Chemistry: Preparative and Microscale' 2nd Ed. (Harwood, L., Moody, C. and Percy, J.), WileyBlackwell, 1998.

The abbreviations or terms used in the Preparations and Examples have the following meanings:

- SCX: Solid phase extraction with a sulfonic acid sorbent
- HPLC: High performance liquid chromatography
- THF: Tetrahydrofuran
- DMF: Dimethylformamide
- NMP: N-Methyl-2-Pyrrolidone
- Triton B: Benzyltrimethylammonium Hydroxide
**Preparation 1**

N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide

**Trifluoroacetic Acid Salt**

**Intermediate 1: 1-(2,4-Dihydroxy-3-nitrophenyl)ethanone**

**Procedure A**

2-Nitrobenzene-1,3-diol (24.5 g) was added portionwise over 15 min to a vigorously stirred solution of aluminium chloride (46.3 g) in nitrobenzene (325 mL). Acetic anhydride (15.65 mL) was then added dropwise to the mixture over a further 15 min and the mixture then heated at 100°C for 5 h. The reaction was cooled to ambient temperature and carefully quenched with ice cold 2M hydrochloric acid (300 mL). The mixture was extracted with ether (2 x 500 mL) and the combined ether extracts then extracted with 2M aqueous...
sodium hydroxide (2 x 400 mL). The combined basic extracts were washed with ether (4 x 500 mL) and then acidified to pH 1 with 2M hydrochloric acid (700 mL). The resulting precipitate was filtered off, washed with water, and dried under vacuum at 40°C to afford the subtitled compound as a yellow/brown solid (29.5 g).

**Procedure B**

Nitrobenzene (87.5 mL) was added to aluminium trichloride (46.33 g). 2-nitroresorcinol (25 g), in nitrobenzene (112.5 mL) was added. The mixture was cooled to 5°C and acetic acid anhydride (15.68 mL) added maintaining the internal temperature below 20°C. The mixture was heated to 100°C for 2 h then cooled to 5°C. Cold (3°C) 3 M aqueous hydrogen chloride (200 mL) was charged. The mixture was heated to 20°C then di-isopropylether (200 mL) charged. The aqueous phase was removed and the organic phase extracted with 2 M aqueous sodium hydroxide (200 mL). The aqueous phase was washed with di-isopropylether (200 mL). The aqueous phase was removed and heated to 50°C. 3 M aqueous hydrogen chloride (467.5 mL) was charged and the mixture cooled to 20°C. The suspension was filtered, washed with water (50 mL) and dried under vacuum to yield the title compound (31.14 g).

In order to improve the final filtration, the following modification may be used: after the di-isopropylether wash, the aqueous phase may added to an identical quantity of pre-heated (50°C) 3 M aqueous hydrogen chloride. On cooling to 20°C the suspension may be filtered to yield the sub-titled compound.

**Procedure C**

2-Nitro-1,3-dihydroxybenzene (10 g) was slurried in methanesulfonic acid (41 mL). After stirring for 25 minutes, acetic acid anhydride (9 mL) was charged over 30 minutes. The reaction was stirred for 25.5 hours then diluted with acetic acid (10 mL) and then charged dropwise to pre-heated (50°C) water (200 mL). The reaction was rinsed through with acetic acid (12 mL). Further acetic acid (9 mL) was charged. The temperature was adjusted
to 60°C and then set to cool to 35°C over 42 minutes. Water (10 mL) was charged and the mixture reheated to 55°C then set to cool to 0°C over 200 minutes.

After 13.5 hours the reaction was filtered under vacuum and washed with water (120 mL) then dried under vacuum at 40°C to constant weight to afford the subtitled compound (10.75 g).

**Intermediate 2: 1-(4-(Benzyloxy)-2-hydroxy-3-nitrophenyl)ethanone**

![Chemical Structure](attachment:image.png)

**Procedure A**

Lithium tert-butoxide (4.06 g) was added to a stirred solution of 1-(2,4-dihydroxy-3-nitrophenyl)ethanone (10 g) in DMF (100 mL), under nitrogen, whilst maintaining the internal temperature below 30°C. After stirring for a further 10 min at ambient temperature, benzyl bromide (6.03 mL) was added and the mixture stirred for a further 20 h. Further benzyl bromide (3 mL) was added and the mixture stirred for 24 h. The reaction was quenched with water (300 mL), 1M aqueous sodium hydroxide (50 mL) was added and the mixture was washed with ether (2 x 300 mL), filtering through Celite to aid separation. The basic solution was cooled in ice/water, acidified with ice cold 2M hydrochloric acid (200 mL) and the resulting precipitate filtered off, washed with water and dried to afford a light brown solid. The solid was slurried with ethanol (100 mL) for 1 h and the solid filtered off, washed with cold ethanol (20 mL), and dried under vacuum at 40°C to afford the subtitled compound as a light brown solid (6.8 g).

**1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.45 - 7.32 (m, 5H), 7.01 (d, J = 9.2 Hz, 1H), 5.42 (s, 2H), 2.64 (s, 3H).**

**Procedure B**

Acetonitrile (700 mL) was added to the product of Intermediate 1 (Procedure B) (100 g) and sodium bicarbonate (49.0 g). The mixture was heated to 60°C and benzyl bromide
(75.62 mL) added. The mixture was heated to reflux. After 6.5 h the mixture was cooled to 60°C and water (450 mL) added. The mixture was cooled to below 45°C and methyl tert-butyl ether (450 mL) added. The mixture was cooled to 20°C and stirred for at least 1.5 hours. The suspension was filtered and washed with water (250 mL) then ethanol (250 mL) to yield the title compound as a damp solid, 155.65 g. Alternatively the material can be dried under vacuum.

**Intermediate 3: l-(3-Amino-4-(benzyloxy)-2-hydroxyphenyl)ethanone**

![Chemical Structure](image)

### Procedure A

Zinc dust (5.5 g) was added portionwise to a suspension of l-(4-(benzyloxy)-2-hydroxy-3-nitrophenyl)ethanone (5.5 g) in acetic acid (55 mL) over 15 min, whilst maintaining the internal temperature below 40 °C with an ice bath. The mixture was allowed to attain ambient temperature and stirred for a further 2 h. The mixture was filtered through Celite (caution gets hot, do not allow to dry), washed with acetic acid, and the filtrate poured onto ice/water (500 mL). The resulting precipitate was filtered off, washed with water, and dried under vacuum at 40°C to afford the subtitled compound as a light brown solid (4.8 g).

**H NMR** (300 MHz, DMSO-d6) δ 7.53 (m, 2H), 7.48 - 7.33 (m, 3H), 7.28 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 5.29 (s, 2H), 2.59 (s, 3H).

### Procedure B

Tetrahydrofuran (1000 mL) and triethylamine (9.70 mL) were added to the product of Intermediate 2 (Procedure B) (100 g) and platinum on carbon (1%; Johnson-Matthey Type 18MA) (6 g). The mixture was hydrogenated at 50°C and 4 barg until complete then cooled to 20°C and filtered. The mixture was concentrated under vacuum to approximately half the initial volume then methyl isobutyl ketone (500 mL) was charged. The mixture was concentrated under vacuum to half the initial volume then methyl isobutyl ketone (500
mL) was charged. The resulting mixture can be directly used in the next step or evaporated to dryness to afford the sub-titled compound as a brown solid.

**Intermediate 4: 8-Acetyl-5-(benzyloxy)-2H-benzo[b][1,4]oxazin-3(4H)-one**

![Chemical structure of Intermediate 4](image)

**Procedure A**

2-Chloroacetyl chloride (1.77 mL) was added dropwise to a stirred mixture of 1-(3-amino-4-(benzyloxy)-2-hydroxyphenyl)ethanone (5.2 g) and sodium hydrogen carbonate (3.74 g) in DMF (30 mL) and then stirred for a further 2 h. Cesium carbonate (7.90 g) was added and heated at 100°C for 20 h. The mixture was cooled to ambient temperature, quenched with water (500 mL), extracted with ethyl acetate (2 x 200 mL), washed with water (3 x 300 mL) and brine, dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The solid residue was treated with ether, filtered and dried to afford the subtitled compound as a beige solid (5.7 g).

1H NMR (400 MHz, DMSO-d6) δ 10.33 (s, 1H), 7.55 (m, 2H), 7.39 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.33 (m, 1H), 6.89 (d, J = 9.2 Hz, 1H), 5.27 (s, 2H), 4.67 (s, 2H), 3.32 (s, 3H).

**Procedure B**

To the product of Intermediate 3 (Procedure B) (62.69 g, prepared as in Step iii), in methyl iso-butyl ketone 414 mL was charged methyl isobutyl ketone (150 mL).Potassium bicarbonate was charged and the mixture heated to 50°C then chloro-acetyl chloride (21.30 mL) in methyl isobutyl ketone (62.69 mL) was charged. After 30 min, further chloro-acetyl chloride (3.87 mL) was charged. After a further 30 min chloro-acetyl chloride (3.87 mL) was charged. After 15 min potassium bicarbonate (60.98 g) in water (344.79 mL) was added. The mixture was heated at reflux for 2 h then cooled to 19°C. The suspension was filtered and the residue washed with water (94.04 mL), then ethanol (94.04 mL) and then dried under vacuum to yield the sub-titled compound (58.4 g).
Intermediate 5: 5-(Benzyloxy)-8-(2-chloroacetyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

Procedure A

Benzyltrimethylammonium dichloroiodate (14.17 g) was added to a stirred solution of 8-acetyl-5-(benzyloxy)-2H-benzo[b][1,4]oxazin-3(4H)-one (5.5 g) in a mixture of dichloromethane (100 mL), acetic acid (33 mL) and water (5.5 mL) and the reaction mixture stirred at 65°C for 20 h. The reaction was cooled to ambient temperature, treated with aqueous sodium bisulphite (5.78 g in 100 mL) and stirred for a further 30 min. The mixture was diluted with diethyl ether (200 mL) and the resulting solid filtered off, washed with water and further diethyl ether, and dried under vacuum at 40°C to afford the subtitled compound as a light brown solid (5.6 g).

$^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.41 (s, 1H), 7.55 (m, 2H), 7.44 (d, J = 9.4 Hz, 1H), 7.39 (m, 2H), 7.32 (m, 1H), 6.95 (d, J = 9.4 Hz, 1H), 5.30 (s, 2H), 4.96 (s, 2H), 4.69 (s, 2H).

Procedure B

To the product from Intermediate 4 (Procedure B) (23 g) and benzyltrimethylammonium dichloroiodate (53.85 g) was added ethanol (230 mL). The mixture was heated at reflux for 1 h then cooled to 50°C and water (230 mL) added. The mixture was cooled to 20°C and stirred for at least 1 h. The suspension was filtered, washed with water (46 mL) and then ethanol (69 mL). To the damp solid was added ethyl acetate (460 mL). The mixture was heated at reflux for 1 h then cooled to 20°C and stirred for at least 1 h. The suspension was filtered and the residue was washed with ethyl acetate (115 mL) and dried under vacuum to yield the sub-titled compound (61.0 g).
Intermediate 6: 8-(2-Azidoacetyl)-5-(benzyloxy)-2H-benzo[b][1,4]oxazin-3(4H)-one

Procedure A
Sodium azide (1.18 g) was added to a suspension of 5-(benzyloxy)-8-(2-chloroacetyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4.8 g) in DMF (50 mL) and stirred for 2 h. The mixture was poured onto ice/water and the resulting solid filtered off, washed with water and dried under vacuum at 40°C to afford the subtitled compound as a light brown solid (4.6 g).

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 10.42 (s, 1H), 7.55 (m, 2H), 7.48 (m, 1H), 7.43 - 7.29 (m, 3H), 6.97 (m, 1H), 5.31 (s, 2H), 4.69 (s, 2H), 4.63 (s, 2H).

Procedure B
To the product from Intermediate 5 (Procedure B) (101.0 g) was added N-methylpyrrolidone (303 mL). To the mixture was added sodium azide (29.69 g). The mixture was stirred at 20°C for 3 h then added into water (1820 mL). A line wash of N-methylpyrrolidone (10.10 mL) was added and the mixture stirred for at least 30 min. The suspension was filtered, washed with water (505 mL), isopropyl alcohol (202 mL) and then dried to afford the sub-titled compound (96.064 g).

