Title: COMBINATIONS COMPRISING A GLUCOCORTICOID RECEPTOR MODULATOR FOR THE TREATMENT OF RESPIRATORY DISEASES

Abstract: The invention provides a pharmaceutical product, kit or composition comprising a first active ingredient which is a glucocorticoid receptor modulator and a second active ingredient selected from an Adenosine A2A receptor antagonist, an anti-inflammatory, an antioxidant, a β2 adrenoceptor agonist, a CCR1 antagonist, a chemokine antagonist, a muscarinic antagonist, a glucocorticosteroid, a CRTH2 antagonist, a DPI antagonist, a formyl peptide receptor antagonist, a Histone Deacetylase activator, a chloride channel hCLC2A blocker, an Epithelial sodium channel blocker, an Inter-cellular adhesion molecule 1 blocker, an iNOS kinase inhibitor, a JNK kinase inhibitor, a COX inhibitor, a lipoxygenase inhibitor, a leukotriene receptor antagonist, a MEK-1 kinase inhibitor, a MPO inhibitor, a PDE4 inhibitor, a PI 3 kinase γ inhibitor, a PPARγ agonist, a protease inhibitor, a p38 inhibitor, a RARγ modulator, a statin, a thromboxane antagonist and a vasodilator; and its use in the treatment of respiratory disease.
COMBINATIONS COMPRISING A GLUCOCORTICOID RECEPTOR MODULATOR FOR THE TREATMENT OF RESPIRATORY DISEASES

THE FIELD OF THE INVENTION

The present invention relates to a combination comprising a glucocorticoid receptor modulator and another pharmaceutically active substance suitable for use in the treatment of respiratory diseases. The invention further relates to pharmaceutical compositions comprising said combination and to methods of treatment of respiratory diseases, including airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma in mammals by administrating said combination. The invention also relates to a kit comprising the combination and use of said kit in treatment of respiratory diseases.

BACKGROUND OF THE INVENTION

Damage or infection of the lungs can give rise to a wide range of diseases of the respiratory system (respiratory diseases). Such 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 COPD conditions 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 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).

It is known that certain non-steroidal compounds interact with the glucocorticoid receptor (GR) and, as a result of this interaction, produce a suppression of inflammation (see, for example, US6323 199). Such compounds can show a clear dissociation between anti-inflammatory and metabolic actions making them superior to earlier reported steroidal and non-steroidal glucocorticoids. The glucocorticoid receptor modulator in the combinations according to the present invention are non-steroidal modulators (for example agonists,
antagonists, partial agonists or partial antagonists) of the glucocorticoid receptor and are expected to beneficial in the treatment of respiratory diseases such as COPD and asthma.

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 \( \beta_2 \) adrenoceptor agonists, muscarinic receptor antagonists and methylxanthines. Bronchodilators are prescribed mainly for symptomatic relief and they are not considered to alter the natural history of respiratory diseases.

Combination products comprising a \( \beta_2 \) adrenoceptor agonist and a corticosteroid are available. One such product is a combination of budesonide and formoterol fumarate (marketed by AstraZeneca under the trade name Symbicort \( \text{®} \)), 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 \( \beta_2 \) adrenoceptor agonist and a corticosteroid deliver significant patient benefits, there remains a medical need for new therapies against respiratory diseases such as asthma and COPD, in particular for therapies with disease modifying potential.

**DETAILED DESCRIPTION OF THE INVENTION**

Accordingly, the present invention provides a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator selected from:

- \( 3-(5-\{(\text{IR},2\text{S})-2-(2,2\text{-difluoropropanoyl})\text{amino}\}-1-(2,3\text{-dihydro-1,4-benzodioxin-6-yl})\text{propyl}\text{oxy}\}-1\text{H-indazol-1-yl})\text{-N-}[\text{(3R)-1,1-dioxidotetrahydrothiophen-3-yl}]\text{benzamide}; \)
- \( 3-\{5-(\{(\text{IR},2\text{S})-1-(4\text{H}-1,3\text{-benzdioxin-7-yl})-2-(2,2\text{-difluoropropanoyl})\text{amino})\text{propyl}\text{oxy}\}-1\text{H-indazol-1-yl}\}-\text{N-}[\text{(3R)-1,1-dioxidotetrahydrothiophen-3-yl}]\text{benzamide}; \)
- \( 3-\{5-(\{(\text{IR},2\text{S})-1-(4\text{H}-1,3\text{-benzdioxin-7-yl})-2-(2,2\text{-difluoropropanoyl})\text{amino})\text{propyl}\text{oxy}\}-1\text{H-indazol-1-yl}\}-\text{N-}[\text{(3S)-1,1-dioxidotetrahydrothiophen-3-yl}]\text{benzamide}; \)
- \( 3-\{5-\{(\text{IR},2\text{S})-2-(2,2\text{-difluoropropanoyl})\text{amino}\}-1-(2,3\text{-dihydro-1,4-benzodioxin-6-yl})\text{propyl}\text{oxy}\}-1\text{H-indazol-1-yl}\}-\text{N-}[\text{(3S)-1,1-dioxidotetrahydrothiophen-3-yl}]\text{benzamide}; \)
- \( 3-\{5-(\{(\text{IR},2\text{S})-1-(4\text{H}-1,3\text{-benzdioxin-7-yl})-2-(2,2\text{-difluoropropanoyl})\text{amino})\text{propyl}\text{oxy}\}-1\text{H-indazol-1-yl}\}-\text{N-}[\text{(3R)-1,1-dioxidotetrahydrothiophen-3-yl}]\text{benzamide}; \)
3-(5-[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-
yl)propyl]oxy)-1H-indazol-1-yl)-N-[tetrahydrofuran-3-yl]benzamide; and
3-(5-[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-
yl)propyl]oxy]-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide;
or a pharmaceutically acceptable salt thereof; and
ii) a second active ingredient selected from:
an Adenosine A2A receptor antagonist;
an anti-infective;
an antioxidant;
a β₂ adrenoceptor agonist;
a CCR1 antagonist;
a chemokine antagonist (not CCR1);
a glucocorticosteroid;
a CRTh2 antagonist;
a DPI antagonist;
a formyl peptide receptor antagonist;
a Histone Deacetylase activator;
a chloride channel hCLCAl blocker
an Epithelial sodium channel blocker (ENAC blocker).
an Inter-cellular adhesion molecule 1 blocker (ICAM blocker);
an IKK2 kinase inhibitor;
a INK kinase inhibitor;
a cyclooxygenase inhibitor (COX inhibitor);
a lipoxigenase inhibitor;
a leukotriene receptor antagonist;
a MEK-1 kinase inhibitor
a myeloperoxidase inhibitor (MPO inhibitor);
a muscarinic antagonist;
a dual muscarinic antagonist adrenoceptor agonist (MABA compound);
a phosphodiesterase PDE4 inhibitor;
a phosphatidylinositol 3 (PD)-kinase γ inhibitor (PI 3 kinase γ inhibitor)
a peroxisome proliferator activated receptor agonist (PPARy agonist);
a protease inhibitor;
a p38 inhibitor;
a retinoic acid receptor modulator (RAR γ modulator)
a Statin;
a thromboxane antagonist; and
a vasodilator.

First Active Ingredient

The first active ingredient may be used in the form a pharmaceutically acceptable salt. Possible acid addition salts of the first active ingredient include, for example, a hydrochloride, hydrobromide, phosphate, sulfate, acetate, ascorbate, benzoate, fumarate, hemifumarate, furoate, succinate, maleate, tartrate, citrate, oxalate, xinafoate, methanesulphonate, p-toluencesulphonate, benzenesulphonate, ethanesulphonate, 2-naphthalenesulphonate, mesitylenesulphonate, nitrate, 1,5-naphthalene-disulphonate, p-xylenesulphonate, aspartate or glutamate.

It is to be understood that the first active ingredient, or a pharmaceutically acceptable salt thereof, may exist in solvated, for example hydrated, as well as unsolvated forms, or as cocrystals and the present invention encompasses all such forms that are useful as a glucocorticoid receptor modulator.

Some compounds of the first active ingredient may exhibit polymorphism. It is to be understood that the present invention encompasses any such polymorphic form, or mixtures thereof, which form possesses properties useful useful as a glucocorticoid receptor modulator.

The compounds of the first active ingredient are chiral. Suitably the compounds are used as a single a single stereoisomer, such as an enantiomer. However the compound may be used in the form of mixtures of stereoisomers in any proportions, including racemic mixtures.

Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention which possess properties useful as a glucocorticoid receptor modulator. The optical isomers of the compound in the first active ingredient may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC. Alternatively the optical isomers may be obtained by asymmetric synthesis, or by synthesis from optically active starting materials. Suitable examples for the preparation of the compounds of the first active ingredient are described in the Examples.
Second Active Ingredient

An Adenosine A2A receptor antagonist is, for example, a compound such as UK-432097.
An anti-infective is, for example, an antibiotic such as Amoxicillin, Doxycycline, Trimethoprim sulph, or a Cephaplosporin.

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).

Also, a CCR1 antagonist is, for example, N-2-[(25)-3-[[l-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenylacetamide, also named as 4-([(25)-3-[2-(acetylamino)-5-hydroxyphenoxy]-2-hydroxy-2-methylpropyl]ammonio)-l-(4-chlorobenzyl)piperidine (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-{[2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl[methyl]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-(trifluormethoxy)phenyl]acetamide) or Vicriviroc.

A β2-adrenoceptor agonist is any compound or substance capable of stimulating the β2-receptors and acting as a bronchodilator. In the context of the present specification, unless otherwise stated, any reference to a β2-adrenoceptor agonist includes an active salt, solvate or derivative that may be formed from said β2-adrenoceptor agonist or any enantiomer or mixture thereof. Examples of possible salts or derivatives of β2-adrenoceptor agonist are acid addition salts such as the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid,
1-hydroxy-2-naphthalenecarboxylic acid, maleic acid, and pharmaceutically acceptable esters (e.g. Ci-C₆ alkyl esters). The β₂-agonists may also be in the form of solvates, e.g. hydrates.

Examples of a β₂-adrenoceptor agonist that may be used in the pharmaceutical product according to one embodiment include metaproterenol, isoproterenol, isoprenaline, hexoprenaline, ibuterol, albuterol, procaterol, repproterol, sulphonterol, tulobuterol, salbutamol (e.g. as sulphate), formoterol (e.g. as fumarate, particularly formoterol fumarate dihydrate), salmeterol (e.g. as xinafoate), fenoterol, terbutaline, carbuterol, clenbuterol, orciprenaline, bitolterol (e.g. as mesylate), pirbuterol or indacaterol.

The β₂-adrenoceptor agonist of an alternative embodiment may be a long-acting β₂-agonist (i.e. a β₂-agonist with activity that persists for more than 24 hours), for example