Intermediate 7: 8-(2-Aminoethyl)-5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride

Procedure A
A slurry of 10% palladium on carbon (1 g) in acetic acid (20 mL) was added to a partial solution of 8-(2-azidoacetyl)-5-(benzyloxy)-2H-benzo[b][1,4]oxazin-3(4H)-one (5.65 g) in
acetic acid (280 mL). Concentrated hydrochloric acid (14.34 mL) was then added, and the mixture hydrogenated at 5 bar for 6 h. Water (50 mL) was added to dissolve any solid, followed by further 10% palladium on carbon (1 g) and the mixture hydrogenated at 5 bar for a further 20 h. Further 10% palladium on carbon (1 g) was added and the mixture hydrogenated for a further 20 h. The mixture was filtered through Celite and the filtrate evaporated under vacuum, and azeotroped with acetonitrile. The solid residue was treated with ether, isolated by filtration and dried to afford the subtitled compound as a white solid (2-2 g).

**Procedure B**

Acetic acid (45 mL), concentrated hydrochloric acid (10.2 mL) and water (45 mL) were added to a hydrogenation vessel containing 8-(2-azidoacetyl)-5-(benzylxylo)-2H-benzo[b][1,4]oxazin-3(4H)-one (5 g) and 10% palladium on carbon (2.5 g) to give a slurry. The mixture was hydrogenated at 4.7 bar and 25°C for 2 h 20 min to give a partial solution. The solution was then warmed to 40°C and hydrogenated at 4.7 bar for 68 h. The mixture was filtered through GF/F filter paper and the filtrate evaporated to 50 mL. 1-Butanol (50 mL) was added and the solution re-evaporated to 50 mL. 1-Butanol (50 mL) was added to give a suspension and this re-evaporated to 50 mL to give a suspension which was stirred at ambient temperature for 2 h then filtered, washed with 1-butanol (2.5 mL) and dried in a vacuum oven at 55°C overnight to afford the sub-titled compound as a white solid (3.2 g).

**H NMR (300 MHz, DMSO-d6)** δ 9.94 (s, 1H), 9.87 (s, 1H), 7.99 - 7.82 (m, 3H), 6.66 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 4.54 (s, 2H), 2.91 (m, 2H), 2.76 (m, 2H).

**Procedure C**

To the product from Intermediate 6 (Procedure B) (5 g), palladium on carbon (60% moisture, Johnson-Matthey 10R39) (2.5 g) was added acetic acid (45.0 mL), 36 wt% aqueous hydrogen chloride (10.21 mL) and water (45.0 mL). The mixture was hydrogenated at 22-25°C, 4.7 barg until 1 mole of hydrogen had been consumed. The reaction was then hydrogenated at 45°C, 4.7 barg until complete then cooled to 22°C and filtered. The solution was concentrated under vacuum by removal of approximately two-thirds of the solvent. 1-butanol (50 mL) was charged and the solution concentrated under
vacuum by removal of approximately half the solvent. 1-butanol (50 mL) was charged and the mixture concentrated under vacuum by removal of approximately half the solvent. The mixture was cooled to 20°C and stirred for at least 3 h. The suspension was filtered and the residue washed with 1-butanol (2.5 mL) and dried to yield the sub-titled compound (2.90 g).

**Intermediate 8: N-(2,2-Dimethoxyethyl)cyclohexanamine**

![Structure](image)

2-Chloro-1,1-dimethoxyethane (206 mL) was treated with cyclohexanamine (575 mL) and the mixture was heated at 120°C for 24 h under an atmosphere of nitrogen before being cooled to room temperature. A solution of sodium hydroxide (100g) in 400 mL water was added, the mixture was stirred at room temperature for 10 min and then the layers were separated. The organic fraction was purified by distillation under reduced pressure (b.p. 105-107 °C, 13mm Hg) to give the title compound as a colourless oil (280 g).

**H NMR** (400 MHz, CDCl₃) δ 4.46 (t, J = 5.5 Hz, 1H), 3.38 (s, 6H), 2.75 (d, J = 5.6 Hz, 2H), 2.45 - 2.35 (m, 1H), 1.92 - 1.57 (m, 5H), 1.31 - 1.00 (m, 6H).

**Intermediate 9: tert-Butyl 3-(3-bromophenethoxy)propanoate**

A solution of 2-(3-bromophenyl)ethanol (5 g) was stirred in toluene (30 mL) followed by the addition of Triton B in methanol (0.57 mL). The volatiles were removed until ~10 mL remained. To this solution was added tert-butyl acrylate (3.94 mL) and the mixture was left to stir for 24 h. The solvent was evaporated and the residue was purified on silica eluting with isohexane-10% ethyl acetate/isohexane. The solvent was evaporated to afford the sub-titled compound as a colourless oil (6.7 g).
H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.39 - 7.30 (m, 2H), 7.17 - 7.12 (m, 2H), 3.68 (t, $J = 6.5$ Hz, 2H), 3.64 (t, $J = 6.9$ Hz, 2H), 2.84 (t, $J = 6.9$ Hz, 2H), 2.48 (t, $J = 6.5$ Hz, 2H), 1.44 (t, 9H)

**Intermediate 10: 3-(3-Bromophenethoxy)propanoic acid**

![Intermediate 10 Structure]

To tert-butyl 3-(3-bromophenethoxy)propanoate (6.7 g) in DCM (10 mL) was added TFA (10 mL). The mixture was stirred overnight before the solvent was evaporated under vacuum. The residue was azeotroped twice with toluene to afford a colourless oil (5.63 g). This material was used in the next step directly.

H-NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.46 (s, 1H), 7.39 (m, 1H), 7.24 (m, 2H), 3.60 (t, 2H), 3.58 (t, 2H), 2.79 (t, 2H), 2.42 (t, 2H)

**Intermediate 11: 3-(3-Bromophenethoxy)-N-cyclohexyl-N-(2,2-dimethoxyethyl)propanamide**

![Intermediate 11 Structure]

To a stirred solution of 3-(3-bromophenethoxy)propanoic acid (3.3 g) in acetonitrile (60 mL) was added TEA (20.21 mL) and N-(2,2-dimethoxyethyl)cyclohexanamine (Intermediate 8) (2.26 g). T3P (1.56 M in THF, 15.39 mL) was then added portionwise. The reaction was stirred overnight, and then worked up by the addition of saturated sodium hydrogen carbonate, which was extracted twice with ethyl acetate. The pooled organics were washed once with water, once with brine, dried over sodium sulphate, filtered and the solvent removed to afford a brown oil, which was purified on silica (5% Ethyl acetate/isohexane to 20% Ethyl acetate/isohexane). The solvent was evaporated to afford an orange oil (4.5 g).

MS [M+H-MeOH]$^+$ = 410/412 (MultiMode+)
H NMR (400 MHz, CD$_2$OD) δ 7.40 - 7.35 (m, 1H), 7.33 - 7.29 (m, 1H), 7.20 - 7.12 (m, 2H), 4.54 (t, J = 5.0 Hz, 0.5H), 4.39 (t, J = 5.4 Hz, 0.5H), 4.08 - 3.98 (m, 1H), 3.73 - 3.59 (m, 4H), 3.39 - 3.36 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 2.83 - 2.78 (m, 2H), 2.67 - 2.61 (m, 2H), 1.82 - 1.74 (m, 2H), 1.70 - 1.55 (m, 3H), 1.55 - 1.42 (m, 2H), 1.38 - 1.26 (m, 2H), 1.19 - 1.04 (m, 1H), a ~1:1 mixture of rotamers is observed.

Intermediate 12: N-Cyclohexyl-N-(2,2-dimethoxyethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide

![Chemical Structure]

To 3-(3-bromophenethoxy)-N-cyclohexyl-N-(2,2-dimethoxyethyl)propanamide (1.4 g), within a 35 mL microwave tube with stirrer were added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.92 g), potassium carbonate (0.88 g) and Pd(Ph$_3$P)$_4$ (0.18 g) followed by methanol (8 mL). The vial was sealed and heated within a CEM Discover microwave at 100°C for 15 min. The mixture was diluted with DCM and washed once with water, once with brine, dried over sodium sulphate and the solvent evaporated to afford crude material as an orange oil. This was purified on silica using ethyl acetate as the eluent to afford the product (1.52 g).

MS [M+H-MeOH]+ = 412 (MultiMode+)

H NMR (400 MHz, CD$_2$OD) δ 7.92 (s, 1H), 7.78 and 7.77 (2 x s, 1H), 7.40 - 7.32 (m, 2H), 7.23 and 7.22 (2 x t, J = 7.6 Hz, 1H), 7.07 - 7.03 (m, 1H), 4.52 and 4.36 (2 x t, J = 5.3 Hz, 1H), 4.05 - 3.95 and 3.69 - 3.60 (2 x m, 1H), 3.901 and 3.898 (2 x s, 3H), 3.75 - 3.64 (m, 4H), 3.34 (s, 3H), 3.32 (s, 3H), 3.34 and 3.25 (2 x d, J = 5.1 Hz, 2H), 2.84 and 2.83 (2 x t, J = 6.6 Hz, 2H), 2.65 and 2.63 (2 x t, J = 6.1 Hz, 2H), 1.79 - 1.04 (m, 10H); a ~1:1 mixture of rotamers is observed.
Intermediate 13: N-Cyclohexyl-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)-N-(2-oxoethyl)propanamide

N-Cyclohexyl-N-(2,2-dimethoxyethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (0.5 g) was stirred in DCM (10 mL) followed by the addition of p-toluenesulfonic acid monohydrate (0.43 g). The mixture was stirred for 1 h. Ethyl acetate was added followed by sodium hydrogen carbonate solution. The aqueous phase was removed and the remaining organic phase washed once with water, once with brine, dried over sodium sulphate, filtered and the solvent removed to afford the desired material as an oil (0.48 g). This material was used directly as prepared.

MS [M+H]+ = 398 (MultiMode+)

Intermediate 14: 3-(3-Bromophenethoxy)-N-cyclohexyl-N-(2-oxoethyl)propanamide

To a stirred solution of 3-(3-bromophenethoxy)-N-cyclohexyl-N-(2,2-dimethoxyethyl)propanamide (Intermediate 11) (1.5 g) in acetone (30 mL) was added 2M hydrochloric acid (15 mL). The mixture was stirred for 2 h before the solvent was removed under vacuum, followed by the addition of water. The aqueous phase was extracted three times with DCM and the pooled DCM was washed once with brine, dried over sodium sulphate, filtered and the solvent removed to afford the desired material (1.5 g). This material was used in the next step directly.
Intermediate 15: tert-Butyl 2-(3-(3-bromophenethoxy)-N-cyclohexylpropanamido)ethyl(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethyl)carbamate

To a stirred solution of 3-(3-bromophenethoxy)-N-cyclohexyl-N-(2-oxoethyl)propanamide (1.5 g) in NMP (10 mL) and water (0.5 mL) was added 8-(2-aminoethyl)-5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (Intermediate 7) (1.02 g) and sodium bicarbonate (0.35 g). The mixture was stirred for 5 min before the addition of sodium triacetoxylborohydride (1.20 g). The reaction was stirred overnight before the addition of sodium hydrogen carbonate solution, which was then extracted three times with DCM. The mixture was evaporated to afford the product in NMP, which was diluted with 50 mL of DCM followed by the addition of BOC anhydride (0.88 mL) and triethylamine (0.53 mL). The reaction was stirred overnight before the addition of water, which was extracted once with DCM. The DCM phase was washed twice with water, twice with brine, dried over sodium sulphate, filtered and the solvent removed to afford product contaminated with NMP. Ethyl acetate was added which was subsequently washed twice with water, twice with brine, dried over sodium sulphate, filtered and the solvent removed. The crude product was purified on silica using 40% Ethyl acetate/isohexane to afford a pale brown/yellow oil (700 mg), which consisted of a mixture of mono and di-protected material. This material was used in the next step without further purification.

N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide

Trifluoroacetic Acid Salt
Procedure A

To a stirred solution of N-cyclohexyl-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)-N-(2-oxoethyl)propanamide (Intermediate 13) (448 mg) in NMP (10 mL) and water (0.5 mL) was added 8-(2-aminoethyl)-5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (Intermediate 7) (303 mg) and sodium bicarbonate (104 mg). The mixture was stirred for 5 min before the addition of sodium triacetoxyborohydride (358 mg). The reaction was stirred overnight before the addition of sodium hydrogen carbonate solution, which was extracted three times with DCM. The solvents were removed under vacuum from the pooled organics followed by the addition of ethyl acetate (100 mL), water (50 mL), sodium bicarbonate followed by BOC anhydride. The reaction was stirred overnight before the layers were separated and the aqueous layer extracted once more with ethyl acetate. The pooled organics were washed once with water, once with brine, dried over sodium sulphate, filtered and the solvent removed to afford crude product, which was purified on silica twice using ethyl acetate. The solvent was removed to afford 200 mg of a mixture of mono-protected and di-protected material. The mixture was taken up in diethyl ether (20 mL) followed by the addition of 4M Hydrochloric acid in dioxane (2 mL), which caused a white solid to form instantly. Diethyl ether (50 mL) was added and the mixture stirred overnight. The solvent was removed, the residue taken up in DCM (20 mL) followed by the addition of 4M Hydrochloric acid in dioxane (4 mL) and stirred overnight. The solvent was removed under vacuum to afford the titled compound (180 mg). This material was basified with sodium hydrogen carbonate solution, which was extracted three times with DCM. The pooled organics were acidified with 0.5 mL of TFA and volatiles removed to afford the TFA salt. This material was purified by reverse phase prep HPLC (Gemini column using 0.2% TFA/ acetonitrile as the eluent) to afford the titled compound as a TFA salt.

MS [M+H]+ = 590 (MultiMode+)

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.89 (s, 1H), 7.77 - 7.75 (m, 1H), 7.39 - 7.37 (m, 1H), 7.35 - 7.31 (m, 1H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.06 - 7.03 (m, 1H), 6.69 (d, $J$ = 8.2 Hz, 1H), 6.47 (d, $J$ = 8.5 Hz, 1H), 4.60 (s, 2H), 3.89 (s, 3H), 3.74 - 3.67 (m, 5H), 3.51 - 3.45 (m, 2H),
3.12 - 3.07 (m, 2H), 3.04 - 2.99 (m, 2H), 2.88 - 2.82 (m, 4H), 2.63 (t, J = 6.0 Hz, 2H), 1.81 - 1.74 (m, 2H), 1.70 - 1.59 (m, 3H), 1.46 - 1.26 (m, 4H), 1.17 - 1.04 (m, 1H)

Procedure B

To tert-butyl 2-(3-(3-(3-bromophenethoxy)-N-cyclohexylpropanamido)ethyl(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethyl)carbamate (Intermediate 15) (500 mg) in a 35 mL microwave vial was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (181 mg), potassium carbonate (201 mg) and Pd(Ph$_3$P)$_4$ (42 mg) in ethanol (10 mL). The vial was sealed and heated at 110 °C within a Discover microwave for 40 min with stirring. The reaction was cooled followed by the addition of ethyl acetate, which was washed once with water, once with brine, dried over sodium sulphate and the solvent removed. The residue was purified on silica using neat ethyl acetate to afford the protected product (250 mg). This material was taken up in DCM followed by the addition of 4M hydrochloric acid in dioxane and stirred overnight. The solvent was removed under vacuum to afford of crude material (330 mg). This was basified with sodium hydrogen carbonate solution, which was extracted three times with DCM. The pooled organics were acidified with 0.5 mL of TFA and the solvent removed to afford the titled compound as a TFA salt.

Preparation 2

N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide Hemi-Fumaric Acid Salt

Intermediate 1: tert-Butyl 3-(3-bromophenethoxy)propanoate
A solution of 2-(3-bromophenyl)ethanol (98.9 g) and tert-butyl acrylate (88.9 mL) in toluene (197.8 mL) was warmed to 50°C. Triton B (as a 40% solution in water, 96.3 mL) was added over 4 h at 50°C and then the mixture stirred overnight at 20°C. The mixture was diluted with toluene (395.6 mL) and washed with 3M hydrochloric acid (395.6 mL) and the layers separated. The organic layer was used directly in the next Step.

Intermediate 2: 3-(3-Bromophenethoxy)propanoic acid

![Intermediate 2](image)

p-Toluenesulfonic acid monohydrate (9.2 g) was added to the solution of tert-butyl 3-(3-bromophenethoxy)propanoate (132 g) in toluene (-590 mL) from the previous Step. The solution was heated to reflux and at reflux for 1.5h then allowed to cool to 20°C. 2-Methyltetrahydrofuran (197.8 mL) was added and the solution extracted with water (194.4 mL) and 1M sodium hydroxide (725.3 mL). The separated aqueous layer was diluted with 2-methyltetrahydrofuran (593.4 mL), extracted with 3M hydrochloric acid (483.5 mL) and the layers separated. The separated organic layer can be evaporated to dryness to afford the sub-titled compound as a colourless oil (99.6 g) or the solution used directly in the next Step.

Intermediate 3: 3-(3-(1-Methyl-1H-pyrazol-4-yl)phenethoxy)propanoic acid

![Intermediate 3](image)

2-Methyltetrahydrofuran (142.1 mL) was added to Pd-118 (4.52 g) to give a red solution. To this solution was added a solution of sodium hydroxide (41.6 g) in water (473.5 mL), followed by a solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (81.81 g) in 2-methyltetrahydrofuran (142.1 mL), followed by the solution of 3-(3-bromophenethoxy)propanoic acid (94.7 g) in 2-methyltetrahydrofuran (585 mL solution volume) from the previous step. The mixture was then heated to reflux and at reflux for 30 min then allowed to cool to 20°C. The mixture was filtered through GF/F filter paper then the layers separated. 20% w/w Citric acid (568.2 mL) was added to the separated aqueous
layer, followed by 2-methyltetrahydrofuran (568.2 mL). After mixing, the layers were separated, the organic layer diluted with 2-methyltetrahydrofuran (to make the solution up to 950 mL) and filtered to give a small sample of the subtitled compound as an off-white solid (5.63 g). 800 mL of the filtrate (total volume 930 mL) was passed through a cartridge filter containing charcoal. The solution was partially evaporated under vacuum to give a solution measuring 490 mL and split into 2 portions. Firstly half of the solution was cooled to 20°C and added to dibutyl ether (400 mL) at 20°C to give a precipitate which was stirred at 20°C for 2 h. The suspension was filtered, washed with dibutyl ether (100 mL) and dried at 50°C under vacuum to afford the subtitled compound (34.1 g). The second half of the solution was added to dibutyl ether (400 mL) at 65°C to give a precipitate which was maintained at 65°C for 10 min then cooled to 15°C and stirred for 1 h. The suspension was filtered, washed with dibutyl ether (100 mL) and dried at 50°C under vacuum to afford the subtitled compound as a white solid (30.5 g).

MS [M+H]+ = 275.2 (MultiMode+)

**NMR (400 MHz, DMSO-d6) δ**

12.15 (s, 1H), 8.09 (s, 1H), 7.83 (s, 1H), 7.43 (s, 1H), 7.37 (d, 1H), 7.24 (t, 1H), 7.05 (d, 1H), 3.86 (s, 3H), 3.62 (t, 2H), 3.61 (t, 2H), 2.80 (t, 2H), 2.45 (t, 2H).

**Intermediate 4:** N-Cyclohexyl-N-(2,2-dimethoxyethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide

A solution of N-(2,2-dimethoxyethyl)cyclohexanamine (Preparation 1, Intermediate 8) (21.5 g) in tetrahydrofuran (30 mL) was added to a solution of 3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanoic acid in tetrahydrofuran (105 mL) at 20°C. Tetrahydrofuran (15 mL) was added, followed by triethylamine (51.8 mL), followed by a solution of T3P in tetrahydrofuran (121.9 mL of a 1.62M solution). The solution was stirred at 20°C for 1 h then cooled to 10°C. Pre-chilled (10°C) 0.5M sodium bicarbonate solution (225 mL) was
added, followed by iso-propyl acetate (150 mL). After mixing the layers were separated and the organic layer washed with 20% w/w sodium chloride solution (150 mL), then evaporated to dryness to afford the subtitled compound as a brown oil (48.6 g).

MS \([\text{M+H-\text{MeOH}}]^+ = 412.20\) (100%) (MultiMode+)

\[\text{[M+H]^+} = 444.20\] (MultiMode+)

H NMR (300 MHz, CDC\textsubscript{3}) \(\delta\) 7.75 (s, 1H), 7.62 (s, 1H), 7.33 - 7.23 (m, 3H), 7.10 - 7.03 (m, 1H), 4.61 (t, 0.7H), 4.36 (t, 0.3H), 3.94 (s, 3H), 3.79 (q, 2H), 3.69 (q, 2H), 3.62 - 3.43 (m, 1.5H), 3.40 (s, 3H), 3.38 (s, 3H), 3.30 (d, 1.5H), 2.89 (q, 2H), 2.69 (quintet, 2H), 1.86 - 0.99 (m, 10H); approx: 2:1 ratio of rotamers

**Intermediate 5: N-Cyclohexyl-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)-N-(2-oxoethyl)propanamide**

A solution of N-cyclohexyl-N-(2,2-dimethoxyethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (50.3 g) in tetrahydrofuran (150.9 mL) was added to a solution of p-toluenesulfonic acid monohydrate (86.3 g) in tetrahydrofuran (100.1 mL) at 20°C to give a solution. A line wash of tetrahydrofuran (50.3 mL) was then added and the solution stirred at ambient temperature for 1 h before being added to a solution of sodium hydroxide (19.6 g) and sodium chloride (100.6 g) in water (502.9 mL) at <5°C. A line wash of tetrahydrofuran (25.1 mL) was then added and the solution warmed to 20°C. 1-Butanol (100.6 mL) was added and the layers separated. The separated organic layer can be evaporated to dryness to afford the sub-titled compound as an orange/brown oil or the solution used directly in the next Step.

MS \([\text{M+H}^+] = 398.2\) (MultiMode+)
N-Cyclohexyl-N(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide Hemi-Fumaric Acid Salt.

A solution of N-cyclohexyl-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)-N-(2-oxoethyl)propanamide (assume 45.1 g) in tetrahydrofuran/l-butanol (~480 mL), prepared by the method described in the previous step was added to 8-(2-aminoethyl)-5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (Preparation 1, Intermediate 7) (25.0 g), washing in with tetrahydrofuran (25.1 mL). Water (221.3 mL) was added, followed by palladium hydroxide on carbon (10.1 g of 20% w/w palladium on carbon). The mixture was hydrogenated at 2 bar of hydrogen and 20°C for 26.5 h then filtered to remove the catalyst. Methyl isobutyl ketone (251.4 mL) was added and the layers separated. The separated organic layer was washed 3 times with 10% w/w aqueous potassium bicarbonate (3 x 251.4 mL) and then twice with water (2 x 251.4 mL) before being filtered through a ¥μη filter. A solution of fumaric acid (3.7 g) in isopropanol/water (111 mL of a 10 vol% solution of isopropanol in water) was then added at 20°C, the resulting solution seeded with N-cyclohexyl-N(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide hemifumaric acid salt (25 mg) and stirred at ambient temperature for 2.15 h to give a precipitate which was filtered, washing with tetrahydrofuran (251.4 mL) and dried at 50°C under vacuum to afford the subtitled compound as a white solid (32.6 g).

MS [M+H]+ = 590.20 (MultiMode+)

H NMR (400 MHz, CD3OD) δ 7.89 (s, IH), 7.78 (s, IH), 7.38 (s, IH), 7.33 (d, IH), 7.23 (t, IH), 7.05 (d, IH), 6.70 (m, 2H, includes 2H of fumaric acid), 6.47 (d, IH), 4.60 (s, 2H), 3.88 (s, 3H), 3.76 - 3.64 (m, 5H), 3.48 (t, 2H), 3.08 (t, 2H), 3.00 (t, 2H), 2.88 - 2.82 (m, 4H), 2.63 (t, 2H), 1.82 - 1.58 (m, 4H), 1.48 - 1.24 (m, 5H), 1.18 - 1.05 (m, IH); approx: 5.2:1 ratio of rotamers
Solid State Data for Preparation 2

N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide Hemi-Fumaric Acid Salt (XRPD - see Figure 1)

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Accuracy - +/- 0.1° 20
A portion of the hemi-fumarate from Preparation 2 (35.46 g) was suspended in 2-methyltetrahydrofuran (177 mL) and ethanol (18 mL) at ambient temperature. To this suspension was charged a solution of potassium carbonate (11.4 g) in water (106 mL). After stirring at ambient temperature for 60 min the reaction was transferred to a separating funnel and the lower aqueous removed to yield the title compound as a solution in 2-methyltetrahydrofuran (226 mL).
Preparation 4

N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide phosphate

To 14 mL of the 2-methyltetrahydrofuran solution from Preparation 3 was charged phosphoric acid (0.26 mL) to yield a biphasic mixture. After 30 min the mixture was charged to stirred tert-butyl methyl ether (20 mL) to yield an oil. After a further 60 min ethanol (2.5 mL) was added. After 19 hours further tert-butyl methyl ether (20 mL) was charged to the precipitated mixture. After 27 days the solid was filtered and washed with tert-butyl methyl ether (25 mL) and dried to a weight of 1.944 g.