- salmeterol (e.g. as xinafoate)
- formoterol (e.g. as fumarate)
- bambuterol (e.g. as hydrochloride)
- carmoterol (TA 2005, chemically identified as [R-(R*,R*)]-8-hydroxy-5-[1-hydroxy-2-
  [2-(4-methoxy-phenyl)-1-methylethyl]-amino]ethyl]-2(1H)-quinolone monohydrochloride, also identified by Chemical Abstract Service Registry Number 137888-1 1-0 and disclosed in U.S. Patent No 4,579,854)
- a benzothiazolone as disclosed in WO2005074924, or WO2006056741 (for example
  7-[(R)-2-((lS,2S)-2-Benzyloxy-cyclopentylamino)-l-hydroxyethyl]-4-hydroxy-3H-
  benzothiazol-2-one)
- an aryl aniline as disclosed in WO 2003042164 or WO2006 133942 (for example N-[2-[4-
  [3-phenyl-4-methoxyphenyl]amino]phenyl]ethyl]-2-hyderabadox-2-(8-hydroxy-1,2-
  dihydro-2-oxoquinolino-5-yl]ethylamine)
- compounds disclosed in WO200607489 (for example 5-[(R)-2-(2-[4-(2-amino-2-
  methyl-propoxy)-phenylamino]-phenyl]-ethylamino]-l-hydroxyethyl]-8-hydroxy-IH-
  quinolin-2-one)
- a formanilide as disclosed in WO200401 1416, WO2005030678, or 2006066907 (for
  example N-(2-[4-((R)-2-hydroxy-2-phenylethylamino)phenyl]ethyl)-(R)-2-hydroxy-2-(3-
  formamido-4-hydroxyphenyl)ethylamine)
- compounds disclosed in WO2005 121065 (for example 8-hydroxy-5-[(lR)-l-hydroxy-2-
  [6-(phenethylamino)hexylamino]ethyl]-lH-quinolin-2-one)
\begin{itemize}
  \item compounds disclosed in WO2003024439 (for example \((\text{IR})\)-4-[2-[6-[2-[(2,6-
dichlorophenyl)methoxy]ethoxy]hexylamino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol)
  \item compounds disclosed in WO2004037773 (for example 4-[(\text{IR})]-2-[6-[4-(3-
cyclopentylsulfonylphenyl)butoxy]hexylamino] -1-hydroxyethyl]-2-
  (hydroxymethyl)phenol).
  \item a benzenesulfonamide derivative as disclosed in WO2002066422 (for example 3-(4-[
  \item a formanilide disclosed in WO2002076933 (for example 3-(4-(6-((2R)-2-[3-(
  formylamino)-4-hydroxyphenyl] -2-hydroxyethyl} amino)hexyl]oxy} -butyl)-
  benzenesulfonamide)
  \item a compound GSK159797, GSK159802, GSK597901, GSK642444 or GSK678007
  \item an indole derivative as disclosed in WO2004032921 (for example N-[(2,6-
dimethoxyphenyl)methyl] -5-[2-[2-hydroxy-2-[4-hydroxy-3-
  \item compounds disclosed in WO2006051375 (for example N-(1-adamantyl)-2-[3-[(2R)-2-
  acetamide).
  \item compounds disclosed in WO2008017637 (for example 8-[(\text{IR})]-2-[[4-[3-(4-chlorophenyl)-
  5-methyl-1,2,4-triazol- 1-yl]-2-methylbutan-2-yl] amino] -1-hydroxyethyl] -6-hydroxy-4H-
  1,4-benzoazin-3-one).
  \item compounds disclosed in WO2008023003 (for example N-[5-[(\text{IR})]-2-[[4-(4,4-diethyl-2-
oxo-3,1-benzoazin- 1-yl)-2-methylbutan-2-yl] amino] - 1-hydroxyethyl] -2-
  hydroxyphenyl]methanesulfonamide).
  \item compounds disclosed in WO2006122788, and WO2008095720 (for example 5-(2-[[
  2,2-difluoro-2-phenylethoxy]hexyl]amino]-1-hydroxyethyl)-8-hydroxyqu
  inolin-2(1H)-one).
  \item compounds disclosed in WO2008046598 (for example 5-[[\text{IR})]-2-[[2-[4,2,2-difuo
  ro-2-phenylethoxy]phenyl] ethylamino]- 1-hydroxyethyl] -8-hydroxy- 1H-quino
  lin-2-one).
  \item compounds disclosed in WO2007124898 (for example 5-(2-[[6-2-[(2,6-
  inolin-2(1H)-one).
\end{itemize}
In yet another alternative embodiment of the invention, the $\beta_2$-adrenoceptor agonist is selected from:

- $N$-[2-(Diethylamino)ethyl]-$N$-[2-[(2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino]ethyl]-3-[2-(1-naphthyl)ethoxy]propanamide; as disclosed in WO20080961

- $N$-[2-(Diethylamino)ethyl]-$N$-[2-[(2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino]ethyl]-3-[2-(3-chlorophenyl)ethoxy]propanamide or a pharmaceutically acceptable salt thereof; as disclosed in WO20080961, WO2007018461 and WO200809612.

- 7-[(1R)-2-((2-[[2-(2-Chlorophenyl)ethyl] amino]propyl)thio)ethyl] amino)-1-hydroxyethyl]-4-hydroxy-1,3-benzothiazol-2(3H)-one; as outlined in WO2008104776

- 4-Hydroxy-7-[(1-hydroxy-2-(2-[[3-(2-methoxy-benzylamino)-methyl]-phenyl]-ethylamino)-ethyl]-3H-benzothiazol-2-one, as disclosed in WO2008106016, and,

- $N$-Cyclohexyl-3-[2-(3-fluorophenyl)ethylamino]-$N$-[2-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]ethyl]propanamide, as disclosed in WO2008075026 or a pharmaceutically acceptable salt thereof.

In yet a further embodiment of the invention, the $\beta_2$-adrenoceptor agonist is selected from:

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

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

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

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

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

In one embodiment the $\beta_2$-agonist of the invention has a fast onset of action, i.e. a $\beta_2$-agonist with an onset of action within 1 hour. Examples of $\beta_2$-agonists with fast onset of action include formoterol, TA 2005, salbutamol and $\beta_2$-agonists as disclosed in WO2005095328 and US2005272769.
In an embodiment of the present invention the $\beta_2$-agonist is formoterol. The chemical name for formoterol is $N$-[2-hydroxy-5-[(l)-1-hydroxy-2-[[[(l)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide. The preparation of formoterol is described, for example, in WO 92/05147. As will be clear from the above, the term formoterol is intended to include all pharmaceutically acceptable salts thereof. In one aspect of this embodiment, the $\beta_2$-agonist is formoterol fumarate, for example formoterol fumarate dihydrate.

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

In a further embodiment of the present invention, the $\beta_2$-agonist is indacaterol. As will be clear from the above, the term indacaterol is intended to include all pharmaceutically acceptable salts thereof, including for example, indacaterol maleate and indacaterol hydrochloride. In one embodiment of the present invention, the $\beta_2$-agonist is selected from $N$-[2-(Diethylamino)ethyl]-$N$-(2-[[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino]ethyl)-3-[2-(1-naphthyl)ethoxy]propanamide or a salt thereof, a $N$-[2-(Diethylamino)ethyl]-$N$-(2-[[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino]ethyl)-3-[2-(3-chlorophenyl)ethoxy]propanamide or a salt thereof, or a 7-[(l)-2-[[2-((3-ethyl(2-Chlorophenyl)ethyl)amino)propyl]thio]ethyl]amino]-1-hydroxyethyl]-4-hydroxy-1,3-benzothiazol-2(3H)-one or a salt thereof.

A muscarinic antagonist is, for example, trospium chloride (ALKS27) (Spiro[8-azoniabicyclo[3.2.1]octane-8,1'-pyrrolidinium], 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-chloride (1:1), (1.alpha.,3.beta.,5.alpha.), tiotropium bromide (3-Oxa-9-azoniatricycl[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.), QAX028, QAT370, PT001, Oxitropium bromide (3-Oxa-9-azoniatricycl[3.3.1.02,4]nonane, 9-ethyl-7-[(2S)-3-hydroxy-1-oxo-2-phenylpropoxy]-9-methyl-, bromide (1:1), (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.), GSK1084838, GSK573719 (3-


A CCR1 antagonist is, for example, a compound disclosed in WO2001/062728 or WO2002/098273, or a pharmaceutically acceptable salt thereof (such as a hydrochloride, trifluoroacetate, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

In one embodiment the CCR1 antagonist is, for example, a compound described in WO 2003/051839, for example N’-[2-][((25)-3-[[l-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl]acetamide, or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).
In another embodiment the CCR1 antagonist is, for example, a compound described in WO 2008/010765, such as 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, or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemif)umarate, benzoate, furoate or succinate salt).

A chemokine antagonist (other than a CCR1 antagonist), for example, 656933 (N-(2-bromophenyl)-N'-\[(2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl\]methyl\}amino)carbonyl]-methyl\}methylbenzamidine), CCX-282, CCX-915, Cyanovirin N, E-921, INCB-003284, INCB-9471, Maraviroc, MLN-3701, MLN-3897, T-487 (N-[\{(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 chloride channel hCLCA1 blocker is, for example, as disclosed in WO2006/091112, WO2004/13286 and WO2001/038530.

A glucocorticosteroid is, for example, alclometasone dipropionate, amelometasone, beclometasone dipropionate, budesonide, butixocort propionate, ciclesonide, clobetasol propionate, desisobutyrylciclesonide, etiprednol dicoacetate, fluocinolone acetonide, fluticasone furoate, fluticasone propionate, lotepredn etabonate (topical), mometasone furoate or a compound described in WO 2009/044200, for example,

(NO,R,3aS,3bS, I0aR, I0bS, II.S, 12aS) l-[\{\{(cyanomethyl)sulfanyl\}carbonyl\} -7-(4-fluorophenyl)-11-hydroxy-10a,12a-dimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,1 l,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-l-yl furan-2-carboxylate.

A CRTh2 antagonist is, for example, a compound from WO 2004/106302, WO2004/089885, WO2005/018529 or WO2007/039741.

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

An ENAC (Epithelial Sodium-channel blocker) is, for example, amiloride, benzamil, triamterene, 552-02, PSA14984, PSA25569, PSA23682, AER002, parion P-522 or a compound from WO2008031048.

A formyl peptide receptor antagonist is, for example, a compound from WO2007/144198.
A histone deacetylase activator is, for example, ADC4022, aminophylline, a methylxanthine or theophylline.

An ICAM blocker is, for example, an anti-ICAM-1 monoclonal antibody (MAb) 1A6 from Antimicrobial Agents and Chemotherapy 2003, 47, 1503-1508.

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

A JNK inhibitor is, for example, a compound from WO2005/003123 or WO2003/051277.

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, Dextubuprofen lysine (monohydrate), Etalocib sodium, Licofelone, Linazolast, Lonapalene, Masoprocol, MN-001 , Tepoxalin, UCB-35440, Veliflapon, ZD-2138, ZD-4007 or Zileuton ((±)-l-(l-Benzol[b]thien-2-ylethyl)-l -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.

A MEK-1 inhibitor is, for example, a compound disclosed in WO2007123939, WO2007025090 or WO2005051906.

An MPO Inhibitor is, for example, a Hydroxamic acid derivative (N-(4-chloro-2-methyl-phenyl)-4-phenyl-4-[(4-propan-2-ylphenyl)sulfonylamino]methyl)piperidine-1-carboxamide), Piceatannol or Resveratrol, or a compound disclosed within US7425560, WO2003/089430, WO2006/062465 and WO2007/120098.

A PDE4 inhibitor is, for example, 6-fluoro-N-((lS,4s)-4-(6-fluoro-2,4-dioxo-1-(4'-(piperazin-1-ylmethyl)-biphenyl-3 -yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl)imidazo[1,2-a]pyridine-2-carboxamide (as disclosed in. WO2008084223), or a salt thereof (for example a (LI)-(+)10-Camphorsulfonic acid or trihydrochloride salt).
A PI 3 kinase \(\gamma\) inhibitor is, for example, a compound from WO2005/105801, WO2003/072557, and WO2007/082956.

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 1-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 Doxycycline); inhibitors of cathepsins for example inhibitors of cathepsin S (for example as disclosed in WO2002/14314), cathepsin L (for example as described within Bioorg. Med. Chem. 2004,12, 4081), cathepsin K (for example WO 2001/47886) , cathepsin B (for example tokaramide A and leupetin) and cathepsin C (dipeptidyl peptidase 1) (for example a compound from WO 2005/000800); inhibitors of neutrophil elastase, for example as disclosed in WO2005/026123 and WO2007/129963 (for example 6-[l-(4-cyanophenyl)-1H-pyrazol-5-yl]-N,5-dimethyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydropyrazine-2-carboxamide) and inhibitors of matrix metallo proteinases (for example ABT-518 or Ro-32-7315).

p38 inhibitors are, 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-[(2S,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl \(-\)-N,N,l-trimethyl-a-oxo-l \(H\)-indole-3-acetamide, VX702 or VX745 (5-(2,6-dichlorophenyl)-2-(phenylthio)-6H-pyrimido[l ,6-b]pyridazin-6-one). In one embodiment the p38 inhibitor is \(N\)-cyclopropyl-3-fluoro-4-methyl-5-[3-[[l]-2-[2-(methylamino)ethoxy]phenyl] cyclopropyl]amino]-2-oxo-l(2 \(H\))-pyrazinyl]-benzamide, or a pharmaceutically acceptable salt thereof such as the hydrochloride or L-tartaric acid salt (WO2009/001 132).

A RAR \(\gamma\) modulator (Retinoic acid gamma receptor modulator) is, for example, palovarotene (R667), a compound disclosed in WO2008064136 (agonists) or WO2006066978 (antagonists).

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 treprostilin, PS-433540, Sitaxsentan sodium, Sodium Ferulate, TBC-1 1241 (Sitaxsentan), TBC-371, Trapidil, Treprostilin diethanolamine or Treprostilin sodium.

All the above second et seq active ingredients may be in the form of solvates, for example hydrates. Unless stated otherwise, all the above second et seq active ingredients may be in the form of pharmaceutically acceptable salts. It is to be understood that where herein one of the second active ingredients is described as a particular salt form, that other suitable pharmaceutically acceptable salts of that second active ingredient may also be used in the invention.

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient selected from:

- a β2 adrenoceptor agonist;
- a CCR1 antagonist;
- a muscarinic antagonist;
- a PDE4 inhibitor; and
- a p38 inhibitor.

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient, which is the β2 adrenoceptor agonist N-[2-(Diethylamino)ethyl \(-N-(2-[[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-
ethylaminoethyl)-3-[2-(3-chlorophenyl)ethoxy]propanamide or a pharmaceutically acceptable salt thereof, for example a dihydrobromide salt.

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient, which is the β2 adrenoceptor agonist 3-[(25)-3-[(1-(4-chlorobenzyl)piperidin-4-yl)amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenylacetamide, or a pharmaceutically acceptable salt thereof, for example a di-D-mandelate salt.