Preparation 5

N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide 2-napthalenesulfonate

To 14 mL of the 2-methyltetrahydrofuran solution from Preparation 3 was charged to 2-napthalenesulfonic acid hydrate (0.86 g) to yield a clear solution. After 30 min the mixture was charged to stirred tert-butyl methyl ether (20 mL) to yield an oil. After a further 60 min ethanol (2.5 mL) was added. After 19 hours further tert-butyl methyl ether (20 mL) was charged. After overnight stirring the organic solvent was decanted away from the oil and both retained. The oil was dissolved in methanol (10 mL) and acetonitrile (10 mL) and charged to tert-butyl methyl ether (20 mL) to yield an oil and the retained decanted organic solvent recharged. After 3 days the solvent was allowed to evaporate. After 6 further days ethyl acetate (50 mL) was charged to the concentrate. After 2 further days additional ethyl acetate (40 mL) was charged. After 14 days the solid was filtered and washed with ethyl acetate (25 mL) and dried to a weight of 2.305 g.
**Preparation 6**

**N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide 2-naphthalene-1,5-disulfonate**

To 14mL of the 2-methyltetrahydrofuran solution in Preparation 3 was charged to 2-naphthalene-1,5-disulfonic acid tetrahydrate (0.68 g) to yield a clear solution. After 30 min the mixture was charged to stirred tert-butyl methyl ether (20 mL) to yield an oil. After a further 60 min ethanol (2.5 mL) was added. After 19 hours further tert-butyl methyl ether (20 mL) was charged. After overnight stirring the organic solvent was decanted away from the oil and both retained. The oil was dissolved in methanol (10 mL) and acetonitrile (10 mL) and charged to tert-butyl methyl ether (20 mL) to yield an oil and the retained decanted organic solvent recharged. After 3 days the solvent was allowed to evaporate. After 6 further days ethyl acetate (50 mL) was charged to the concentrate. After 16 days the solid was filtered and washed with ethyl acetate (25 mL) and dried to a weight of 2.546g.

**H NMR** (500 MHz, DMSO) δ 8.86 (d, J = 8.6 Hz, 2H), 8.07 (s, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.84 (s, 1H), 7.50 (dd, J = 7.3, 8.4 Hz, 2H), 7.45 - 7.32 (m, 2H), 7.30 - 7.19 (m, 1H), 7.05 (t, J = 9.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.51 (t, J = 7.7 Hz, 1H), 4.55 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 3.72 - 3.54 (m, 5H), 3.42 (t, J = 6.4 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 2.83 - 2.73 (m, 4H), 2.59 (t, J = 6.3 Hz, 2H), 1.71 (d, J =
12.4 Hz, 2H), 1.59 (t, $J = 16.2$ Hz, 3H), 1.49 - 1.15 (m, 5H), 1.09 - 0.95 (m, 1H).

**Preparation 7**

N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][l,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide saccharide

To 14mL of the 2-methyltetrahydrofuran solution in Preparation 3 was charged to saccharin (0.69 g) to yield a clear solution. After 30 min the mixture was charged to stirred tert-butyl methyl ether (20 mL) to yield an oil. After a further 60 min ethanol (2.5 mL) was added. After 19 hours further tert-butyl methyl ether (20 mL) was charged. After overnight stirring further tert-butyl methyl ether (20 mL) was charged to the solution to yield and oil. After 3 days the solvent was allowed to evaporate. After 6 further days ethyl acetate (50 mL) was charged to the concentrate. After 2 further days additional ethyl acetate (40 mL) was charged. After 1 day the mixture was concentrated by evaporation of approximately $\frac{3}{4}$ of the solvent and ethyl acetate (50 mL) charged. After 12 days the solid was filtered and washed with ethyl acetate (25 mL) and dried to a weight of 2.036g.

$^1$H NMR (500 MHz, DMSO) $\delta$ 8.07 (s, 1H), 7.83 (s, 1H), 7.74 - 7.63 (m, 4H), 7.45 - 7.33 (m, 2H), 7.30 - 7.19 (m, 1H), 7.05 (d, $J = 9.4$ Hz, 1H), 6.71 (d, $J = 4.9$, 8.4 Hz, 1H), 6.52 (d, $J = 8.2$ Hz, 1H), 4.55 (s, $J = 5.7$ Hz, 2H), 3.86 (s, 3H), 3.73 - 3.56 (m, 5H), 3.42 (t, $J = 6.5$ Hz, 2H), 3.05 (t, $J = 7.6$ Hz, 2H), 2.95 (t, $J = 6.5$ Hz, 2H), 2.85 - 2.75 (m, 4H), 2.59 (t, $J = 9.6$, 16.0 Hz, 2H), 1.71 (d, $J = 12.0$ Hz, 2H), 1.65 - 1.51 (m, 3H), 1.48 - 1.21 (m, 4H), 1.11 - 0.95 (m, 1H).
Preparation 8

N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (1S)-(+)-10-camphorsulfonate

To 14mL of the 2-methyltetrahydrofuran solution in Preparation 3 was charged to (1S)-(+)-10-camphorsulfonic acid (0.89 g) to yield a clear solution. After 30 min the mixture was charged to stirred tert-butyl methyl ether (20 mL) to yield an oil. After a further 60 min ethanol (2.5 mL) was added. After 19 hours further tert-butyl methyl ether (20 mL) was charged. After overnight stirring further tert-butyl methyl ether (20 mL) was charged to the solution to yield and oil. After 3 days the solvent was allowed to evaporate. After 6 further days ethyl acetate (50 mL) was charged to the concentrate. After 2 further days additional ethyl acetate (40 mL) was charged. After 1 day the mixture was concentrated by evaporation of approximately ¾ of the solvent and ethyl acetate (50 mL) charged. After 12 days the solid was filtered and washed with ethyl acetate (25 mL) and dried to a weight of 2.343 g.

1H NMR (500 MHz, DMSO) δ 8.04 (s, J = 3.3 Hz, 1H), 7.83 (s, 1H), 7.45 - 7.34 (m, 2H), 7.32 - 7.19 (m, 1H), 7.06 (t, J = 10.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.57 - 6.47 (m, 1H), 4.56 (s, J = 9.2 Hz, 2H), 3.86 (s, 3H), 3.76 - 3.55 (m, 5H), 3.43 (t, J = 6.1 Hz, 2H), 3.12 - 2.88 (m, 5H), 2.81 (t, J = 6.8 Hz, 4H), 2.34 - 2.23 (m, 1H), 2.01 (t, J = 4.4 Hz, 1H), 1.96 - 1.81 (m, 2H), 1.72 (d, J = 11.4 Hz, 2H), 1.65 - 1.52 (m, 3H), 1.47 - 1.15 (m, 7H), 1.12 - 0.96 (m, 4H), 0.75 (s, 3H) [4H obscured by solvent peak.]

Preparation 9

N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide benzenesulfonic acid salt, hydrochloric acid salt, hydrobromic acid salt, methanesulfonic acid salt, benzensulfonic acid salt, p-toluenesulfonic acid salt, maleic acid salt, citric acid salt, l-hydroxy-2-naphthoic acid salt, benzoic acid salt, (R)(-)-mandelic acid salt or L-(+)-tartaric acid salt
p-Toluenesulfonic acid monohydrate (5.31 g) was added in one portion to N-cyclohexyl-N-(2,2-dimethoxyethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (7.74 g, prepared as in Example 2a, Step ii) in tetrahydrofuran (60 mL). The resulting solution was stirred at 20°C for 30 min. This solution was added to a stirred mixture of 8-(2-aminoethyl)-5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one hydrochloride (4.27 g), sodium bicarbonate (4.40 g), water (6 mL) and NMP (60 mL). The mixture was stirred for 10 min. and sodium triacetoxyborohydride (9.25 g) and acetic acid (1 mL) were added. The mixture was stirred for 3 h. The reaction mixture was neutralised with saturated sodium bicarbonate (100 mL) and extracted into ethyl acetate (5 x 100 mL). Methanol (50 mL) was added and the organic was washed with a 1:1 mixture of water and saturated brine (2 x 70 mL). The organic was dried over magnesium sulfate, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% isohexane in ethyl acetate, then elution gradient 2 to 10% methanol in dichloromethane to afford N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (5.38 g) as a gum.

A solution of N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (0.160 g) in ethanol (8 mL) was mixed with corresponding acid (1 eq for benzenesulfonic acid, p-toluenesulfonic acid monohydrate, methanesulfonic acid, 1-hydroxy-2-naphthoic acid, benzoic acid, (R)-(−)-mandelic acid; 0.5 eq. for L-(+)-tartaric acid, maleic acid or 0.33 eq. for citric acid). The solution was divided into 8 aliquots (1 mL) each into separate vials and the solvent allowed to evaporate under a nitrogen stream at 55°C.

A solution of N-cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide (0.160 g) in ethanol (8 mL) was mixed with hydrochloric acid (0.3 mL) or hydrobromic acid (0.2 mL). The mixtures were concentrated in vacuo. Ethanol (8 mL) was added to each salt and the solution was divided into 8 aliquots (1 mL) each into separate vials and the solvent allowed to evaporate under the nitrogen stream at 55°C.
Solvents (ethanol, acetonitrile, tetrahydrofuran, dichloromethane, 2-propanol, nitromethane, ethyl acetate, 1,4-dioxane; 1 mL each) were then added to these residues and the mixtures were slurried for 7 days to form corresponding salts.

If formed, solids were filtered using micro-filtration cartridges by centrifuge and dried under vacuum.

**Preparation 10 (Form A)**

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-l-azonia-bicyclo[2.2.2]octane bromide (Form A)

**Intermediate 1 (Isomers 1 & 2): 2-Phenyl-2-piperidin-1-yl-propionic acid methyl ester**

A solution of methyl 2-bromo-2-phenylpropanoate (1 g) in acetonitrile (30 mL) was treated with piperidine (1 mL). The solution was stirred and heated under reflux for 3 h then concentrated to dryness. The residue was purified by flash column chromatography on silica gel using ether/isohexane (3:7) to afford the racemic sub-titled compound as a colourless oil (0.8 g). The mixture of enantiomers was separated by chiral HPLC using a chiracel OJ-H column using an isocratic system of 80% isohexane/ethanol to afford the two enantiomers, which were defined as Isomer 1 and Isomer 2 in order of elution.

2-Phenyl-2-piperidin-1-yl-propionic acid methyl ester (Isomer 1)

Chiral HPLC 80:20 isohexane:ethanol (isocratic). Chiracel OJ-H 4.6mm x 50mm

Retention time 1.09min.

H NMR (400 MHz, CDCl3) δ 7.56 - 7.49 (2H, m), 7.35 - 7.20 (3H, m), 3.68 (3H, s), 2.54 - 2.45 (2H, m), 2.41 - 2.32 (2H, m), 1.64 - 1.54 (7H, m), 1.50 - 1.42 (2H, m).

2-Phenyl-2-piperidin-1-yl-propionic acid methyl ester (Isomer 2)
Chiral HPLC 80:20 hexane : ethanol (isocratic). Chiracel OJ-H 4.6mm x 50mm
Retention time 2.52min.

$^1$H NMR (400 MHz, CDC$_3$) $\delta$ 7.56 - 7.49 (2H, m), 7.35 - 7.20 (3H, m), 3.68 (3H, s), 2.54 - 2.45 (2H, m), 2.41 - 2.32 (2H, m), 1.64 - 1.54 (7H, m), 1.50 - 1.42 (2H, m).

Intermediate 2: 2-Phenyl-2-piperidin-1-yl-propionic acid (R)-(l-aza-bicyclo [2.2.2]oct-3-yl) ester (Isomer 1)

A mixture of 2-phenyl-2-piperidin-1-yl-propionic acid methyl ester (Intermediate A, Isomer 1) (0.9 g), (i?)-quinuclidin-3-ol (1.157 g) and sodium hydride (60% in mineral oil, 0.335 g) in dry toluene (20 mL) was heated at 120°C under an atmosphere of nitrogen for 8h. The cooled reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (2 x 150 mL). The combined extracts were dried (Mg$\text{SO}_4$) and concentrated to give an oil. The crude product was purified by flash column chromatography on silica eluting with (ethyl acetate / methanol 9:1) to afford the titled compound (0.500 g).

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.59 - 7.51 (2H, m), 7.40 - 7.21 (3H, m), 4.72 - 4.62 (1H, m), 3.34 - 3.26 (1H, m), 3.04 - 2.92 (1H, m), 2.75 - 2.13 (7H, m), 1.89 - 1.75 (1H, m), 1.71 - 1.20 (14H, m).
(R)-l-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-l-azonia-bicyclo[2.2.2]octane bromide (Form A)

2-Phenyl-2-piperidin-1-yl-propionic acid (i?)-(l-aza-bicyclo[2.2.2]oct-3-yl) ester

(Intermediate B, Isomer 1) (3 g) in acetonitrile (25 mL) was treated with l-(2-bromoethyl)-4-fluorobenzene (2.384 g) and the mixture stirred at RT for 24 h. The mixture was concentrated to dryness, and the residue purified on silica gel eluting with 10% methanol in dichloromethane. The product containing fractions were combined, concentrated to dryness and the foam residue re-dissolved in acetonitrile (20 mL). To the solution was added diethyl ether (40 mL) and the resulting solid collected by filtration. The solid was dissolved in hot acetone (75 mL) and then allowed to cool overnight. The resulting solid was collected by filtration and dried at 50°C to afford the titled compound (3.70 g).

MS [M]+ = 465

H NMR (400 MHz, DMSO-d6) δ 7.58 - 7.54 (2H, m), 7.40 - 7.32 (4H, m), 7.31 - 7.26 (1H, m), 7.23 - 7.16 (2H, m), 5.14 - 5.09 (1H, m), 3.95 - 3.85 (1H, m), 3.62 - 3.51 (1H, m), 3.50 - 3.36 (4H, m), 3.25 - 3.16 (2H, m), 2.95 (2H, t), 2.48 - 2.31 (4H, m), 2.24 - 2.18 (1H, m), 2.02 - 1.69 (4H, m), 1.57 (3H, s), 1.56 - 1.48 (4H, m), 1.47 - 1.40 (2H, m).

Solid State Data for Preparation 10 (Form A)

Single crystal X-ray diffraction data obtained for Preparation 1 proved the structure to be (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-l-azonia-bicyclo[2.2.2]octane bromide. The data set was collected at RT with graphite monochromatized MoKα radiation on a KappaCCD Single-Crystal X-Ray diffractometer.
equipped with a k-axis goniometer and a CCD area detector (Nonius, 1998). The
diffraction raw data were processed within the Denzo-SMN program package (Otwinowski
& Minor, 1998) converting the information from the digital image frame to a file
containing h, k, l indices, background and Lp corrected intensities of the diffraction spots,
along with estimate of errors.

On the basis of the crystal structure determined for Preparation 4, the absolute
configuration of Intermediate A - Isomer 1 used has been assigned as (5)-2-Phenyl-2-
piperidin-l-yl-propionic acid methyl ester.

The melting temperature of Preparation 4 bromide Form A as determined by DSC gave
found a double endothermic events occurring at 171°C (1st onset) and 183 °C (2nd onset)
(±2°C). Weight loss observed prior to melting by TGA was negligible. GVS determination
gave 0.1% weight increase (%w/w) at 80% RH (±0.2%).

An XRPD spectrum of [(i?)-l-[2-(4-fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin-l-yl-
propionyloxy)-l-azonia-bicyclo[2.2.2]octane bromide (Form A) is presented in Figure 2.
Preparation 10 (Form C):

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

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((S)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane bromide (above) (1 g) was dissolved in methanol (5 mL) and the mixture warmed to 60°C. The mixture was allowed to cool to 40°C whereupon solid started to form and the mixture was then re-heated to 50°C. Three 10 mL aliquots of methyl acetate were added to the mixture which was then allowed to slowly cool to room temperature and stirred for 18 h. The resulting solid was collected by filtration and then dried under reduced pressure at 50°C to afford the titled compound (50 mg).
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.51 - 7.60 (2H, m), 7.31 - 7.41 (4H, m), 7.25 - 7.31 (1H, m), 7.13 - 7.21 (2H, m), 5.08 - 5.15 (1H, m), 3.88 - 3.97 (1H, m), 3.53 - 3.63 (1H, m), 3.38 - 3.52 (4H, m), 3.15 - 3.26 (2H, m), 2.92 - 3.01 (2H, m), 2.31 - 2.48 (4H, m), 2.20 - 2.25 (1H, m), 1.72 - 2.04 (4H, m), 1.58 (3H, s), 1.48 - 1.56 (4H, m), 1.39 - 1.48 (2H, m).

Solid State Data for Preparation 10 (Form C)

(R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane bromide (Form C)

The melting temperature of Preparation 4 bromide Form C as determined by DSC was found to be 184°C (onset) (±2°C). Weight loss observed prior to melting by TGA was 4%. GVS determination gave 4% weight increase (%w/w) at 80% RH (±0.2%).

An XRPD spectrum of (R)-1-[2-(4-fluoro-phenyl)-ethyl]-3-((5)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane bromide (Form C) is presented in Figure 3.
Preparation 11

Synthesis of (R)-l-(4-fluorophenethyl)-3-(S)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate.

General Experimental Details for Preparation 11:

Analytical HPLC and GC Conditions used during Preparation 11, for Intermediates 1-5:
The step forming Intermediate 1 was monitored by HPLC using an Ace phenyl column with standard aqueous/acetonitrile/TFA mobile phase on a gradient, with UV detection at 230 nm.

The steps forming Intermediates 2, 3 and 4 were monitored by GC using DB-5 capillary column with FID detection and standard oven gradient from 40 °C to 300 °C, with split injection.

The steps forming Intermediates 5, 6, 7 and 8 are monitored by HPLC using C18 phase with standard aqueous/acetonitrile/TFA mobile phase on a gradient, with UV detection at 220 nm.

For Intermediate 5, solvent composition was monitored by GC using a DB-624 capillary column with FID detection and oven gradient from 40°C to 250°C, with split injection.

During the preparation of Intermediate 5, levels of quinuclidinol were monitored by GC using an HP-1 capillary column with FID detection and oven gradient from 40°C to 300°C, with split injection.

**Intermediate 1: Methyl 2-phenylpropanoate**

\[ \text{(+/-)-2-Phenylpropionic acid (20.5g) was dissolved in methanol (62mL) in a reaction vessel. Sulfuric acid (98%, 0.82mL) was then charged followed by methanol (20.5mL) as a line rinse. The reaction was then heated to 63°C (±3°C) and stirred at this temperature for up to 4hrs. The reaction was monitored by HPLC analyzing the methyl 2-phenylpropanoate: (+/-)-2-phenylpropionic acid ratio (specification >97:3). Upon completion the reaction mixture was cooled to 23°C (±3°C). Cyclohexane (102mL) was added followed by Na₂CO₃ (aq) (3.7% wt/wt, 61.5mL). Layers were allowed to separate and the lower aqueous phase discarded. Water (61.5mL) was then charged and the mixture stirred for 10mins before the layers were separated discarding the lower aqueous phase. Cyclohexane (205mL) was then charged to the organic phase. The reaction mixture was then distilled under reduced pressure at 45°C, 150-240mbar removing 180mL solvent.} \]
reaction mixture was then cooled to 23°C (±3°C) yielding methyl 2-phenylpropanoate in a solution in cyclohexane.

**Intermediate 2: Methyl 2-bromo-2-phenylpropanoate**

Methyl 2-phenylpropanoate in a solution in cyclohexane (Intermediate 1) (22.42g; based on 100% yield from step a) was charged to a reaction vessel. Hydrobromic acid (48%, 0.62mL) was then charged followed by cyclohexane (22.4mL) as a line wash. Dibenzoyl peroxide (75%, 2.21g) and N-bromosuccinimide (31.61g) were then charged to the vessel and the reaction heated to 50°C (±3°C) and stirred at this temperature for at least 4hrs. The reaction was monitored by GC analyzing the methyl 2-bromo-2-phenylpropanoate : methyl 2-phenylpropanoate ratio (specification >96:4). Upon completion the reaction mixture was cooled to 20°C (±3°C). The reaction mixture was filtered to remove the solid succinimide by-product, washing the filter cake twice with cyclohexane (22.4mL). The solid by-product was discarded. NaHSO₃ (aq) (10% w/w, 81.9mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. Water (81.9mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. 3-Pentanone (201.9mL) was then charged and the mixture was distilled at 45°C, 150-280mbar removing 210mL of solvent. The reaction mixture was cooled to 23°C (±3°C). 3-Pentanone (101mL) was then charged and the solvent composition analyzed by GC (specification <30% cyclohexane) to yield methyl 2-bromo-2-phenylpropanoate in a solution of 3-pentanone.

**Intermediate 3: Methyl 2-phenyl-2-piperidin-1-ylpropanoate**

[Diagram of Intermediate 3]
Methyl 2-bromo-2-phenylpropanoate in a solution of 3-pentanone (Intermediate 2) (33.21g; based on 100% yield from step b) was charged to a reaction vessel followed by piperidine (40.5mL). The reaction was heated to 40°C (±3°C) and held for at least 4hrs. The reaction was monitored by GC analyzing the methyl 2-phenyl-2-piperidin-1-ylpropanoate : methyl 2-bromo-2-phenylpropanoate ratio (specification >97:3). The reaction mixture was then cooled to 23°C (±3°C) and then filtered to remove the piperidine hydrobromide salt by-product, and the filter cake washed with methyl 'butyl ether (66.4mL). The filter cake was discarded. Methyl 'butyl ether (133mL) and hydrogen chloride (2.74M, 172.6mL) were then added and the reaction mixture stirred for 15mins before taking a pH reading to ensure pH <4. The layers were then allowed to separate retaining the lower aqueous phase. Hydrogen chloride (2.74M, 60.4mL) was then added to the organic phase and the mixture stirred for at least 15mins before allowing the phases to separate retaining the lower aqueous phase. The two aqueous phases were then combined, sampled and analyzed by GC to ensure all impurities were <0.5 % with the exception of methyl 2-phenyl-3-(piperidin-1-yl)propanoate impurity. The aqueous phase was then charged to a mixture of Na₂CO₃ (32.29g), water (232mL) and methyl 'butyl ether (332mL). The mixture was stirred for at least 15mins before taking a pH reading to ensure pH >6. The layers were then allowed to separate discarding the lower aqueous phase. Water (66.4mL) was then charged and stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. Citric acid (0.8wt%, 66.4mL) was then charged to the organic phase and the mixture stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. A second charge of citric acid (0.8wt%, 66.4mL) was then added to the organic phase and the mixture stirred for 15mins before allowing the phases to separate discarding the lower aqueous phase. The organic phase was sampled and analyzed by GC to ensure methyl 2-phenyl-3-(piperidin-1-yl)propanoate impurity was less than 0.5%. The mixture was then distilled at 45°C, 80-220mbar removing 265mL solvent. Methanol (332mL) was then charged to the vessel and the mixture again distilled at 45°C, 80-220mbar removing 332mL solvent. The reaction mixture was cooled to 23°C (±3°C) to yield methyl 2-phenyl-2-piperidin-1-ylpropanoate in
a solution of methanol. The product was then analyzed by NMR assay and HPLC for purity. 23.8g (at 100w/w%) 70.5% yield, >99.5% HPLC purity.

**Intermediate 4: (S)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate**

![Chemical structure](image)

Racemic methyl 2-phenyl-2-piperidin-l-ylpropanoate (Intermediate 3) was purified by Simulated Moving Bed (SMB) chromatography to yield methyl (S)-2-phenyl-2-piperidin-1-ylpropanoate. (5)-methyl 2-phenyl-2-(piperidin-l-yl)propanoate was isolated as a 40w/w% solution in toluene. Typical conditions for the SMB purification were as follows:

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</table>

**Intermediate 5: (S)-((R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-l-yl)propanoate**

![Chemical structure](image)
(S)-methyl 2-phenyl-2-(piperidin-1-yl)propanoate (Intermediate 4) (17.6 g as a 40w/w% solution in toluene) was charged to a reaction vessel followed by (i?)-(−)-3-quinuclidinol (9.5 g) and toluene (106 mL). The mixture was distilled at 60°C, 180-450 mbar removing 52 mL solvent. A sample was taken and analyzed by HPLC assay (specification 180-220 mg/mL (S)-methyl 2-phenyl-2-(piperidin-1-yl)propanoate. The reaction was then heated to 60°C (±5°C) and potassium tert-pentoxide (25 w/w%, 43.12 g) was added. The reaction mixture was stirred at 60°C (±5°C) for at least 2 hrs and monitored by HPLC analyzing the methyl (S)-methyl 2-phenyl-2-(piperidin-1-yl)propanoate : (S)-(R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate ratio (specification >95:5) followed by toluene (8.8 mL) as a line rinse. The reaction mixture was cooled to 20°C (±5°C). Butanenitrile (88 mL) and water (88 mL) were charged and the mixture stirred for 20 mins before allowing the phases to separate discarding the lower aqueous phase. Water (88 mL) was charged and the mixture stirred for 20 mins before allowing the phases to separate discarding the lower aqueous phase. The organic phase was analysed by GC to ensure residual (i?)-(−)-3-quinuclidinol levels were below 0.5%. The organic phase was distilled at 60°C, 100-430 mbar removing 142 mL of solvent. The reaction was then weighed and analysed by; NMR assay (w/w% of product) and GC (solvent composition) to determine the amount of product in solution and the solvent composition, toluene (18.5 mL, 1.05 vol) and butanenitrile (52.5 mL, 3 vol) was then added to the mixture to yield (S)-(R)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-1-yl)propanoate (19.67 g, 81% yield) in a 7:3 butanenitrile : toluene solvent composition at 140 mg/mL concentration.
Intermediate 6: (R)-l-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane bromide