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient which is the CCR1 antagonist [2-[(2S)-3-[(1-(4-chlorobenzyl)piperidin-4-yl)amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenylacetamide, or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient which is the CCR1 antagonist 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, or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and
ii) a second active ingredient which is the PDE4 inhibitor 6-fluoro-N-((1S,4S)-4-(6-fluoro-2,4-dioxo-1-(4′-(piperazin-1-ylmethyl)-3-phenyl-3-yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl)imidazo[1,2-a]pyridine-2-carboxamide, or a pharmaceutically acceptable salt thereof (for example a (1S)-(+)10-Camphorsulfonic acid or trihydrochloride salt).

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient which is the p38 inhibitor N-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-[2H]-pyrazinyl]-benzamide, or a pharmaceutically acceptable salt thereof such as the hydrochloride or L-tartaric acid salt.

In another embodiment of the invention there is provided a pharmaceutical product comprising, in combination:

i) a first active ingredient which is a glucocorticoid receptor modulator as hereinbefore defined; and

ii) a second active ingredient which is tiotropium bromide.

It is to be understood that the present invention discloses all combinations comprising any one of the compounds of the first active ingredient with any of the second active ingredients disclosed herein.

Accordingly in one embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-(5-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy]-1H-indazol-1-yl)-N-[(3S)-l,l-dioxidotetrahydrothiophen-3-yl]benzamide or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.

In another embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-(5-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy]-1H-indazol-1-yl)-N-[(3R)-l,l-dioxidotetrahydrothiophen-3-yl]benzamide, or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.
In another embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-[(1R,2S)-1-(4H-1,3-Benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl oxy]-1H-indazol-1-yl]-N-[3R]-1,1-dioxidotetrahydrothiophen-3-yl]benzamide, or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.

In another embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl oxy]-1H-indazol-1-yl]-N-[3R]-tetrahydrofuran-3-yl]benzamide, or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.

In another embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide, or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.

In another embodiment there is provided a pharmaceutical product comprising, in combination, a first active ingredient which is 3-[(1R,2S)-1-(4H-1,3-Benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide, or a pharmaceutically acceptable salt thereof and any one of the second active ingredients disclosed herein.

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 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.

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 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. The active ingredients of the present invention may also be
administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or
intraarticular) administration using conventional systemic dosage forms, such as tablets,
capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile
injectable aqueous or oily solutions or suspensions. As will be understood by those skilled in
the art, the most appropriate method of administering the active ingredients is dependent on a
number of factors.

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 a glucocorticoid receptor
modulator as hereinbefore defined, 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 a glucocorticoid receptor modulator as hereinbefore defined or in salt form, solvate form, or, solvate of salt form) will generally be in the range of from 0.1 microgram \(^g\) to 5000 \(\mu g\), 0.1 to 1000 \(\mu g\), 0.1 to 500 \(\mu g\), 0.1 to 100 \(\mu g\), 5 to 5000 \(\mu g\), 5 to 100 \(\mu g\), 5 to 50 \(\mu g\), 5 to 1000 \(\mu g\), 10 to 1000 \(\mu g\), 10 to 500 \(\mu g\), 20 to 5000 \(\mu g\), 20 to 1000 \(\mu g\), 20 to 500 \(\mu g\), 20 to 100 \(\mu g\), 50 to 5000 \(\mu g\), 50 to 1000 \(\mu g\), 50 to 500 \(\mu g\), 50 to 100 \(\mu g\), 100 to 5000 \(\mu g\), 100 to 1000 \(\mu g\) or 100 to 500 \(\mu g\). 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 \(^g\) to 5000 \(\mu g\), 0.1 to 1000 \(\mu g\), 0.1 to 500 \(\mu g\), 0.1 to 100 \(\mu g\), 0.1 to 50 \(\mu g\), 0.1 to 10 \(\mu g\), 0.1 to 5 \(\mu g\), 5 to 5000 \(\mu g\), 5 to 1000 \(\mu g\), 5 to 500 \(\mu g\), 5 to 100 \(\mu g\), 5 to 50 \(\mu g\), 5 to 10 \(\mu g\), 10 to 5000 \(\mu g\), 10 to 1000 \(\mu g\), 10 to 500 \(\mu g\), 10 to 100 \(\mu g\), 10 to 50 \(\mu g\), 20 to 5000 \(\mu g\), 20 to 1000 \(\mu g\), 20 to 500 \(\mu g\), 20 to 100 \(\mu g\), 20 to 50 \(\mu g\), 50 to 5000 \(\mu g\), 50 to 1000 \(\mu g\), 50 to 500 \(\mu g\), 50 to 100 \(\mu g\), 100 to 5000 \(\mu g\), 100 to 1000 \(\mu g\) or 100 to 500 \(\mu g\).

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. heptafluoroalkane) propellant, or a mixture of any such propellants, for example in a pressurised metered dose inhaler (pMDI). Preferred propellants are PI34a and P227, each of which may be used alone or in combination with 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.

Certain of the glucocorticoid receptor modulators described herein may exist in form of polymorphs and solvates (particularly hydrates). Accordingly, as independent features of the present invention there is provided the crystalline forms described hereafter.

We have found that the compound 3-[5-(((2R,2S)-1-((4H-1,3-benzodioxin-7-yl)-2-[2,2-difluoropropanoyl]amino)propyl)oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide, hereafter "Compound (I)" can exist in different crystalline forms. Compound (I) Form A is characterised in that it provides an X-ray powder diffraction as shown in Figure 1. Compound (I) Form A is non-hygroscopic and is stable even under conditions of high humidity. Compound (I) Form A may therefore be particularly suitable for use in dry powder formulations suitable for administration from a dry powder inhaler. Compound (I) Form A has characteristic XRPD peaks at about 2-theta = 7.5°, 8.9°, 12.6°, 13.3°, 15.7°, 17.8°, 18.9°, 20.1°.

Therefore according to a further aspect of the present invention there is provided crystalline Compound (I) Form A.

According to a further aspect of the invention there is provided Compound (I) Form A, wherein said Compound (I) Form A has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 12.6° or 18.9°.

According to a further aspect of the invention there is provided Compound (I) Form A, wherein said Compound (I) Form A has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 7.5°, 8.9°, 12.6°, 13.3°, 15.7°, 17.8°, 18.9° or 20.1°.

According to a further aspect of the invention there is provided Compound (I) Form A, wherein said Compound (I) Form A has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 12.6° and 18.9°.
According to a further aspect of the invention there is provided Compound (I) Form A, wherein said Compound (I) Form A has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 7.5°, 8.9°, 12.6°, 13.3°, 15.7°, 17.8°, 18.9° and 20.1°.

According to another aspect of the invention there is provided Compound (I) Form A, wherein said Compound (I) Form A has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 1.

The DSC thermogram for Compound (I) Form A is shown in Figure 2. Compound (I) Form A, shows a sharp melting endotherm with an onset temperature of about 159°C, as determined by differential scanning calorimetry (DSC) analysis as described in the Examples. Accordingly Compound (I) Form A has a melting point of about 159°C.

We have also found that Compound (I) may exist in another crystalline form, hereafter referred to as Compound (I) Form B, which is characterised in that it provides an X-ray powder diffraction as shown in Figure 3. Compound (I) Form B is slightly hygroscopic and transforms to a hydrate form (Compound (I) Form C described hereafter). However, upon drying the hydrate transforms back to Compound (I) Form B. It is expected that the properties of Compound (I) Form B will make this form particularly suitable for use in an aqueous suspension formulation, for example a composition suitable for use in a nebulizer or metered dose inhaler. Compound (I) Form B has characteristic peaks at about 2-theta = 6.8°, 8.1°, 12.1°, 12.9°, 13.1°, 13.5°, 15.2° and 19.8°.

Therefore according to a further aspect of the present invention there is provided crystalline Compound (I) Form B.

According to a further aspect of the invention there is provided Compound (I) Form B, wherein said Compound (I) Form B has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 8.1° or 13.5°.

According to a further aspect of the invention there is provided Compound (I) Form B, wherein said Compound (I) Form B has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 6.8°, 8.1°, 12.1°, 12.9°, 13.1°, 13.5°, 15.2° or 19.8°.

According to a further aspect of the invention there is provided Compound (I) Form B, wherein said Compound (I) Form B has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 8.1° and 13.5°.
According to a further aspect of the invention there is provided Compound (I) Form B, wherein said Compound (I) Form B has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 6.8°, 8.1°, 12.1°, 12.9°, 13.1°, 13.5°, 15.2° and 19.8°.

According to another aspect of the invention there is provided Compound (I) Form B, wherein said Compound (I) Form B has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 3.

The DSC thermogram for Compound (I) Form B is shown in Figure 4. Compound (I) Form B, shows a sharp melting endotherm with an onset temperature of about 148°C, as determined by differential scanning calorimetry (DSC) analysis as described in the Examples. Accordingly Compound (I) Form B has a melting point of about 148°C.

We have also found that Compound (I) may exist in another crystalline form, hereafter referred to as Compound (I) Form C hydrate, which is characterised in that it provides an X-ray powder diffraction as shown in Figure 5. Compound (I) Form C hydrate is formed when Compound (I) Form B is exposed to high humidity. Compound (I) Form C is also formed when Compound (I) Form A is stored in an aqueous medium under certain conditions. As mentioned above, when Compound (I) Form C hydrate is dried by storing at an elevated temperature the Compound (I) Form C hydrate transforms to Compound (I) Form B. The dehydration Compound (I) Form C hydrate provides a convenient method for the preparation of Compound (I) Form B in pure form. Compound (I) Form C has characteristic peaks at about 2-theta = 7.5°, 11.7°, 12.9°, 13.0°, 14.1°, 19.4°, 19.7° and 20.8°.

Therefore according to a further aspect of the present invention there is provided crystalline Compound (I) Form C hydrate.

According to a further aspect of the invention there is provided Compound (I) Form C hydrate, wherein said Compound (I) Form C hydrate has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 7.5°, 11.7°, 12.9°, 13.0°, 14.1°, 19.4°, 19.7° or 20.8°.

According to a further aspect of the invention there is provided Compound (I) Form C hydrate, wherein said Compound (I) Form C hydrate has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 7.5°, 11.7°, 12.9°, 13.0°, 14.1°, 19.4°, 19.7° and 20.8°.
According to another aspect of the invention there is provided Compound (I) Form C hydrate, wherein said Compound (I) Form C hydrate has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5.

The DSC thermogram for Compound (I) Form C hydrate is shown in Figure 4. Compound (I) Form C hydrate, shows a broad endotherm between about 30°C to about 70°C, followed by a sharp melting endotherm with an onset temperature of about 148°C, as determined by differential scanning calorimetry (DSC) analysis as described in the Examples.

We have also found that the compound 3-(5-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy]-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide hereafter "Compound (II)" can exist in different crystalline forms. Compound (II) Form A is characterised in that it provides an X-ray powder diffraction as shown in Figure 6. Compound (II) Form A has characteristic peaks at about 2-theta = 7.4°, 11.4°, 15.1°, 16.3°, 17.1°, 17.8°, 19.9° and 21.8°.

Therefore according to a further aspect of the present invention there is provided crystalline Compound (II) Form A.

According to a further aspect of the invention there is provided Compound (II) Form A, wherein said Compound (II) Form A has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 15.1° or 17.8°.

According to a further aspect of the invention there is provided Compound (II) Form A, wherein said Compound (II) Form A has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta = 7.4°, 11.4°, 15.1°, 16.3°, 17.1°, 17.8°, 19.9° or 21.8°.

According to a further aspect of the invention there is provided Compound (II) Form A, wherein said Compound (II) Form A has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 15.1° and 17.8°.

According to a further aspect of the invention there is provided Compound (II) Form A, wherein said Compound (II) Form A has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 7.4°, 11.4°, 15.1°, 16.3°, 17.1°, 17.8°, 19.9° and 21.8°.

According to another aspect of the invention there is provided Compound (II) Form A, wherein said Compound (II) Form A has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 6.
We have also found another crystalline form of Compound (II), Compound (II) Form B, which is characterised in that it provides an X-ray powder diffraction as shown in Figure 7. Compound (II) Form B has characteristic peaks at about 2-theta =10.2°, 11.5°, 14.0°, 16.1°, 16.5°, 17.2°, 18.5° and 20.1°.

Therefore according to a further aspect of the present invention there is provided crystalline Compound (II) Form B.

According to a further aspect of the invention there is provided Compound (II) Form B, wherein said Compound (II) Form B has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta =10.2° or 18.5°.

According to a further aspect of the invention there is provided Compound (II) Form B, wherein said Compound (II) Form B has an X-ray powder diffraction pattern with at least one specific peak at about 2-theta =10.2°, 11.5°, 14.0°, 16.1°, 16.5°, 17.2°, 18.5° or 20.1°.

According to a further aspect of the invention there is provided Compound (II) Form B, wherein said Compound (II) Form B has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 10.2° and 18.5°.

According to a further aspect of the invention there is provided Compound (II) Form B, wherein said Compound (II) Form B has an X-ray powder diffraction pattern with specific peaks at about 2-theta = 10.2°, 11.5°, 14.0°, 16.1°, 16.5°, 17.2°, 18.5° or 20.1°.

According to another aspect of the invention there is provided Compound (II) Form B, wherein said Compound (II) Form B has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 7.

Suitably the crystalline forms described herein are substantially free of other forms of that compound. Suitably at least 80, 90, 95, 98 or 99% of the crystalline form described is present in that form. By way of example, Compound (I) Form B is substantially free of other forms of Compound (I). Suitably, at least 80%> of the Compound (I) is in the form of Form B, particularly at least 90%, more particularly, at least 95% and still more particularly at least 99% of the Compound (I) is in the form of Form B. In a particular embodiment at least 98% of the Compound (I) is in the form of Form B. Reference herein to, for example, 80% of the Compound (I) Form B. Similar purity is also desirable for Compound (I) Forms A and C and Compound (II) Forms A and B.
The crystalline forms of Compounds (I) and (II) described herein are crystalline. Suitably the degree of crystallinity as determined by X-ray powder diffraction data is for example greater than about 60%, such as greater than about 80%, particularly greater than about 90% and more particularly greater than about 95%. In embodiments of the invention, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 98%, wherein the % crystallinity refers to the % by weight of the total sample mass which is crystalline.

In the preceding paragraphs defining the X-ray powder diffraction peaks for the crystalline forms of Compounds (I) and (II), the term "at about" is used in the expression "...at about 2-theta =..." to indicate that the precise position of peaks (i.e. the recited 2-theta angle values) should not be construed as being absolute values because, as will be appreciated by those skilled in the art, the precise position of the peaks may vary slightly between one measurement apparatus and another, from one sample to another, or as a result of slight variations in measurement conditions utilised. It is also stated in the preceding paragraphs that the Compounds (I) Form B provides X-ray powder diffraction patterns 'substantially' the same as the X-ray powder diffraction patterns shown in Figure 3. It is to be understood that the use of the term 'substantially' in this context is also intended to indicate that the 2-theta angle values of the X-ray powder diffraction patterns may vary slightly from one apparatus to another, from one sample to another, or as a result of slight variations in measurement conditions utilised, so the peak positions shown in the Figures or quoted in the Tables are again not to be construed as absolute values.

In this regard, it is known in the art that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not
to be construed as absolute (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996). Therefore, it shall be understood that the crystalline forms of Compound (I) and (II) described herein are not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction pattern shown herein, and any crystals providing X-ray powder diffraction patterns substantially the same as those shown herein for a particular compound fall within the scope of the present invention. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

Generally, a measurement error of a diffraction angle in an X-ray powder diffractogram is about 2-theta = 0.5° or less, and such degree of a measurement error should be taken into account when considering the X-ray powder diffraction patterns in Figures 1, 3, 5, 6 and 7, and when interpreting the peak positions referred to in the text above.

The melting points and DSC data described herein were determined using the apparatus and method described in the Examples. A person skilled in the art will appreciate that slight variations in the melting point measured by DSC may occur as a result of variations in sample purity, sample preparation and the measurement conditions (e.g. heating rate). It will be appreciated that alternative readings of melting point may be given by other types of equipment or by using conditions different to those described hereinafter. Hence the melting point and endotherm figures quoted herein are not to be taken as absolute values and such measurement errors are to be taken into account when interpreting DSC data. Typically, measurement errors using DSC may vary by ± 0.5°C or less. However, as a skilled person will realise, melting point can vary with sample purity and degree of crystallinity of the sample. Even low levels of impurities can affect the measured melting point. Therefore, the melting points disclosed herein may vary by ± 5°C from the values quoted herein and reference to a substance having a melting point of "about" are to be interpreted as having a value of ± 5°C from the values quoted. It is to be understood that references to melting points disclosed herein refer to the onset temperature of the melting endotherm.

The crystalline forms of Compounds (I) and (II) according to the invention may also be characterised and/or distinguished from other physical forms using other suitable analytical techniques, for example NIR spectroscopy or solid state nuclear magnetic resonance spectroscopy.
**Brief Description of Figures**

**Figure 1** is an XRPD diffractogram of 3-[5-({(IR,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl}oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form A. The x-axis shows the 2-theta value and the y-axis the counts.

**Figure 2** is a DSC thermogram for Compound (I) form A. The x-axis shows temperature (°C) and the y-axis shows heat flow (Watts/gram).

**Figure 3** is an XRPD diffractogram of 3-[5-({(IR,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl}oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form B. The x-axis shows the 2-theta value and the y-axis the counts.

**Figure 4** shows the DSC thermograms for Compound (I) Form B and Form C hydrate. The x-axis shows temperature (°C) and the y-axis shows heat flow (Watts/gram). The solid line is the trace for Form B and the dotted line is the trace for Form C hydrate.

**Figure 5** is an XRPD diffractogram of 3-[5-({(IR,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl}oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form C hydrate. The x-axis shows the 2-theta value and the y-axis the counts.

**Figure 6** is an XRPD diffractogram of 3-[5-({(IR,2S)-2-[(2,2-difluoropropanoyl)amino]l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl}oxy)-IH-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form A. The x-axis shows the 2-theta value and the y-axis the counts.

**Figure 7** is an XRPD diffractogram of 3-[5-({(IR,2S)-2-[(2,2-difluoropropanoyl)amino]l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl}oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form B. The x-axis shows the 2-theta value and the y-axis the counts.

**Examples**

**General Preparative Methods**

The following Examples illustrate the invention. The following abbreviations are used in the Examples:

- **TEA** triethylamine
- **TFA** trifluoroacetic acid
- **THF** tetrahydrofuran
- **DCM** dichloromethane
- **DMF** N,N-dimethylformamide
- **HPLC** High Performance Liquid Chromatography
LC/MS Liquid Column Chromatography / Mass Spectroscopy
GC Gas Chromatography
SFC Supercritical Fluid Chromatography
DMSO dimethylsulfoxide

APCI-MS Atmospheric Pressure Chemical Ionisation Mass Spectroscopy
NMP 1-methyl-2-pyrrolidinone
DIEA N,N-diisopropylethylamine
EtOAc ethylacetate
HBTU 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)
CDI 1,1'-carbonyldiimidazole

rt retention time
r.t. room temperature, which is a temperature in the range from of 16°C to 25°C
m.p. melting point

TBME tert-butyl methyl ether
[a]_D specific rotation measured with sodium D light
c concentration of solution in g per 100mL

**Synthetic Experimental**

**General Methods**

NMR spectra were recorded on a Varian Mercury-VX 300 MHz instrument or a Varian Inova 400MHz instrument. The central peaks of chloroform-<i>c</i> (H 7.27 ppm), acetone-<i>j</i> (H 2.05 ppm), dichloromethane-<i>c</i> (H 5.32 ppm) or DMSO-<i>d</i> (H 2.50 ppm) were used as internal references. Alternatively, NMR spectra were recorded on a Varian Inova Unity 500MHz instrument. Proton-NMR experiments were acquired using dual suppression of residual solvent peak and H2O.

The following methods was used for chiral SFC analysis:

Using an Analytical Method Development System from Thar Technologies, Inc. using CO2 as mobile phase at 150 bar and MeOH as modifier. Columns used were kept at +37°C by using a column oven. Detection was carried out on 254nm.

Chiral SFC (method A): Chiralpak® AS, 0.46x25cm column, 30% MeOH, 3 mL/min.
Chiral SFC (method B): Chiralpak® IB, 0.46x25cm column, 35% MeOH, 2 mL/min.
LC/MS analysis were run on an Agilent 1100 instrument; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 mL/min; Wavelength 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA; Gradient 15-95%/B 2.7 min, 95% B 0.3 min.

GC-MS analyses were run on a Hewlett-Packard GC-MS system equipped with El ionisation chamber, 70eV.

The following method was used for HPLC analysis:

LC Method A: HPLC method A was performed with Agilent 1100 series machines on Kromasil © C18 5µm 3.0x100mm column. Aqueous phase was water/TFA (99.8/0.1) and organic phase was acetonitrile/TFA (99.92/0.08). Flow was 0.6 ml/min and gradient was set from 10 to 100% of organic phase during 20 minutes. Detection was carried out on 220, 254 and 280 nm.

LC Method B: HPLC method B was performed with Agilent 1100 series machines on XTerra® RP8 5µm 3.0x100mm column. Aqueous phase was 15 mM NH3 in water and organic phase was acetonitrile. Flow was 0.6 ml/min and gradient was set from 10 to 100% of organic phase during 20 minutes. Detection was carried out on 220, 254 and 280 nm.

X-Ray Powder Diffraction (XRPD): Measurements were generally made using a Panalytical X'Pert PRO MPD instrument using the following parameters:

- CuKα (1.5418A)
- 45 kV and 40 mA
- 2θ ≤ 2θ ≤ 40°
- 4.7min, incr. 0.016°
- Rotating Silicon wafer
- Ambient conditions
- Approximately 2 mg of a test sample was placed on the sample holder and smeared out on the silicon surface using a flat Teflon bar.

General:

(i) Temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C and under an atmosphere of an inert gas such as argon.

(ii) In general, the course of reactions was followed by TLC and reaction times are given for illustration only.

(iii) Yields are given for illustration only and are not necessarily those which can be obtained
by diligent process development; preparations were repeated if more material was required.

(iv) Chemical symbols have their usual meanings; SI units and symbols are used.

(v) Solvent ratios are given in volume : volume (v/v) terms.

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

(vii) Melting point was determined by Differential Scanning Calorimetry: Using standard methods, for example those described in Hohne, G. W. H. et al (1996), Differential Scanning Calorimetry, Springer, Berlin, the calorimetric response of a test sample to increasing temperature was investigated using a TA Instruments Q2000 Modulated Temperature Differential Scanning Calorimeter (MTDSC) using a modulation of ±0.50°C in intervals of 40 seconds and a ramp rate of 5°C per minute. Approximately 1 mg of test sample was placed in aluminium cups with lids (no crimping) under a nitrogen atmosphere. Where a melting point is quoted, this refers to the onset temperature of the melting endotherm.

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

**Intermediate II**

Isobutyl 3-(5-iodo-lH-indazol-l-yl)benzoate (II)

![Intermediate II](image)

A 50 mL flask was charged with sodium carbonate (0.700 g, 6.60 mmol), 3-(5-iodo-lH-indazol-l-yl)benzoic acid (Ila) (2.185 g, 6 mmol) and NMP (15 mL) at 40 °C with magnetic stirring. After a couple of minutes 1-bromo-2-methylpropane (0.971 mL, 9.00 mmol) was added in one portion. After one hour at 40°C, the temperature was raised to 55 °C and another portion of 1-bromo-2-methylpropane (0.971 mL, 9.00 mmol) was added. The stirring was continued overnight. After cooling, the reaction mixture was partitioned between water and
ethyl acetate. The organic phase was washed twice with water, dried over Na₂SO₄, filtered and evaporated to dryness to afford the title compound as a syrup (2.5 g, 99%). The product solidified to a beige material upon standing.

APCI-MS: m/z = 421 [MH+]

1H NMR (400 MHz, CDCl₃) δ 8.38 (IH, t), 8.19 (IH, d), 8.16 (IH, d), 8.07 (IH, dt), 7.92 (IH, ddd), 7.70 (IH, dd), 7.64 (IH, t), 7.56 (IH, d), 4.17 (2H, d), 2.12 (IH, m), 1.05 (6H, d).

LC (method A) rt = 17.6 min

3-(5-Iodo-1H-indazol-1-yl)benzoic acid (IIa)

3-(2-(2-Fluoro-5-iodobenzylidene)hydrazinyl)benzoic acid (lib, 3.47 g, 9 mmol) and potassium tert. butoxide (2.3 g, 20.5 mmol) were stirred under an argon atmosphere in NMP (45 mL) at 150 °C for 30 minutes. After cooling, the mixture was diluted with water (100 mL), acidified with aqueous HCl (1.7 M) and extracted three times with ethyl acetate. The combined organic phases were washed twice with water and then with brine. Evaporation of the organic phase afforded crude title compound (3.52 g, quant.) as a light brown, amorphous, gummy solid.

APCI-MS: m/z 365 [MH+]

1H-NMR (300 MHz, DMSO-^): δ 13.2 (IH, b), 8.38 (IH, s), 8.33 (IH, s), 8.24 (IH, bs), 8.04 (IH, bd, ), 7.97 (IH, d, further coupled), 7.81-7.68 (3H).