(5)-((i?)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-l-yl)propanoate  (Intermediate 5) (19.67g as a 140mg/mL solution in butanenitrile : toluene) was charged to a reaction vessel followed by 4-fluorophenethylbromide (13.99g) and butanenitrile (19.7mL). The reaction mixture was heated to 60°C (±5°C) and stirred at this temperature for at least 8hrs. The reaction was monitored by HPLC analyzing the (5)-((i?)-quinuclidin-3-yl) 2-phenyl-2-(piperidin-l-yl)propanoate : product ratio (specification >96:4). The reaction mixture was cooled to 40°C over at least 40mins (0.5°C/min) and then cooled to -5°C over at least 6hrs (0.125°C/min). During the cool no crystallisation had occurred when at 20°C. Therefore the reaction was seeded with a sample of (i?)-l-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane bromide (25mg - obtainable by methods described in WO 2008/075005 - Form A). After the reaction mixture reached -5°C toluene (39.3mL) was added and the slurry stirred at -5°C for at least 1hr. (i?)-l-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin- l-yl)propanoyloxy)- l-azoniabicyclo[2.2.2]octane bromide was then collected by filtration, washing the filtercake with butanenitrile (39.3mL). The (i?)-l-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin- l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane bromide product was then dried under vacuum at 45°C. The product was then analysed by HPLC purity and NMR assay. 30g, 96% yield, >99.5% HPLC purity, >99.5w/w% assay.
(R)-1-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate

Procedure A

(R)-1-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide salt (Preparation 4) (0.6 g) prepared as described in WO2008/075005 (Example 44) was dissolved in dichloromethane (50 mL) and shaken with a solution of sodium 4-methylbenzenesulfonate (3.1 g) in water (100 mL), in three equal portions (~33 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The white foam was dissolved in hot acetonitrile (~5 mL) and allowed to cool to RT with stirring for 3 days. A white solid formed which was collected by filtration, washed with cold acetonitrile (~2 mL) and dried in vacuo at 60°C for 2 days to yield the product (0.490 g).

**MS** M⁺ = 465

H NMR (400 MHz, DMSO-d6) δ 7.55 (2H, d), 7.47 (2H, d), 7.40-7.31 (4H, m), 7.28 (1H, t), 7.19 (2H, t), 7.11 (2H, d), 5.1-5.08 (1H, m), 3.9-3.83 (1H, m), 3.59-3.50 (1H, m), 3.47-3.35 (4H, m), 3.25-3.14 (2H, m), 2.99-2.90 (2H, m), 2.47-2.31 (4H, m), 2.28 (3H, s), 2.24-2.18 (1H, m), 2.02-1.70 (4H, m), 1.57 (3H, s), 1.56-1.48 (4H, m), 1.48-1.38 (2H, m).

Procedure B

A solution of sodium p-toluenesulfonate (26.97 g) in water (300 mL; 16.65 moles) was prepared. A 500 mL jacketed vessel was charged with (i?)-1-(4-fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide (Intermediate 5) (15.00 g). Butanenitrile (225 mL) and half of the sodium tosylate solution were added to the reaction vessel. The vessel was then stirred and heated to 35°C. When
the vessel contents reached 35°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. The second half of the sodium tosylate solution was added and the vessel contents heated to 35°C with stirring. When the vessel contents reached 35°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. Water (75 mL) was added and the mixture heated to 70°C. When the vessel contents reached 70°C and were adequately mixed the stirring was stopped and the phases allowed to settle. The lower aqueous phase was removed and discarded. The hot organic phase was filtered into a clean vessel. The original vessel was washed with butanenitrile (30 mL) and this solvent was added to the filtrate via the filter into the clean vessel. The wet organic solution was distilled in order to azedry it (120-150mbar - vessel jacket at 80°C). After ca. 60 mL of solvent had been distilled a precipitate was observed; contents were at 48°C. In total, 110 mL of solvent (10 mL water: 100 mL butanenitrile) was collected. At this point the vacuum was released and the vessel contents warmed to 75°C. Acetonitrile (45 mL) was added and the vessel contents re-heated to 75°C (not all material dissolved). More acetonitrile (45 mL) was added and the vessel contents re-heated to 75°C (all material dissolved). The solution was cooled to 5°C over 120 minutes (precipitation started at 65°C). With the vessel contents at 5°C the product was collected by filtration, washed with cold (5°C) butanenitrile (30 mL) and pulled as dry as possible on the filter to give 15.27 g of solid. This solid was left open in a fume cupboard overnight to give (R)-1-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (15.22 g). The ratio of quaternary species to tosylate was determined as 1:1.01 by 400MHz 1HNMR using a 30s relaxation delay.

**Recrystallisation of (R)-1-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate**

(R)-1-(4-Fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-1-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (7.50 g) and acetonitrile (90.00 mL) were charged to a vessel. The mixture was heated to 80°C and the resulting solution
held at 80°C for 30 mins. The mixture was then cooled to 65°C over 20 minutes. The solution was seeded with seed crystals of (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate (6mg) and stirred at 65°C for 1 hour. The reaction was then cooled to 5°C over 10 hours and stirred at 5°C for 6 hours. The solid product was then isolated by filtration, washing the filter cake with acetonitrile (15.00 mL). The product was then dried under vacuum at 45°C to yield (i?)-l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate as a white solid (6.6g).

**Solid State Data for Preparation 11**

(R)- l-(4-fluorophenethyl)-3-((S)-2-phenyl-2-(piperidin-1-yl)propanoyloxy)- l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate

**Instrument Details:**

X-Ray Powder Diffraction (XRPD) - PANalytical X'Pert machine in 20-0 configuration or a PANalytical Cubix machine in 0-0 configuration over the scan range 2° to 40° 20 with 100-second exposure per 0.02° increment. The X-rays were generated by a copper long-fine focus tube operated at 45kV and 40mA. The wavelength of the copper X-rays was 1.5418 Å. The Data was collected on zero background holders on which ~ 2mg of the compound was placed. The holder was made from a single crystal of silicon, which had been cut along a non-diffracting plane and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction.

Differential Scanning Calorimetry (DSC) thermograms were measured using a TA Q1000 Differential Scanning Calorimeter, with aluminium pans and pierced lids. The sample weights varied between 0.5 to 5mg. The procedure was carried out under a flow of nitrogen gas (50mL/min) and the temperature studied from 30 to 230°C at a constant rate of temperature increase of 10°C per minute.
Gravimetric Vapour Sorption (GVS) profiles were measured using a Surface Measurements Systems Dynamic Vapour Sorption DVS-1 or a DVS Advantage instrument. The solid sample ca. 1-5mg was placed into a glass vessel and the weight of the sample was recorded during a dual cycle step method (40 to 90 to 0 to 90 to 0% relative humidity (RH), in steps of 10% RH).

A sample of material obtained by Preparation 11 as described herein above was analysed by XRPD (PANalytical X'Pert or Cubix system), GVS and DSC. The melting temperature as determined by DSC was found to be 189°C (onset) (±2°C). GVS determination gave 0.1% weight increase (%w/w) at 80% Relative Humidity (±0.2%).

An XRPD spectrum of (i?)-l-(4-Fluorophenethyl)-3-((5)-2-phenyl-2-(piperidin-l-yl)propanoyloxy)-l-azoniabicyclo[2.2.2]octane 4-methylbenzenesulphonate prepared according to Preparation 11 is presented in Figure 4.

Figure 4
BIOLOGICAL ASSAYS

Adrenergic β2 mediated cAMP production

Cell preparation
H292 cells were grown in 225cm² flasks incubator at 37°C, 5% CO₂ in RPMI medium containing, 10% (v/v) FBS (foetal bovine serum) and 2 mM L-glutamine.

Experimental Method
Adherent H292 cells were removed from tissue culture flasks by treatment with Accutase™ cell detachment solution for 15 min. Flasks were incubated for 15 min in a humidified incubator at 37°C, 5% CO₂. Detached cells were re-suspended in RPMI media (containing 10% (v/v) FBS and 2 mM L-glutamine) at 1 x 10⁶ cells per mL. 10000 cells in 100 µL were added to each well of a tissue-culture-treated 96-well plate and the cells incubated overnight in a humidified incubator at 37°C, 5% CO₂. The culture media was removed and cells were washed twice with 100 µL assay buffer and replaced with 50 µL assay buffer (HBSS solution containing 10mM HEPES pH7.4 and 5 mM glucose). Cells were rested at room temperature for 20 min after which time 25 µL of rolipram (1.2 mM made up in assay buffer containing 2.4% (v/v) dimethylsulphoxide) was added. Cells were incubated with rolipram for 10 min after which time test compounds were added and the cells were incubated for 60 min at room temperature. The final rolipram concentration in the assay was 300 µM and final vehicle concentration was 1.6% (v/v) dimethylsulphoxide. The reaction was stopped by removing supernatants, washing once with 100 µL assay buffer and replacing with 50 µL lysis buffer. The cell monolayer was frozen at -80°C for 30 min (or overnight).

AlphaScreen™ cAMP detection
The concentration of cAMP (cyclic adenosine monophosphate) in the cell lysate was determined using AlphaScreen™ methodology. The frozen cell plate was thawed for 20 min on a plate shaker then 10 µL of the cell lysate was transferred to a 96-well white plate. 40 µL of mixed AlphaScreen™ detection beads pre-incubated with biotinylated cAMP,
was added to each well and the plate incubated at room temperature for 10 h in the dark. The AlphaScreen™ signal was measured using an EnVision spectrophotometer (Perkin-Elmer Inc.) with the recommended manufacturer’s settings. cAMP concentrations were determined by reference to a calibration curve determined in the same experiment using standard cAMP concentrations. Concentration response curves for agonists were constructed and data was fitted to a four parameter logistic equation to determine both the pEC$_{50}$ and Intrinsic Activity. Intrinsic Activity was expressed as a fraction relative to the maximum activity determined for formoterol in each experiment. Results for compounds of the invention are to be found in Table 1.

**Selectivity Assays**

**Adrenergic α1D**

**Membrane Preparation**
Membranes were prepared from human embryonic kidney 293 (HEK293) cells expressing recombinant human α1D receptor. These were diluted in Assay Buffer (50mM HEPES, 1mM EDTA, pH 7.4) to provide a final concentration of membranes that gave a clear window between maximum and minimum specific binding.

**Experimental Method**
Assays were performed in U-bottomed 96-well polypropylene plates. 10 µL [³H]-prazosin (0.3 nM final concentration) and 10 µL of test compound (10x final concentration) were added to each test well. For each assay plate 8 replicates were obtained for [³H]-prazosin binding in the presence of 10 µL vehicle (10% (v/v) DMSO in Assay Buffer; defining maximum binding) or 10µL BMY7378 (10 µM final concentration; defining non-specific binding (NSB)). Membranes were then added to achieve a final volume of 100 µL. The plates were incubated for 2 h at room temperature and then filtered onto PEI coated GF/B filter plates, pre-soaked for 1 h in Assay Buffer, using a 96-well plate Tomtec cell harvester. Five washes with 250 µL wash buffer (50mM HEPES, 1mM EDTA, pH 7.4) were performed at 4°C to remove unbound radioactivity. The plates were dried then sealed from underneath using Packard plate sealers and MicroScint-0 (50 µL) was added to each
well. The plates were sealed (TopSeal A) and filter-bound radioactivity was measured with a scintillation counter (TopCount, Packard Bioscience) using a 3-minute counting protocol.

Total specific binding (Bo) was determined by subtracting the mean NSB from the mean maximum binding. NSB values were also subtracted from values from all other wells. These data were expressed as percent of B₀. Compound concentration-effect curves (inhibition of [³H]-prazosin binding) were determined using serial dilutions typically in the range 0.1 nM to 10 µM. Data was fitted to a four parameter logistic equation to determine the compound potency, which was expressed as pIC50 (negative log molar concentration inducing 50% inhibition of [³H]-prazosin binding). Results are shown in Table 1 below.

Adrenergic β₁

Membrane Preparation
Membranes containing recombinant human adrenergic beta 1 receptors were obtained from Euroscreen. These were diluted in Assay Buffer (50mM HEPES, 1mM EDTA, 120mM NaCl, 0.1% gelatin, pH 7.4) to provide a final concentration of membranes that gave a clear window between maximum and minimum specific binding.