3-(2-(2-Fluoro-5-iodobenzylidene)hydrazinyl)benzoic acid (lib)

3-Hydrazinylbenzoic acid (1.52 g, 10 mmol), 2-fluoro-5-iodobenzaldehyde (2.5 g, 10 mmol) and cesium carbonate (3.26 g, 10 mmol) were stirred in DMF (10 mL) at r.t. under an argon atmosphere for 2.5 h. Water (40 mL) was added and the clear solution was acidified with aqueous HCl (1.7 M). The beige-orange precipitate that formed was collected by filtration, washed with water and dried in vacuo to give the title compound (3.75 g, 98%).

APCI-MS: m/z 385 [MH⁺]

1H-NMR (300 MHz, DMSO-^): δ 12.9 (IH, b), 10.85 (IH, s), 8.17 (IH, dd), 7.94 (IH, s), 7.65 (IH, qd), 7.63-7.60 (2H), 7.40-7.31 (3H), 7.09 (IH, dd).
Intermediate 12

\( (1R,2S)-2\text{-amino-} \quad 1-(2,3\text{-dihydrobenzo}[b][1,4]\text{dioxin-6-yl})\text{propan-1-ol hydrochloride. (12)} \)

\[
\begin{align*}
\text{HCl} & \quad \text{CH}_3 \\
\text{N} & \quad \text{OH} \\
\text{O} & \quad \text{O}
\end{align*}
\]

5-6 N HCl in 2-propanol (8 mL, 40-48 mmol) was added to tert-butyl \((1R,2S)-1\text{-}(2,3\text{-dihydrobenzo}[b][1,4]\text{dioxin-6-yl})\text{-1-hydroxypropan-2-ylcarbamate (I2a)} \) (3.1 g, 10.02 mmol) in ethyl acetate (40 mL) at 40°C and stirred for 3 hours. The reaction mixture was allowed to reach r.t. and was concentrated by evaporation. Ether was added and the salt was filtered off and washed with ether. The salt was found to be hygroscopic. Yield 2.10 g (85%)

APCI-MS: m/z 210 [MH\(^+\)-HCl]

1H-NMR (300 MHz, DMSO-\(^{-}\)): \( \delta \) 8.01 (brs, 3H), 6.87-6.76 (m, 3H), 5.93 (brd, 1H), 4.79 (brt, 1H), 4.22 (s, 4H), 3.32 (brm, 1H), 0.94 (d, 3H).

tert-butyl \((1R,2S)-1\text{-}(2,3\text{-dihydrobenzo}[b][1,4]\text{dioxin-6-yl})\text{-1-hydroxypropan-2-ylcarbamate. (I2a)} \)

The diastereoselective catalytic Meerwein-Ponndorf-Verley reduction was made by the method described by Jingjun Yin et al. \( J. \text{Org. Chem. 2006, 71, 840-843.} \)

(S)-tert-butyl \( \text{1-(2,3\text{-dihydrobenzo}[b][1,4]\text{dioxin-6-yl})-1-oxopropan-2-ylcarbamate (I2b)} \) (3.76 g, 12.23 mmol), aluminium isopropoxide (0.5 g, 2.45 mmol) and 2-propanol (12 mL, 157.75 mmol) in toluene (22 mL) were stirred at 50°C under argon for 16 hours. The reaction mixture was poured into 1M HCl (150 mL) and the mixture was extracted with ethyl acetate (250 mL). The organic phase was washed with water (2x50 mL) and brine (100 mL), dried over Na\(_2\)SC\(_4\), filtered and concentrated. The crude product was purified by flash-chromatography on silica using ethyl acetate/hexane (1/2) as eluent. Fractions containing product were combined. Solvent was removed by evaporation to give the desired product as a colourless solid. Yield 3.19 g (84%)
APCI-MS: m/z 236, 210, 192 [MH⁺-tBu-18, MH⁺-BOC, MH⁺-BOC- 18]  
H NMR (300 MHz, DMSO-^): δ 6.80-6.70 (m, 3H), 6.51 (d, IH), 5.17 (d, IH), 4.36 (t, IH), 4.19 (s, 4H), 3.49 (m, IH), 1.31 (s, 9H), 0.93 (d, 3H).

(S)-tert-butyl 1-(2,3-dihydrobenzo[bl][1,4]dioxin-6-yD)-1-oxopropan-2-ylcarbamate. (I2b)

A suspension of (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (3 g, 12.92 mmol) in THF (30 mL) was placed under a protective atmosphere of argon and cooled down to -15 to -20°C. Isopropylmagnesium chloride, 2M in THF (6.5 mL, 13.00 mmol), was added keeping the temperature below -10°C. The temperature was allowed to reach 0°C. A freshly prepared solution of (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)magnesium bromide, 0.7M in THF (20 mL, 14.00 mmol) was added. The temperature was allowed to reach r.t. overnight. The reaction mixture was poured into ice cooled IN HCl (300 mL). TBME (300 mL) was added and the mixture was transferred to a separation funnel. The water phase was back extracted with TBME (200 mL). The ether phases were washed with water, brine and dried (Na₂SO₄). The crude product was purified by flash chromatography using TBME /Heptane 1/2 as eluent. Fractions containing the product were combined and solvents were removed by evaporation to give the subtitle compound as a slightly yellow sticky oil/gum. Yield 3.76g (95%)

APCI-MS: m/z 208 [MH⁺ - BOC]  
H NMR (300 MHz, DMSO-^): δ 7.50 (dd, IH), 7.46 (d, IH), 7.24 (d, IH), 6.97 (d, IH), 4.97 (m, IH), 4.30 (m, 4H), 1.36 (s, 9H), 1.19 (d, 3H).

Intermediate 13

(1R,2S)-2-amino-l-(4H-benzo[d][1,3]dioxin-7-yl)propan-1-ol hydrochloride (13)
propanol (1.5 mL, 7.5-9 mmol) was added. The mixture was stirred at 50 °C for 1.5 hours. The solvents was removed by evaporation. The residual sticky gum was treated with ethyl acetate and evaporated again to give a solid material that was suspended in acetonitrile and stirred for a few minutes. The solid colourless salt was collected by filtration and was found to be somewhat hygroscopic. The salt was quickly transferred to a desiccator and dried under reduced pressure. Yield 293 mg (92%)

APCI-MS: m/z 210 [MH⁺-HCl]

H NMR (300 MHz, DMSO-^d6) δ 8.07 (3H, s), 7.05 (IH, d), 6.92 (IH, dd), 6.85 (IH, d), 6.03 (IH, d), 5.25 (2H, s), 4.87 (3H, m), 3.42 - 3.29 (IH, m), 0.94 (3H, d).

(4S,5R)-5-(4H-benzordirin-31dioxin-7-yl)-4-methyloxazolidin-2-one (I3a)

A mixture of (1R,2S)-2- amino-1-(4H-benzo[d][1,3]dioxin-7-yl)propan-1-ol hydrochloride (I3b) (120 mg, 0.49 mmol), DIEA (0.100 mL, 0.59 mmol) and CDI (90 mg, 0.56 mmol) in THF (2 mL) was stirred at r.t. for 2 hours. The reaction mixture was concentrated by evaporation and the residual material was partitioned between ethyl acetate and water. The organic phase was washed with 10% NaHSO₄, dried over MgSO₄, filtered and evaporated. The crude product was analysed by LC/MS and was considered pure enough for further analysis by NMR. Yield 66 mg (57%)

The relative cis conformation of the product was confirmed by comparing the observed 1H-NMR with the literature values reported for similar cyclised norephedrine (Org. Lett. 2005 (07), 13, 2755-2758 and Tetrahedron Assym. 1993, (4), 12, 2513-2516). In a 2D NOESY experiment a strong NOE cross-peak was observed for the doublet at 5.64 with the multiplet at 4.19 ppm. This also confirmed the relative cис-conformation.

APCI-MS: m/z 236 [MH⁺]

H NMR (400 MHz, CDC1₃) δ 6.99 (d, J = 8.0 Hz, IH), 6.88 (dd, J = 8.0, 1.4 Hz, IH), 6.83 (s, IH), 5.81 (brs, IH), 5.64 (d, J = 8.0 Hz, IH), 5.26 (s, 2H), 4.91 (s, 2H), 4.19 (m, IH), 0.85 (d, J = 6.4 Hz, 3H).
Tert-butyl (1R,2S)-1-(4H-benzod[1,3]dioxin-7-yl)-1-hydroxypropan-2-ylcarbamate (I3b)

A mixture (S)-tert-butyl 1-(4H-benzo[d][1,3]dioxin-7-yl)-1-oxopropan-2-ylcarbamate (I3c) (680 mg, 2.21 mmol), triisopropoxyaluminum (140 mg, 0.69 mmol) and propan-2-ol (3 mL, 38.9 mmol) in toluene (3 mL) was stirred at 65 °C for 15 hours. The reaction mixture was allowed to cool down, poured into 1M HCl (50 mL) and extracted with ethyl acetate (2x50 mL). The organic phase was washed with water, brine, dried over MgSO4, filtered and solvents were removed by evaporation to afford a colourless solid. The crude product was purified by flash chromatography, (solvent A = Heptane, solvent B = EtOAc + 10% MeOH. A gradient of 10%B to 50%B in A was used). The obtained product was crystallised from DCM / heptane to afford the subtitle compound as colourless needles. Yield 414 mg (60%)

APCI-MS: m/z 210 [MH+ -BOC]

H NMR (400 MHz, DMSO-d6) δ 6.97 (1H, d), 6.88 (1H, d), 6.77 (1H, s), 6.56 (1H, d), 5.27 (1H, d), 5.22 (2H, s), 4.83 (2H, s), 4.44 (1H, t), 3.53 (1H, m), 1.32 (9H, s), 0.93 (3H, d).

7-Bromo-4H-benzo[d][1,3]dioxine (1 g, 4.65 mmol) was dissolved in THF (5 mL) and added to magnesium (0.113 g, 4.65 mmol) under a protective atmosphere of argon. One small iodine crystal was added. The coloured solution was heated with an heat gun in short periods to initiate the Grignard formation. When the iodine colour vanished the reaction was allowed to proceed at r.t. for 1.5 hours.

In a separate reaction tube (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1 g, 4.31 mmol) was suspended in THF (5 mL) and cooled in an ice/acetone bath to below -5 °C. Isopropylmagnesium chloride, 2M solution in THF (2.5 mL, 5.00 mmol) was slowly added to form a solution. To this solution was added the above freshly prepared Grignard reagent. The mixture was allowed to reach r.t. and stirred for 4 hours. The reaction
mixture was slowly poured into ice-cold 150 mL 1M HCl. Ethyl acetate (150 mL) was added and the mixture was stirred for a few minutes and transferred to a separation funnel. The organic phase was washed with water and brine, dried over MgSO4, filtered and concentrated. The obtained crude product was further purified by flash chromatography using a prepacked 70g silica column with a gradient of 10% TBME to 40% TBME in heptane as eluent. The subtitle compound was obtained as a colourless solid. Yield 790 mg (59%) >

APCI-MS: m/z 208 [MH+ -BOC]

1H NMR (400 MHz, DMSO-d6) δ 7.53 (IH, dd), 7.39 (IH, s), 7.30 (IH, d), 7.22 (IH, d), 5.30 (2H, s), 4.98 (IH, m), 4.95 (2H, s), 1.35 (9H, s), 1.20 (3H, d).

**Intermediate 14**

3-(5-((lR,2S)-2-(2,2-difluoropropanamido)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prooxy)-lH-indazol-1-yl)benzoic acid (14)

A solution of isobutyl 3-(5-((lR,2S)-2-(2,2-difluoropropanamido)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)prooxy)-lH-indazol-1-yl)benzoate (I4a) (350 mg, 0.59 mmol) in THF (5 mL) and acetonitrile (2 mL) was treated with 0.25 M NaOH (4.72 mL, 1.18 mmol). Additional 1M NaOH (0.590 mL, 0.59 mmol) was added after stirring at ambient temperature for 23 hours and the mixture was stirred at 45 °C for 2 hours. The reaction mixture was allowed to cool down and acidified to pH 2.5 - 3 by adding 1N HCl. THF and acetonitrile was added to obtain a solution, which was purified by HPLC (Kromasil 100-10-C18, 50x250 mm, a 30 min gradient from 50% to 90% MeCN in water+ 0.1%TFA in solvents with a flow=40 mL/min). Fractions containing the product were combined and freeze-dried. The material was re-dissolved in TBME. Addition of heptane gave a slurry that was evaporated to afford the subtitle compound as a colourless solid. Yield 315 mg (99 %)

APCI-MS: m/z 538 [MH+]

1H NMR (300 MHz, DMSO-d6) δ 13.27 (IH, s), 8.66 (IH, d), 8.25 (IH, d), 8.22 (IH, t), 8.00 (IH, ddd), 7.92 (IH, dt), 7.77 (IH, d), 7.69 (IH, t), 7.22 (IH, ddd), 7.14 (IH, d), 6.89 - 6.78 (3H, m), 5.17 (IH, d), 4.22 - 4.11 (5H, m), 1.54 (3H, t), 1.29 (3H, d).
Isobutyl 3-(5-((1R,2S)-2-(2,2-difluoropropanamido)-1-(2,3-dihydrobenzob[d]indoxin-6-yl)propoxy)-1H-indazol-1-yl)benzoate (I4a)

DIEA (0.696 mL, 3.99 mmol) was added to a mixture of isobutyl 3-(5-((1R,2S)-2-amino-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propoxy)-1H-indazol-1-yl)benzoate (I4b) (0.5 g, 1.00 mmol), 2,2-difluoropropanoic acid (0.16 g, 1.45 mmol) and HBTU (0.567 g, 1.50 mmol) in DCM (4 mL). The mixture was stirred at ambient temperature for 1 hour. The reaction was quenched by addition of 10% NaHSO4 (aq). Brine was added to help phase separation. The water phase was extracted with one portion of ethyl acetate. The combined organic solutions were dried over MgSO4, filtered and evaporated. The crude material was purified by flash chromatography (70 g prepacked silica column, a gradient of 0% to 50% ethyl acetate in heptane). Fractions with product were combined and solvents were removed by evaporation. Yield 540 mg (91%).

APCI-MS: m/z 594 [MH]+

1H NMR (300 MHz, DMSO-d6) δ 8.65 (1H, d), 8.26 (1H, d), 8.25 (1H, t), 8.05 (1H, ddd), 7.95 (1H, dt), 7.78 (1H, d), 7.73 (1H, t), 7.22 (1H, dd), 7.14 (1H, d), 6.90 - 6.77 (3H, m), 5.17 (1H, d), 4.18 (4H, s), 4.15 (1H, m), 4.12 (2H, d), 2.05 (1H, m), 1.55 (3H, t), 1.29 (3H, d), 0.99 (6H, d).

Isobutyl 3-(5-((1R,2S)-2-amino-1-(2,3-dihydrobenzob[d]indoxin-6-yl)propoxy)-1H-indazol-1-yl)benzoate (I4b)

A mixture of cesium carbonate (78 g, 240.00 mmol), (1R,2S)-2-amino-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propan-1-ol hydrochloride (12) (19.66 g, 80.00 mmol, 2-(dimethylamino)acetic acid (4.12 g, 40.00 mmol) and copper(1) iodide (0.678 ml, 20.00 mmol) in butyronitrile (188 ml) was stirred at 115 °C for 60 min under a protective atmosphere of argon. A solution of isobutyl 3-(5-iodo-1H-indazol-1-yl)benzoate (II) (33.6 g,
80 mmol) in butyronitrile (62.6 ml) was generated by heating at 80 °C for 20 min. The solution was pumped to the above mixture within 2-3 minutes. The vessel was rinsed with further butyronitrile (15.6 ml) which also was added. The grayish reaction mixture was sealed and stirred at 115 °C for 45 hours. The cooled reaction mixture was extracted between water (500 ml) and ethyl acetate (1.5L). The organic phase was washed with water (3 x 700 ml) and the solvents removed by reduced pressure affording 38 g of a gummy greenish residue.

The crude product was dissolved in approx 60-70 mL DCM and purified by flash chromatography on silica (d=13 cm, l=18 cm; eluting with ethyl acetate:heptane 1:1 with 2% TEA (6 L), ethyl acetate:heptane 3:1 with 2% TEA (8 L) and ethyl acetate (12 L) with 2% TEA). Product containing fractions were pooled and evaporated to give the subtitle compound (16.4 g, 41%).

**APCI-MS:** m/z 502 [MH+]

**1H NMR** (400 MHz, DMSO-d_6) δ 8.24 (2H, m), 8.05 (1H, ddd), 7.94 (1H, dt), 7.77-7.72 (2H, m), 7.22 (1H, dd), 7.17 (1H, d), 6.88 (2H, m), 6.81 (1H, d), 4.97 (1H, d), 4.19 (4H, s), 4.12 (2H, d), 3.11 (1H, m), 2.05 (1H, m), 1.35 (2H, bs), 1.07 (3H, d), 0.99 (6H, d).

**LC** (method A) rt = 12.3 min

**LC** (method B) rt = 14.2 min

**Intermediate 5**

3-(5-((lR,2S)-l-(4H-Benzodiri,31dioxin-7-yl)-2-(2,2-difluoropropanamido)propoxy)-lH-indazol-l-yl)benzoic acid (15)

Isobutyl 3-(5-((lR,2S)-l-(4H-benzol[d][l,3]dioxin-7-yl)-2-(2,2-difluoropropanamido)propoxy)-lH-indazol-l-yl)benzoate (15a) (398 mg, 0.67 mmol) was dissolved in methanol (3 mL) and THF (3.0 mL). Lithium hydroxide (0.032 mL, 2.01 mmol) dissolved in water (2.5 mL) was added. A clear slightly pink solution was obtained. After 2h the solution was ice-cold. Ethyl acetate was added and then hydrochloric acid (1M) to acidic pH. The water phase was once more extracted with ethyl acetate. The collected organic phases were dried over magnesium sulfate and evaporated. It was dissolved in methanol and
the solution was applied onto a 1 g SCX column. The methanol eluate (ca 15 mL) was concentrated. Freeze-drying from acetonitrile/water gave the title compound (362 mg, 100%).

APCI-MS: m/z 538 [MH^+]

H NMR (400 MHz, CD_2Cl_2) δ 8.40 (IH, t), 8.05 (IH, dt), 8.02 (IH, d), 7.98 (IH, ddd), 7.70 (IH, d), 7.65 (IH, t), 7.22 (IH, dd), 7.02 (IH, d), 7.00 (IH, d), 6.91 (IH, d), 6.67 (IH, s), 5.22 (2H, q), 4.87 (2H, s), 4.46 - 4.36 (IH, m), 1.75 (3H, t), 1.25 (3H, d).

Isobutyl 3-(5-((lR,2S)-2-amino-l-(4H-benzo[d][l,3]dioxin-7-yl)propoxy)-1H-indazol-1-yl)benzoate (I5a)

A mixture of isobutyl 3-(5-((lR,2S)-2-amino-l-(4H-benzo[d][l,3]dioxin-7-yl)propoxy)-1H-indazol-1-yl)benzoate (420 mg, 0.84 mmol) (I5b), 2,2-difluoropropanoic acid (213 mg, 1.94 mmol) and HBTU (420 mg, 1.11 mmol) were suspended in dichloromethane (10 mL). DIPEA (0.85 mL, 5.13 mmol) was added and the mixture was stirred at r.t. overnight. Water (ca 10 mL) was added to the solution. After stirring for some minutes the mixture was added to a phase separator. The water phase was stirred with dichloromethane (5 mL) and added to the phase separator. The combined organic phases were concentrated to a brown oil. Purification by flash chromatography on silica (dichloromethane/ethyl acetate 10/1) gave the title compound as a white foam (400 mg, 80%).

APCI-MS: m/z 594 [MH^+]

H NMR (400 MHz, DMSO-d_6) δ 8.71 (IH, d), 8.27 - 8.23 (2H, m), 8.07 - 8.03 (IH, m), 7.95 (IH, d), 7.78 (IH, d), 7.73 (IH, t), 7.23 (IH, dd), 7.14 (IH, d), 7.04 - 6.96 (2H, m), 6.86 (IH, s), 5.26 - 5.17 (3H, m), 4.82 (2H, s), 4.24 - 4.15 (IH, m), 4.12 (2H, d), 2.11 - 2.00 (IH, m), 1.56 (3H, t), 1.30 (3H, d), 0.99 (6H, d).

Isobutyl 3-(5-((lR,2S)-2-amino-l-(4H-benzo[d][l,3]dioxin-7-yl)propoxy)-1H-indazol-1-yl)benzoate (I5b)
A 250 mL one-neck round bottomed flask with magnetic stirring and argon atmosphere was charged with cesium carbonate (30.3 g, 93.00 mmol), (lR,2S)-2-amino-1-(4H-benzo[d][1,3]dioxin-7-yl)propan-1-ol hydrochloride (13) (7.37 g, 30.00 mmol), 2-(dimethylamino)acetic acid (1.547 g, 15.00 mmol), copper(I) iodide (1.428 g, 7.50 mmol) and butyronitrile (72 mL) and heated at 110 °C for 30 min. A solution of isobutyl 3-(5-iodo-1H-indazol-1-yl)benzoate (II) (12.61 g, 30 mmol) in butyronitrile (12.00 mL) was generated by heating at 80 °C for 10 minutes. The solution was pumped to the above mixture within 3 minutes. The vessel was rinsed with further butyronitrile (6.00 mL) which also was added. The reaction mixture was sealed and stirred at 110 °C for 19 h. The reaction mixture was cooled and extracted between water and ethyl acetate (1L). The organic phase was washed three times with water (3 x 500 mL), dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica (eluting with ethyl acetate:heptane 1:1 with 2% TEA, followed by ethyl acetate:heptane 3:1 with 2% TEA and finally with ethyl acetate with 2% TEA). Product containing fractions were pooled and evaporated to give the subtitle compound (5.1 g, 34 %).

APCI-MS: m/z 502.2 [MH+]

H NMR (400 MHz, DMSO-^d) δ 8.25 (1H, t), 8.23 (1H, s), 8.05 (1H, ddd), 7.94 (1H, dt), 7.78-7.70 (2H, m), 7.24 (1H, dd), 7.17 (1H, d), 7.01 (2H, m), 6.89 (1H, s), 5.22 (2H, dd), 5.05 (1H, d), 4.83 (2H, ds), 4.11 (2H, d), 3.15 (1H, m), 2.05 (1H, m), 1.39 (2H, bs), 1.07 (3H, d), 0.98 (6H, d).

LC (method A) rt = 10.6 min
LC (method B) rt = 12.2 min

Intermediate 16

(S)-(−)-tetrahydrothiophene-3-amine-1,1-dioxide hydrochloride (16)
The described procedure is a somewhat modified, optimized and complementary one to the literature synthesis of 3-aminotetrahydrothiophene enantiomer(s):


(S)-(−)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide (I6a) (7.08 g) was suspended in aqueous 5M HCl (250 mL). The mixture was heated at 130 °C for 13 hours. After cooling in an ice-bath solid benzoic acid was removed by filtration and washed with 1M aqueous HCl. The combined filtrates were evaporated to dryness. The residue was re-suspended in 1,4-dioxane (40 mL). The colourless solid subtitle compound was isolated by filtration, washed with dioxane (10 mL) and dried to constant weight. Yield 4.99 g (98%).

\[ \text{H NMR (400 MHz, D}_2\text{O): } \delta 4.12 (1H, pent, further coupled), 3.60 (1H, dd), 3.38 (1H, m), 3.27-2.15 (2H), 2.64 (1H, m), 2.21 (1H, m). \]

\[ [\alpha]_D = -13.5^\circ \text{ (c=1.1, H}_2\text{O) } \]

(S)-(-)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide (I6a)

(S)-N-(tetrahydrothiophen-3-yl)benzamide (I6b) (7.1 g) was dissolved in ethyl acetate (1.2 L). Saturated aqueous NaHCO₃ (0.6 L) was added. 3-Chlorobenzoperoxoic acid (77%, 27 g) was added in portions during 10 min. Stirring was continued for 4 hours. Then dimethylsulphide (3.5 mL) was added and the stirring was continued for additional 100 min to completely destroy excess m-chloroperbenzoic acid. The phases were separated. The organic phase was washed twice with water and evaporated at reduced pressure. The colourless residue was re-crystallized from EtOAc (-350 mL) to yield pure subtitle compound (6.3 g). The mother liquid was evaporated and re-crystallized from ethyl acetate to give additional product (0.72 g). Total yield 7.02 g (85.7%)

\[ \text{H NMR (400 MHz, DMSO-d}_6\text{): } \delta 8.74 (1H, d), 7.88-7.84 (2H), 7.55 (1H, t, further coupled), 7.51-7.45 (2H), 4.70 (1H, sext.), 3.50 (1H, dd), 3.37 (1H, ddd), 3.25-3.15 (1H m), 3.97 (1H, dd), 2.44 (1H, sext.), 2.28-2.16 (1H, m). \]

\[ [\alpha]_D = -39.8^\circ \text{ (c=1.0, MeOH) } \]
(S)-(−)-N-(tetrahydrothiophen-3-yl)benzamide (I6b)

A 1.36 M stock solution of HCl in acetic acid was prepared from 100 ml acetic acid, 11 mL acetyl chloride and 2.8 mL water.

(S)-(−)-4-[2-(methylsulfonyl)ethyl]-2-phenyl-4,5-dihydro-1,3-oxazole (I6c) (1.7g) was dissolved in 25 mL of acetic acid being 1.36 M in respect to HCl. The solution was heated at 130 °C for 18 h. The reaction mixture was then cooled and freeze dried to afford the subtitle compound as a colourless fluffy solid. Yield 1.59 g (100%)

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 8.41 (1H, d, NH), 7.86-7.82 (2H), 7.53 (1H, m), 7.49-7.43 (2H), 4.49 (1H, sext.), 3.03 (1H, dd), 2.96-2.88 (1H, m), 2.88-2.80 (1H, m), 2.75 (1H, dd), 2.19-2.10 (1H, m), 2.07-1.97 (1H, m).