Experimental Method
Assays were performed in U-bottomed 96-well polypolypropylene plates. 10 µl of [³H]-Iodocyanopindolol (0.036 nM final concentration) and 10 µL of test compound (10x final concentration) were added to each test well. For each assay plate 8 replicates were obtained for [³H]-Iodocyanopindolol binding in the presence of 10 µL vehicle (10%> (v/v) DMSO in Assay Buffer; defining maximum binding) or 10 µL Propranolol (10 µM final concentration; defining non-specific binding (NSB)). Membranes were then added to achieve a final volume of 100 µL. The plates were incubated for 2 h at room temperature and then filtered onto PEI coated GF/B filter plates, pre-soaked for 1 h in Assay Buffer, using a 96-well plate Tomtec cell harvester. Five washes with 250 µl wash buffer (50mM HEPES, 1mM EDTA, 120mM NaCl, pH 7.4) were performed at 4°C to remove unbound
radioactivity. The plates were dried then sealed from underneath using Packard plate
sealers and MicroScint-0 (50 µL) was added to each well. The plates were sealed
(TopSeal A) and filter-bound radioactivity was measured with a scintillation counter
(TopCount, Packard Bioscience) using a 3-minute counting protocol.

Total specific binding (Bo) was determined by subtracting the mean NSB from the mean
maximum binding. NSB values were also subtracted from values from all other wells.
These data were expressed as percent of Bo. Compound concentration-effect curves
(inhibition of [125I]-Iodocyanopindolol binding) were determined using serial dilutions
typically in the range 0.1 nM to 10 µM. Data was fitted to a four parameter logistic
equation to determine the compound potency, which was expressed as pIC50 (negative log
molar concentration inducing 50% inhibition of [125I]-Iodocyanopindolol binding). Results
are shown in Table 1 below.

**Dopamine D2**

**Membrane Preparation**
Membranes containing recombinant human Dopamine Subtype D2s receptors were
obtained from Perkin Elmer. These were diluted in Assay Buffer (50mM HEPES, 1mM
EDTA, 120mM NaCl, 0.1% gelatin, pH 7.4) to provide a final concentration of membranes
that gave a clear window between maximum and minimum specific binding.

**Experimental Method**
Assays were performed in U-bottomed 96-well polypropylene plates. 30 µL [3H]-
spiperone (0.16 nM final concentration) and 30 µL of test compound (10x final
concentration) were added to each test well. For each assay plate 8 replicates were
obtained for [3H]-spiperone binding in the presence of 30 µL vehicle (10%> (v/v) DMSO in
Assay Buffer; defining maximum binding) or 30 µL Haloperidol (10 µM final
concentration; defining non-specific binding (NSB)). Membranes were then added to
achieve a final volume of 300 µL. The plates were incubated for 2 h at room temperature
and then filtered onto PEI coated GF/B filter plates, pre-soaked for 1 h in Assay Buffer,
using a 96-well plate Tomtec cell harvester. Five washes with 250 µL wash buffer (50mM
HEPES, ImM EDTA, 120mM NaCl, pH 7.4) were performed at 4°C to remove unbound radioactivity. The plates were dried then sealed from underneath using Packard plate sealers and MicroScint-0 (50 µL) was added to each well. The plates were sealed (TopSeal A) and filter-bound radioactivity was measured with a scintillation counter (TopCount, Packard Bioscience) using a 3-minute counting protocol.

Total specific binding (Bo) was determined by subtracting the mean NSB from the mean maximum binding. These data were expressed as percent of B₀. Compound concentration-effect curves (inhibition of [³H]-spiperone binding) were determined using serial dilutions typically in the range 0.1 nM to 10 µM. Data was fitted to a four parameter logistic equation to determine the compound potency, which was expressed as pIC₅₀ (negative log molar concentration inducing 50% inhibition of [³H]-spiperone binding).

The results obtained for a representative selection of the compounds of the Preparations are shown in Table 1 below.

### Table 1

<table>
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<tr>
<th>Preparation</th>
<th>β2 pEC50</th>
<th>β2 Int Act</th>
<th>α1 bind pIC50</th>
<th>β1 bind pIC50</th>
<th>D2 bind pIC50</th>
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<td>0.96</td>
<td>6.0</td>
<td>&lt;5.1</td>
<td>5.3</td>
</tr>
</tbody>
</table>

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

### Example 1

**Evaluation of compound activity on intra-alveolar neutrophil migration after aerosol challenge with lipopolysaccharide (LPS) in the CRL:CD rat.**

LPS challenge in CRL:CD rats causes an influx of inflammatory cells into the lungs. Rats are challenged either with an aerosol of 0.9% w/v saline or 0.1mg/mL LPS in 0.9% saline for 30 min or an intratracheal dose of 0.1-10µg/kg. This is repeated up to 8 times according to the experimental protocol. Rats are dosed with vehicle, standard compound or test compound by the appropriate route and frequency at various time points before and after
challenge depending upon the experimental protocol. Test compound groups could either be the same compound at different doses or single doses of different compounds or a combination of the two. Test compounds are given by intraperitoneal, intravenous or subcutaneous injection or by inhalation or intratracheal administration.

The rats are euthanized at various time points after challenge depending upon the nature of the study, but typically 4hr after LPS challenge with 1mL pentobarbitone sodium. A tracheotomy is performed and a cannula inserted. The airway is then lavaged using 3 mL sterile PBS at room temperature. The PBS is left in the airway for 10 seconds before being removed. The PBS containing cells is placed into a 15 mL centrifuge tube on ice. This process is repeated three times.

An aliquot of BAL fluid is removed and counted on Sysmex (Sysmex UK, Milton Keynes). Cytospin slides are prepared by adding a 100 µl aliquot of BAL fluid into cytospin funnels in a Shandon Cytospin3 operated at 700 rpm for 5 min. Slides are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and typically, 200 cells are counted under a microscope. Cells are classified as eosinophils, neutrophils and mononuclear cells (mononuclear cells included monocytes, macrophages and lymphocytes) and are expressed as a percentage of the total count.

Example 2

Evaluation of compound activity on intra-alveolar neutrophil migration after aerosol challenge with lipopolysaccharide (LPS) in the guinea-pig.

Male Dunkin-Hartley guinea-pigs (300-600g) are placed into open fronted guinea-pig holding cones attached at random around a cylindrical aerosol chamber. Guinea-pigs are held in the challenge cones and exposed to an aerosol of vehicle, or LPS at concentrations of 0.1-30µg/ml in 0.9% saline per group. Aerosols are generated using 2 jet nebulisers per column with a flow rate of 12 L/m. 10ml of the challenge agent is placed into each nebuliser. Alternatively animals receive an intratracheal dose of 0.1-10µg/kg. This is repeated up to 8 times according to the experimental protocol.
Guinea-pigs are dosed with vehicle, standard compound or test compound by the appropriate route and frequency at various time points before and after challenge depending upon the experimental protocol. Test compound groups could either be the same compound at different doses or single doses of different compounds or a combination of the two. Test compounds are given by intraperitoneal, intravenous or subcutaneous injection or by inhalation or intratracheal administration. Challenged guinea-pigs are killed by anaesthesia overdose (0.5ml Euthetal i.p.) at 4h-24h post challenge. The lungs are then lavaged. After the trachea is exposed and cannulated using a luer fitting cannula (orange =size 8FG), the lungs are lavaged with 3 x 5ml aliquots of Hanks Buffered Salt Solution (HBSS, EDTA-free). The lavaging is performed with gentle massaging of the chest to ensure appropriate agitation of the fluid in the lungs. The washes are harvested into a 15ml conical, polypropylene centrifuge tube, an aliquot of BAL fluid is removed and counted on Sysmex (Sysmex UK, Milton Keynes). Cytospin slides are prepared by adding a 100 µl aliquot of BAL fluid into cytospin funnels in a Shandon Cytospin3 operated at 700 rpm for 5 min. Slides are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and typically, 200 cells are counted under a microscope. Cells are classified as eosinophils, neutrophils and mononuclear cells (mononuclear cells included monocytes, macrophages and lymphocytes) and are expressed as a percentage of the total count.

**Example 3**

**Evaluation of compound activity on intra-alveolar neutrophil migration after aerosol challenge with lipopolysaccharide (LPS) in the mouse.**

Male C57BL/6J or BALB/C mice (20-35g) are placed in Perspex exposure boxes in groups of up to 20 and exposed to an aerosol of either 0.3 mg/ml LPS or 0.9% w/v saline. The LPS (Sigma, E.Coli, Ref L-3755, Serotype 026:B6, Lot no. 11lk4078) is made up in 0.9%, w/v saline. An aerosol is generated using two jet nebulisers operated at a flow rate of 12 L/min (6L/min for each nebuliser) for 15 min. Alternatively animals receive an intratracheal dose of 0.1-10µg/kg. This may be repeated up to 8 times.

Mice are dosed with vehicle, standard compound or test compound by the appropriate route and frequency at various time points before and after challenge depending upon the
experimental protocol. Test compound groups could either be the same compound at different doses or single doses of different compounds or a combination of the two. Test compounds are given by intraperitoneal, intravenous or subcutaneous injection or by inhalation or intratracheal administration.

Mice are killed with an overdose of Euthatal i.p 30 minutes, 1-24hr after LPS challenge. When circulation has ceased, the trachea is cannulated (Portex intravenous cannula) and the airways lavaged with 3 x 0.3ml of Isoton II (Beckman Coulter Ref. 844801 I Lot no.25775). For cytopsins, 100µl of the BALF is added to a cytopsin funnel and spun, using a ThermoShandon Cytospin model 3 or 4, at 700 rpm for 5 min. Cells on the slide are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and differential cell counts carried out to differentiate eosinophils, neutrophils and lymphomononuclear cells (including monocytes, macrophages and lymphocytes). Typically, 200 cells are counted per slide and each cell type expressed as a percentage of the total count. BALF total white cell count is measured using a Sysmex (Sysmex UK, Milton Keynes).

**Example 4**

**Evaluation of lung function in anaesthetised guinea-pigs.**

Male Dunkin-Hartley guinea-pigs (300-600g) are weighed and dosed with either vehicle or compound in an appropriate vehicle according to the experimental protocol via the intratracheal route under recoverable gaseous anaesthesia (5% halothane in oxygen). Following dosing, the animals are administered supplemental oxygen and monitored until full recovery. Typically a dose volume of 0.5 mL/kg is used for the intratracheal route. In a dose response study, animals are dosed with compound or vehicle two hours prior to the administration of histamine. Test compound groups could either be the same compound at different doses or single doses of different compounds or a combination of the two.

The guinea-pigs are anaesthetised with pentobarbitone (1 mL/kg of 60 mg/mL solution intraperitoneally) approximately 30 minutes prior to the first bronchoconstrictor administration. The trachea is cannulated (Portex intravenous cannula, 200/300/070 (orange) or 200/300/060 (yellow)) and the animal ventilated using a constant volume
respiratory pump (Harvard Rodent Ventilator model 683) at a rate of 60 breath/min and a
tidal volume of 5 ml/kg. A jugular vein is cannulated (Portex intravenous catheter
200/300/010 (green)) for the administration of histamine or maintenance anaesthetic (0.1
mL of pentobarbitone solution, 60 mg/mL, as required).

The animals are then transferred to a Flexivent System (SCIREQ, Montreal, Canada) in
order to measure airway resistance. The animals are ventilated (quasi-sinusoidal
ventilation pattern) at 60 breaths/min at a tidal volume of 5 mL/kg. A positive end
expiratory pressure of 2-3 cmH₂O is applied. Respiratory resistance is measured using the
Flexivent "snapshot" facility (1 second duration, 1 Hz frequency). Once stable baseline
resistance value has been obtained the animals are given histamine dihydrochloride or
methacholine in ascending doses (Histamine; 0.5, 1, 2, 3 and 5µg/kg, i.v., methacholine; 3,
10 and 30 µg/kg, i.v.) at approximately 4-minute intervals via the jugular catheter. After
each administration of histamine the peak resistance value is recorded. Guinea pigs are
euthanised with approximately 1.0mL pentobarbitone sodium (Euthatal) intravenously
after the completion of the lung function measurements.

Percentage bronchoprotection produced by a compound is calculated at each dose of
histamine as follows:

\[
\% \text{bronchoprotection} = \frac{\% \text{change } R_{\text{veh}} - \% \text{change } R_{\text{cmpd}}}{\% \text{change } R_{\text{veh}}} 
\]

Where \( \% \text{ change } R_{\text{veh}} \) is the mean of the maximum percentage change in airway resistance
in the vehicle treated group.