$[\alpha]_D^{20}$ = −32.4° (c=0.95, MeOH)

$^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.81-7.75 (2H), 7.50-7.42 (1H, m), 7.42-7.34 (2H), 4.42 (1H, dd), 4.29-4.18 (1H, m), 3.98 (1H, t), 2.60-2.45 (2H), 1.99 (3H, s), 1.80-1.66 (2H).

$[\alpha]_D^{20}$ = −89.8° (c=1.5, EtOAc)

**Intermediate 7**

$^{L}$-(S)-2-amino-4-(methylthio)butan-1-ol (10.0 g) and zinc(II) bromide (0.5 g) were mixed in benzonitrile (18 mL). The mixture was stirred at 120 °C for 45 hours.

The major part of the excess benzonitrile was distilled off by Kugelrohr distillation. The residue was diluted with a small volume of DCM and subjected to autoflash chromatography on silica (330 g) using a gradient of 0-70% ethyl acetate in heptane to afford the subtitle compound as an oil. Yield 12.09 g (74%).

$^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.81-7.75 (2H), 7.50-7.42 (1H, m), 7.42-7.34 (2H), 4.42 (1H, dd), 4.29-4.18 (1H, m), 3.98 (1H, t), 2.60-2.45 (2H), 1.99 (3H, s), 1.80-1.66 (2H).

$[\alpha]_D^{20}$ = −89.8° (c=1.5, EtOAc)

(R)-(−)-tetrahydrothiophene-3-amine-1,1-dioxide hydrochloride (17)
The subtitle compound was prepared similarly as described for compound (16), but starting from (R)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide (I7a) (3.0g). Yield 2.10 g (98%).

\[ \text{[a]}_D = +12.5^\circ \quad (c=1.1, \ H_2O) \]

IH-NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \) 4.13 (IH, pent), 3.61 (IH, dd), 3.39 (IH, m), 3.27-3.17 (2H), 2.65 (IH, dtd), 2.29-2.16 (2H).

(R)-N-(1,1-dioxidotetrahydrothiophen-3-yl)benzamide (I7a)

\[
\begin{align*}
\text{\textbf{H}} & \quad \text{\textbf{N}} \\
\text{\textbf{O}} & \quad \text{\textbf{S}} \\
\text{\textbf{S}} & \quad \text{\textbf{O}} \\
\end{align*}
\]

The subtitle compound was prepared similarly as described for compound (I6a), but starting from (R)-N-(tetrahydrothiophen-3-yl)benzamide (I7b) (3.06 g). Yield 3.0 g (85.5%).

\[ [a]_D +40.1^\circ \quad (c=1.0, \ MeOH) \]

H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \) 8.74 (IH, d), 7.88-7.83 (2H), 7.55 (IH, t, further coupled), 7.48 (2H, t, further coupled), 4.69 (IH, sext.), 3.50 (IH, dd), 3.37 (IH, m), 3.20 (IH, ddd), 3.07 (IH, dd), 2.28-2.16 (IH, m).

(R)-N-(tetrahydrothiophen-3-vObenzamide (I7b)

\[
\begin{align*}
\text{\textbf{O}} & \quad \text{\textbf{N}} \\
\text{\textbf{S}} & \quad \text{\textbf{S}} \\
\end{align*}
\]

The subtitle compound was prepared similarly as described for compound (I6b), but starting from (R)-4-(2-(methylthio)ethyl)-2-phenyl-4,5-dihydrooxazole (I7c) (3.04 g). Yield 2.78 g (98%).

\[ [a]_D +32.2^\circ \quad (c=1.1, \ MeOH) \]

H NMR (400 MHz, DMSO-d\textsubscript{6}) \( \delta \) 8.41 (IH, d), 7.87 - 7.81 (2H, m), 7.53 (IH, m), 7.49 - 7.42 (2H, m), 4.49 (IH, sextet), 3.03 (IH, dd), 2.96 - 2.88 (IH, m), 2.88 - 2.80 (IH, m), 2.75 (IH, ddd), 2.19 - 2.09 (IH, m), 2.07 - 1.96 (IH, m).

(R)-4-(2-(methylthio)ethyl)-2-phenyl-4,5-dihydrooxazole (I7c)

\[
\begin{align*}
\text{\textbf{O}} & \quad \text{\textbf{N}} \\
\text{\textbf{S}} & \quad \text{\textbf{S}} \\
\end{align*}
\]

The subtitle compound was prepared similarly as described for compound (I6c), but starting from D-(R)-2-amino-4-(methylthio)butan-1-ol (7.75 g). Yield 3.04 g (24%).
\[^{\text{[9]}}\]D = +89.8° (c=1.5, EtOAc)

\[\text{H NMR (400 MHz, DMSO-} d_6) \delta 7.89 - 7.84 (2H, m), 7.57 - 7.51 (1H, m), 7.50 - 7.44 (2H, m), 4.51 (1H, dd), 4.32 (1H, dq), 4.07 (1H, t), 2.60 (2H, m), 2.07 (3H, s), 1.81 (2H, m).\]

**Preparation 1**

3-(5-{[(IR,2S)-2-(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propoxy}-1H-indazol-1-vl)-N-{(3S,1l-dioxidotetrahydrothiophen-3-yl}benzamide

DIPEA (1.803 mL, 10.33 mmol) was added to a mixture of 3-(5-{[(IR,2S)-2-(2,2-difluoropropanamido]-1-(2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)propoxy]-1H-indazol-1-yl}benzoic acid (14) (1.85 g, 3.44 mmol), (3S)-(−)-3-aminosulfolane hydrochloride (16) (0.650 g, 3.79 mmol) and HBTU (1.436 g, 3.79 mmol) in DMF (18 mL). The solution was stirred at ambient temperature for 1 hour, then poured into water (150 mL). The formed precipitate was collected by filtration and washed with water. The solid was partitioned between ethyl acetate and brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was dissolved in ethyl acetate (10 mL) and added dropwise to a stirred volume of iso-hexane (150 mL). After stirring for 44 hours, the solid was collected by filtration, washed with iso-hexane and dried. The material was suspended in refluxing methanol (approx. 40 mL) and allowed to cool to r.t. over night. Filtration and drying gave the title compound (1.69 g, 75%).

APCI-MS: m/z 655 [MH⁺]

\[\text{H NMR (400 MHz, DMSO-} d_6) \delta 8.90 (1H, d), 8.65 (1H, d), 8.25 (1H, d), 8.19 (1H, s), 7.92 (1H, d), 7.86 (1H, d), 7.77 (1H, d), 7.68 (1H, t), 7.21 (1H, dd), 7.14 (1H, d), 6.89 - 6.78 (3H, m), 5.17 (1H, d), 4.73 (1H, m), 4.24 - 4.1 l (5H, m), 3.52 (1H, dd), 3.37 (1H, m), 3.20 (1H, m), 3.10 (1H, dd), 2.45 (1H, m), 2.23 (1H, m), 1.55 (3H, t), 1.29 (3H, d).\]

LC (method A) rt = 11.98 min

LC (method B) rt = 10.96 min

Chiral SFC (method A) rt = 4.93 min
M.p. = 180 °C

**Preparation 2**

3-(5-((1R,2S)-2-(2,2-difluoropropanamido)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propoxy)-1H-indazol-1-yl)benzoic acid (14) (3.2 g, 5.83 mmol), (R)-(+-)tetrahydrothiophene-3-amine-1,1-dioxide hydrochloride (17) (1.152 g, 6.71 mmol) and HBTU (2.54 g, 6.71 mmol) were dissolved in DCM (30 mL). DIPEA (4.08 mL, 23.34 mmol) was added and the mixture was stirred at r.t. over night. The reaction was quenched by addition of brine and dilution with EtOAc. The aqueous phase was extracted with ethyl acetate (x2) and DCM (x1). The combined organic phases were dried over magnesium sulfate and concentrated. The crude material was slurried in methanol/aceton (approx. 250 mL) methanol/aceton 1/1), heated to reflux and allowed to cool to r.t. After stirring over the weekend the solid was filtered off and washed with ice cold methanol. Drying under vacuum yielded the title compound (3.1 g, 81%) as a white crystalline solid.

APCI-MS: m/z 655 [MH+]

H NMR (400 MHz, DMSO-d6) δ 8.90 (1H, d), 8.65 (1H, d), 8.25 (1H, s), 8.19 (1H, s), 7.92 (1H, d), 7.85 (1H, d), 7.77 (1H, d), 7.68 (1H, t), 7.21 (1H, dd), 7.14 (1H, d), 6.89 - 6.78 (3H, m), 5.17 (1H, d), 4.72 (1H, m), 4.24 - 4.11 (5H, m), 3.52 (1H, dd), 3.38 (1H, m), 3.20 (1H, m), 3.10 (1H, dd), 2.44 (1H, m), 2.23 (1H, ddd), 1.55 (3H, t), 1.29 (3H, d).

LC (Method A) rt = 11.89 min
LC (Method B) rt = 10.17 min

Chiral SFC (method A) rt = 5.87 min

M.p. = 218 °C

**Preparation 3**
3-[(2S)-1-[(2,2-difluoropropanoyl)amino]-2-propyl]-5-[(3R)-tetrahydrofuran-3-yl]benzamide

5 DIPEA (2.105 mL, 12.06 mmol) was added to a stirred mixture of 3-(5-[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy)-1H-indazol-1-yl)-N-[(3R)-tetrahydrofuran-3-yl]benzamide (15) (1.62 g, 3.01 mmol), (R)-(+)-tetrahydrothiophene-3-amine-1,1-dioxide hydrochloride (17) (0.569 g, 3.32 mmol) and HBTU (1.257 g, 3.32 mmol) in DMF (22 mL). The solution was stirred at r.t. for 1 h, then poured into water (260 mL). The formed suspension was stirred at r.t. for 1 h, filtered, washed with water twice and dried in vacum at 40°C for 10 h. The solid was dissolved in hot acetonitrile (500 ml) and water (165 ml) was added under stirring. The mixture was allowed to cool down to ambient temperature over night. The precipitate was filtered, washed with water and dried at 40°C in vacum to give the title compound (1.01 g, 51%).

APCI-MS: m/z 655 [MH+]

H NMR (400 MHz, DMSO-\(\text{d6}\)) \(\delta\) 8.90 (IH, d), 8.71 (IH, d), 8.25 (IH, s), 8.18 (IH, s), 7.91 (IH, d), 7.86 (IH, d), 7.78 (IH, d), 7.68 (IH, t), 7.23 (IH, dd), 7.14 (IH, d), 7.00 (2H, q), 6.86 (IH, s), 5.26 - 5.17 (3H, m), 4.82 (2H, s), 4.78 - 4.67 (IH, m), 4.24 - 4.13 (IH, m), 3.52 (IH, dd), 3.42 - 3.32 (IH, m), 3.25 - 3.16 (IH, m), 3.10 (IH, dd), 2.49 - 2.41 (IH, m), 2.29 - 2.17 (IH, m), 1.56 (3H, t), 1.30 (3H, d).

LC (Method A) rt = 11.88 min
LC (Method B) rt = 11.04 min

M.p. = 239 °C

**Preparation 4**

3-(5-[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy)-1H-indazol-1-yl)-N-[(3R)-tetrahydrofuran-3-yl]benzamide
TEA (2.0 g, 20.65 mmol) was added to a mixture of 3-(5-((lR,2S)-2-(2,2-
difluoropropanamido)-1-(2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)propoxy)-1 H-indazol-1-
yl)benzoic acid (14) (3.6 g, 6.70 mmol), (R)-tetrahydrofuran-3-amine hydrochloride (0.99 g, 8.0 mmol) and HBTU (2.65 g, 6.99 mmol) in DCM (15 mL). The reaction was stirred at r.t. for 3h, then quenched by addition of a mixture of water and ethyl acetate. The mixture was shaken and the organic layer was collected. The water phase was extracted twice with ethyl acetate. The combined organic layers were washed with a small portion of water and dried over magnesium sulphate. The product was purified by flash chromatography (silica, eluent: a gradient of ethyl acetate in heptane). The residue was crystallized by dissolving in refluxing acetonitrile (50 mL) and then allowing to cool to r.t. over night. The solid was collected by filtration, washed with a small volume of acetonitrile and dried at 40°C in vaccum to give the title compound (2.5 g, 61%).