**Example 5**

**Evaluation of Compounds on Antigen induced Eosinophilia in Ovalbumin Sensitised
Brown Norway Rats.**

On day 0 of the study Brown Norway rats are given a subcutaneous injection of 500 µg
ovalbumin adsorbed onto 100 mg aluminium hydroxide in 0.4 mL saline in two distinct
sites, approximately 0.2 mL per site. Day 14 and 15 following sensitisation the rats are
challenged with aerosolised ovalbumin for 15 minutes. The rats are placed in groups of 10
in an acrylic box (internal dimensions 320mm wide x 320mm deep x 195 mm high, 20L
volume). 8mL of 10 mg/mL ovalbumin in 0.9% saline, or 0.9% saline alone, is placed in each of two jet nebulizers (Sidestream®, Profile Respiratory Systems Ltd.). Compressed air at 6 L/min is passed through each nebulizer and the output of the nebulizers is passed into the box containing the rats.

Rats are dosed via the appropriate route with vehicle, standard compound or test compound at various time points before and after challenge depending upon the experimental protocol. Rats are euthanised with 0.5 mL pentobarbitone sodium (Euthatal) intraperitoneally at various times after challenge. A tracheotomy is performed and the trachea cannulated. The airway is then lavaged using 3 mL sterile PBS at room temperature. The PBS is left in the airway for 10 seconds before being removed. The PBS containing cells is placed into a 15 mL centrifuge tube on ice. This process is repeated three times. The final volume recovered is recorded. An aliquot of BAL fluid is removed and counted using a Sysmex (Sysmex UK, Milton Keynes).

Cytospin slides are prepared by adding a 100 µl aliquot of BAL fluid into cytospin funnels in a Shandon Cytospin 3 operated at 700 rpm for 5 min. Slides are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and typically, 200 cells are counted under a microscope. Cells are classified as eosinophils, neutrophils and mononuclear cells. Mononuclear cells included monocytes, macrophages and lymphocytes.

Example 6
Evaluation of Compounds on Antigen induced eosinophilia in ovalbumin sensitised mice.

20-25g male BALB/c mice are sensitized to ovalbumin by i.p administration of 100 µg of grade V ovalbumin (Sigma) adsorbed onto 1mg of aluminium hydroxide gel mixture (Fisher Scientific UK) in 0.3 ml saline. Groups of mice are pre-dosed with compound if required, a minimum of two weeks after sensitization. They are then dosed daily for 1-8 days as study protocol specified, with test compound or 0.25 ml vehicle.

Each day of the 1-8 days, 1 hour after dosing, the mice are placed in perspex chambers (20x1x1 1cm, 10 mice max./chamber) and administered an aerosol challenge of 20mg ml⁻¹
ovalbumin for 36 min (8 ml for 18 min followed by another 8 ml for 18 min). Aerosol delivery is achieved using a DeVilbiss jet nebulizer with a flow rate of 61 min⁻¹. 24h after the last dose the mice are killed with euthatal 0.2 ml i.p. and blood samples are taken (in EDTA tubes) for differential cell count analysis, the trachea is cannulated using a pink luer mount Portex cannula cut to 1cm and the lungs are lavaged using 3 washes of 1ml of Isoton II. For cytospins, 100µl of the BALF is added to a cytospin funnel and spun, using a ThermoShandon Cytospin model 3 or 4, at 700 rpm for 5 min. Cells on the slide are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and differential cell counts carried out to differentiate eosinophils, neutrophils and lymphomononuclear cells (including monocytes, macrophages and lymphocytes).

Typically, 200 cells are counted per slide and each cell type expressed as a percentage of the total count. BALF total white cell count is measured using a Sysmex (Sysmex UK, Milton Keynes).

**Example 7**

*Evaluation on the effect of compound on lung function and BAL-neutrophilia following acute smoke exposure in the mouse*

BALB/c or C57BL6/J mice undergo whole body exposure to main stream smoke (50 min/12 cigarettes) and fresh air once or twice a day for 1-9 days. Mice are dosed via the appropriate route with vehicle, standard compound or test compound at various time points before and after challenge depending upon the experimental protocol. On the final day of the experiment, mice are either killed with euthatal 0.2 ml i.p. and broncho-aveolar lavage fluid obtained for analysis of white blood cell infiltration (as described above) or lung function is assessed using a Flexivent System (SCIREQ, Montreal, Canada). Alternatively lung mechanics are measured using a forced manoeuvres system (EMMS).

Mice are anaesthetised with pentobarbitone (1/10 dilution at a dose volume of 1 mL/kg intraperitoneally). The trachea is cannulated and the animal transferred to the Flexivent System where they are ventilated (quasi-sinusoidal ventilation pattern) at a rate of 150 breath/min and a tidal volume of 10 ml/kg in order to measure airways resistance.
Respiratory resistance is measured using the Flexivent "snapshot" facility (1 second duration, 1 Hz frequency). Mice are euthanised with approximately 0.5mL pentobarbitone sodium (Euthatal) intravenously after the completion of the lung function measurements.

**Example 8**
**Evaluation of bronchodilator activity in the guinea pig isolated tracheal ring preparation.**

Guinea pigs (300-500g) are killed by cervical dislocation and the trachea is isolated. The trachea is cut into segments 2-3 cartilage rings in width and suspended in 10ml organ baths in modified Krebs' solution (mM; NaCl, 90; NaHCO\(_3\), 45; KCl, 5; MgSO\(_4\).7H\(_2\)O, 0.5; Na\(_2\)HP0\(_4\).2H\(_2\)O, 1; CaCl\(_2\), 2.25; glucose, 10; pH 7.4 gassed with 5% CO\(_2\), 95% O\(_2\) at 37°C). The tracheal rings are attached to an isometric force transducer for the measurement of isometric tension. The tissues are washed and a force of 1g is applied to each tissue. The rings are contracted with methacholine (1 µM). Once the contraction reaches a plateau, vehicle (0.01% DMSO in distilled H\(_2\)O), a compound W (InM or 3nM), a compound X (InM), and a combination of compound W (3nM) and compound X (InM) are added and the tissue left for 60 min. The tension is measured in each ring at 60 min following compound addition and is expressed as a % relaxation of the constriction to methacholine (1µM) (mean ± s.e.mean). Data are collected using the Chart 4 software (ADInstruments, Charlgrove, UK).
Claims

1. A pharmaceutical product comprising, in combination, a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a salt thereof, and a second active ingredient selected from:
   - a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;
   - an antioxidant;
   - a CCR1 antagonist;
   - a chemokine antagonist (not CCR1);
   - a corticosteroid;
   - a CRTh2 antagonist;
   - a DPI antagonist;
   - an Histone Deacetylase Inducer;
   - an IKK2 inhibitor;
   - a COX inhibitor;
   - a lipoygenase inhibitor;
   - a leukotriene receptor antagonist;
   - an MPO inhibitor;
   - a muscarinic antagonist;
   - a p38 inhibitor;
   - a PDE inhibitor;
   - a PPARγ agonist;
   - a protease inhibitor;
   - a Statin;
   - a thromboxane antagonist;
   - a vasodilator; or,
   - an ENAC blocker (Epithelial Sodium-channel blocker).

2. A pharmaceutical product as claimed in claim 1 wherein the first active ingredient is in the form of a salt which is a hydrochloride, hydrobromide, trifluoroacetate, sulphate, sulfonate, phosphate, acetate, fumarate (such as a hemi-fumaric acid salt),
maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate, \( p - \)toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, olate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, R-mandelate, S-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulfonate), camsylate (such as (1S)-(+)-10-camphor-sulphonate), formate, glutamate, glutarate, glycolate, hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulphonate), pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate), palmitate or 1-hydroxy-2-naphthoate.

3. A pharmaceutical product as claimed in claim 1 wherein the first active ingredient is in the form of a salt which is a hemi-fumaric acid salt.

4. A pharmaceutical product as claimed in claim 1, 2 or 3 wherein the second active ingredient selected from:
   - a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;
   - a CCR1 antagonist;
   - a chemokine antagonist (not CCR1);
   - a corticosteroid;
   - an IKK2 inhibitor;
   - a muscarinic antagonist;
   - a p38 inhibitor; or,
   - a PDE inhibitor.

5. A pharmaceutical product comprising, in combination, a first active ingredient which is \( N \)-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a
pharmaceutically acceptable salt thereof, and a second active ingredient that is Tiotropium bromide.

6. A pharmaceutical product comprising, in combination, a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof, and a second active ingredient that is Glycopyrrolate.

7. A pharmaceutical product comprising, in combination, a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof, and a second active ingredient that is (R)-1-[2-(4-Fluoro-phenyl)-ethyl]-3-(5)-2-phenyl-2-piperidin-1-yl-propionyloxy)-1-azonia-bicyclo[2.2.2]octane wherein the counter-ion is chloride, bromide, sulfate, methanesulfonate, benzenesulfonate (besylate), toluenesulfonate (tosylate), naphthalenebissulfonate (napadisylate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, fumarate or succinate.

8. Use of a product according to any one of claims 1 to 7 in therapy.

9. Use of a product according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of a respiratory disease.

10. Use according to claim 9, wherein the respiratory disease is chronic obstructive pulmonary disease.

11. A method of treating a respiratory disease, which method comprises simultaneously, sequentially or separately administering:

(a) a therapeutically effective dose of a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-
yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof; and,
(b) a therapeutically effective dose of a second active ingredient which is a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist; an antioxidant; a CCR1 antagonist; a chemokine antagonist (not CCR1); a corticosteroid; a CRTh2 antagonist; a DPI antagonist; an Histone Deacetylase Inducer; an IKK2 inhibitor; a COX inhibitor; a lipoxygenase inhibitor; a leukotriene receptor antagonist; an MPO inhibitor; a muscarinic antagonist; a p38 inhibitor; a PDE inhibitor; a PPARγ agonist; a protease inhibitor; a Statin; a thromboxane antagonist; a vasodilator; or, an ENAC blocker (Epithelial Sodium-channel blocker);

to a patient in need thereof.

12. A kit comprising a preparation of a first active ingredient which is as defined in claim 1, a preparation of a second active ingredient which is as defined in claim 1, and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

13. A pharmaceutical composition comprising, in admixture, a first active ingredient which is N-Cyclohexyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)ethylamino)ethyl)-3-(3-(1-methyl-1H-pyrazol-4-yl)phenethoxy)propanamide or a pharmaceutically acceptable salt thereof, and a second active ingredient which is selected from: a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist; an antioxidant; a CCR1 antagonist; a chemokine antagonist (not CCR1); a corticosteroid; a CRTh2 antagonist; a DPI antagonist; an Histone Deacetylase Inducer; an IKK2 inhibitor; a COX inhibitor; a lipoxygenase inhibitor; a leukotriene receptor antagonist; an MPO inhibitor; a muscarinic antagonist; a p38 inhibitor; a PDE inhibitor; a PPARγ agonist; a protease inhibitor; a Statin; a thromboxane antagonist; a vasodilator; or, an ENAC blocker (Epithelial Sodium-channel blocker); and a carrier, diluent or adjuvant therefore.
INTERNATIONAL SEARCH REPORT

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

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

EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>1-6,8-13</td>
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<td>7 October 2010 (2010-10-07)</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search

24 February 2011

Date of mailing of the international search report

07/03/2011

Authorized officer

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<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>wo 2007/027133 AI (ASTRAZENECA AB [SE]; BAI LEY ANDREW [GB]; BONNERT ROGER [GB]; FLAHERTY) 8 March 2007 (2007-03-08) the whole document</td>
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* abstract
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<th>Publication date</th>
<th>Patent family member(s)</th>
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<tbody>
<tr>
<td>WO 2009154557 Al</td>
<td>23-12-2009</td>
<td>AR 072189 Al</td>
<td>11-08-2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2009260899 Al</td>
<td>23-12-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2726746 Al</td>
<td>23-12-2009</td>
</tr>
<tr>
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<td>US 2010105642 Al</td>
<td>29-04-2010</td>
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<td></td>
<td>UY 31905 A</td>
<td>29-01-2010</td>
</tr>
<tr>
<td>WO 2010114472 Al</td>
<td>07-10-2010</td>
<td>US 2010261690 Al</td>
<td>14-10-2010</td>
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<td></td>
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<td>UY 32521 A</td>
<td>29-10-2010</td>
</tr>
<tr>
<td>WO 2007027133 Al</td>
<td>08-03-2007</td>
<td>AR 055617 Al</td>
<td>29-08-2007</td>
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<tr>
<td></td>
<td></td>
<td>CN 101300240 A</td>
<td>05-11-2008</td>
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<tr>
<td></td>
<td></td>
<td>EP 1957471 Al</td>
<td>20-08-2008</td>
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<td>JP 2009506110 T</td>
<td>12-02-2009</td>
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<td>13-08-2009</td>
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<tr>
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<td></td>
<td>UY 29768 Al</td>
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