APCI-MS: m/z 607 [MH+]

H NMR (400 MHz, DMSO-d_6) δ 8.71 (IH, d), 8.65 (IH, d), 8.24 (IH, s), 8.18 (IH, s), 7.90-
7.84 (2H, m), 7.77 (IH, d), 7.65 (IH, t), 7.21 (IH, dd), 7.13 (IH, d), 6.89 - 6.78 (3H, m), 5.17
(IH, d), 4.48 (IH, m), 4.23 - 4.10 (5H, m), 3.89 - 3.82 (2H, m), 3.72 (IH, td), 3.61 (IH, dd),
2.16 (IH, m), 1.94 (IH, m), 1.55 (3H, t), 1.29 (3H, d).

LC (method A) rt = 12.03 min
LC (method B) rt = 11.13 min
Chiral SFC (method B) rt = 4.71 min
M.p. = 177 °C

**Preparation 5**

3-(5-((lR,2S)-2-((2,2-difluoropropanoyl)aminol)-1-(2,3-dihydro-1,4-benzodioxin-6-
vl]propyl]oxy]-1H-indazol-1-yl)-N-(pyridin-3-ylmethyQbenzamide

Crystalline Form A
To a mixture of 3-(5-((lR,2S)-2-(2,2-difluoropropanamido)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propoxy)-1H-indazol-1-yl)benzoic acid (80 mg, 0.15 mmol) (14), pyridin-4-ylmethanamine (24.14 mg, 0.22 mmol) and HBTU (67.7 mg, 0.18 mmol) in DCM (4.5 mL) was added TEA (0.207 mL, 1.49 mmol) and the reaction mixture was stirred at r.t. over night. The volatiles were removed in vacuo and the residue was purified by HPLC (Kromasil 100-5 µι-8, 250-20 mm, 25-95% acetonitrile in water as gradient over 30 min, flow rate 11 mL/min). Product containing fractions were pooled and freeze dried. The solid was dissolved in ethyl acetate (10 mL) and petroleum ether (34 mL) was added with stirring to get a milky solution. This was stirred at r.t. with a loose stopper (allowing for slow reduction of volume) for 24h, then sealed and stirred for an additional 60 h. The precipitate was filtered and dried to give the title compound (65 mg, 70%).

APCI-MS: m/z 628 [MH+]
1H NMR (400 MHz, DMSO-^) δ 9.24 (IH, t), 8.66 (IH, d), 8.57 (IH, d), 8.46 (IH, dd), 8.24 (IH, s), 8.21 (IH, s), 7.89 (2H, m), 7.79 (IH, d), 7.74 (IH, m), 7.67 (IH, t), 7.36 (IH, dd), 7.21 (IH, dd), 7.14 (IH, d), 6.88 - 6.78 (3H, m), 5.17 (IH, d), 4.53 (2H, d), 4.25 - 4.09 (5H, m), 1.54 (3H, t), 1.29 (3H, d).

LC (method A) rt = 9.61 min
LC (method B) rt = 9.58 min

M.p. = 135 °C

Preparation 6

3-(5-[(lR,2S)-2-(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy)-1H-indazol-1-yl)-N-(pyridin-3-ylmethyObenzamide

Crystalline Form B

3-(5-((lR,2S)-2-(2,2-difluoropropanamido)-1H-indazol-1-yl)benzoic acid (14) (898 mg, 1.67 mmol), HBTU (950 mg, 2.51 mmol) and DIPEA (830 µL, 5.01 mmol) were dissolved in DMF (5 mL). Pyridin-3-ylmethanamine (253 µL, 2.51 mmol) in DMF (2 mL) was added. The reaction was stirred at r.t. over the week end. The reaction was quenched by adding a mixture of water and ethyl acetate. The water phase was extracted twice with ethyl acetate. The combined organic layers
were washed with a small portion of water and dried over sodium sulphate. Purification was
done by preparative HPLC (Kromasil 100-10-C18, 250 x 50 mm, using a gradient of 45-75%
acetonitrile in water for 25 min) followed by flash chromatography on silica (eluting with
ethyl acetate followed by methanol/ethyl acetate 10/90). The residue was crystallized from
ethyl acetate and heptane to give the title compound (689 mg, 66%).

M.p. = 127 °C

Preparation 7

3-[(1R,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)aminopropyl]oxy]-
1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide

Crystalline Form A

To a mixture of 3-[(1R,2S)-1-(4H-benzo[d][1,3]dioxin-7-yl)-2-(2,2-
difluoropropanamido)propoxy]-1H-indazol-1-yl]benzoic acid (15) (75 mg, 0.14 mmol),
pyridin-3-ylmethanamine (0.042 mL, 0.42 mmol) and HBTU (63.5 mg, 0.17 mmol) in DCM
(4 mL) was added TEA (0.292 mL, 2.09 mmol) and the reaction mixture was stirred at r.t.
over night. The volatiles were removed in vacuo and the residue was purified by HPLC
(Kromasil 100-5 µm-C18, 250-20 mm, 25-95% acetonitrile in water as gradient over 30 min).
Product containing fractions were pooled to give a volume of approx 55 mL. To this solution,
water was added with stirring until a milky type appearance occurred but disappeared quickly
and the total volume became approx 200 mL. The mixture was stirred at r.t. over the week
end. After 66 h, more water (50 mL) was added and the mixture was stirred at r.t. for an
additional 24h. The precipitate was filtered off, washed with water, and dried to give the title
compound (64 mg, 73%).

APCI-MS: m/z 628 [MH+]

1H NMR (400 MHz, DMSO-d6) δ 9.26 (IH, t), 8.71 (IH, d), 8.57 (IH, d), 8.46 (IH, dd), 8.24
(IH, s), 8.22 - 8.19 (IH, m), 7.89 (2H, t), 7.80 (IH, d), 7.76 - 7.72 (IH, m), 7.67 (IH, s), 7.36
(IH, dd), 7.22 (IH, dd), 7.13 (IH, d), 7.04 - 6.96 (2H, m), 6.86 (IH, s), 5.25 - 5.17 (3H, m),
4.82 (2H, s), 4.52 (2H, d), 4.24 - 4.13 (IH, m), 1.56 (3H, t), 1.30 (3H, d).

LC (method A) rt = 9.86 min
LC (method B) \( \text{rt} = 11.18 \text{ min} \)
M.p. = 159 °C

**Preparation 8**

3-\{5-(((\text{IR},2\text{S})-\text{l-(4H-l},3\text{-benzodioxin-7-yl})-2-\{(2,2\text{-difluoropropanoyl)aminolpropyl|oxy})-\text{lH-indazol-1-yl|N-(pyridin-3-ylmethyQbenzamide}

Crystalline form C hydrate

TEA (4.93 mL, 35.35 mmol) was added to a suspension of 3-\{(\text{IR},2\text{S})-\text{l-(4H-l},benzo[d] \{1,3\}dioxin-7-yl}-2-(2,2\text{-difluoropropanamido} propoxy)- \text{lH-indazol-1-yl} \text{benzoic acid (15)} (1900 mg, 3.53 mmol) and pyridin-3\text{-ylmethanamine (573 mg, 5.30 mmol) in DCM (80 mL). After stirring overnight the mixture was extracted between water and dichloromethane. The water phase was once more extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, concentrated and purified by flash chromatography (silica, 1x d 30 x 4 cm, dichloromethane/methanol 15/1). Pooling and evaporation of product containing fractions gave a residue that was dissolved in warm acetonitrile/water (30 mL/60 mL). A precipitate was formed on cooling. XRPD on the suspension after ca 2 h shows crystalline material.

**Preparation 9**

3-\{5-(((\text{IR},2\text{S})-\text{l-(4H-l},3\text{-benzodioxin-7-yl})-2-\{(2,2\text{-difluoropropanoyl)aminolpropyl|oxy})-\text{lH-indazol-1-yl|N-(pyridin-3-ylmethyQbenzamide}

Crystalline form B

The suspension in Preparation 8 was stirred overnight, then filtered and dried in vacumm at 40°C overnight to give the title compound (1560 mg, 70.3 %) as a white powder,
M.p. = 148 °C

**Glucocorticoid Receptor Modulator Biological Activity**

The biological activity of the glucocorticoid receptor modulators described herein (the first active ingredient) was measured as follows:

**Human Glucocorticoid Receptor (GR) Assay**

The radioligand GR binding assay is based on a competition assay using \(^{3} \text{H}\)-labeled Dexamethasone. Dexamethasone is known to bind in the ligand binding domain of GR and compete for binding with endogenous ligands like e.g. Cortisol (Necela, 2003).

In the GR radioligand binding assay, test compounds were serially diluted in semi-log steps (10 concentrations) with a final concentration of 10 \( \mu \text{M} \). Test compounds (1\( \mu \text{L} \)) and controls...
(1µL) in 100% DMSO were added to 96 Greiner V-bottom polypropylene plates. 0% control was 6.7% DMSO (final concentration in assay) and 100% control was 6.7 µM Dexamethasone.

The full length GR was diluted to a final concentration of 3.3% (0.495 mg/ml) in assay buffer (20mM Tris-HCl, 1mM EDTA, 10% (w/v) Glycerol, 20mM Sodium molybdate, pH 7.4). 45 µL of GR was added to each well and the plates were incubated for 15 min at room temperature.

3H-dexamethasone solution was diluted to a concentration of 70 nM in assay buffer (7nM final assay concentration) and 5 µl was added to each well. The samples were mixed for 5 min using a plate shaker at 700 rpm, before incubation for 2 h at room temperature.

50 µl ice-cold charcoal solution (pH 7.4: 2% Charcoal, 0.2% Dextran T70 in 20mM Tris-HCl, 1mM EDTA and 20mM Sodium molybdate) was added to each well and the samples were mixed on plate shaker for 5 minutes.

The plate was then centrifuged for 1.5 min at 1500 rpm, the samples (80 µL) were transferred from each well to a filter plate (Millipore, 0.45 µm, MHVBN45) on a vacuum manifold and then collected into new plates (Greiner, 96 well white/transparent, 655095). The filter plate was washed once with 20µl of water and then 100 µl of scintillation liquid was added to each well and mixed by incubation on plate shaker for 5 min. Radioactivity was measured in a 1450 Microbeta Trilux Reader (Wallac) counting cpm for 2 minutes per well. The data obtained from each replicate experiment were analysed using the software ActivityBase, version 5.4.3 (ID Business Solutions Ltd) and IC50 values were calculated.


Transrepression reporter gene assay
The human bronchogenic carcinoma cell-line, ChaGo-K-1 (ATCC; HTB 168), were transfected with 5xTRE-LacZ (clone 16:15:5 s5), i.e. TRE transfected cells, to measure transrepression activity of the selected compounds. Before use, the cells were grown for one to two weeks in selection medium containing 0.7 mg geneticin (G418)/ml medium. The cells were cultured at 37 °C, 5% CO₂ and 100% humidity in 96 well microtiter plates in RPMI-medium complemented with 10 % fetal calf serum, 1 % non-essential amino acids and 1 % sodium pyruvate. The cells were passaged once weekly.

The TRE transfected cells were seeded in 96 well plates with 25-30 000 cells/well and grown for 72-96 h, to reach about 80 % confluence. To stimulate the upregulation of the AP-I/TRE-
activity, the cells were stimulated with 10 ng/ml Phorbol Myristate acetate (PMA) 3-5 h prior to addition of compounds. The PMA was present during the whole experiment. The TRE mediated effects (transrepression) in the transfected ChagGo-K-1 cells was measured as downregulation of β-galactosidase activity. The β-galactosidase activity for the transrepression experiments was measured by a fluorometric assay performed in microtiter plates. Cells were washed once in PBS. 180 µl of a reaction mixture containing 5 parts of Z-buffer and one part 4-methylumbelliferyl -P-D-galactosidase (MUG)-solution was then added (150 µl Z-buffer [18 µl 0.6 M Na$_2$HP04, 12 µl 0.6 M NaH$_2$PO4, 7.2 µl 0.25 M KC1, 18 µl 0.01 M MgSO4, 1.8 µl 10% Triton X-100, 93 µl H$_2$O] + 30 µl 3 mM 4-methylumbelliferyl -P-D-galactosidase). After 60 min incubation at 37°C, 70 µl stop buffer was added to each well and the fluorescence was read in a fluorometer (Spectramax Gemini) with emission filter at 460 nm and excitation filter at 360 nm. The TRE activity was calculated as the relative activity compared to cells not treated with compounds. Inhibition of β-galactosidase by the compounds is expressed as percent inhibition compared to Dexamethasone 10⁻⁶ M set as a 100 percent control within each experiment and DMSO 0.1 % set as background control. The effect of Dexamethasone is well documented in this system and was therefore chosen as a positive control for comparison of the potency and efficacy of the compounds.

Table 1. Binding data, for the glucocorticoid receptor modulators described herein

<table>
<thead>
<tr>
<th>Preparation Number</th>
<th>GR Hu Bind Filter Mean Control IC50 [nM]</th>
<th>Agonism TRE IC50 [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>0.21</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>0.17</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>0.34</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>0.055</td>
</tr>
<tr>
<td>5-6⁺</td>
<td>0.80</td>
<td>0.037</td>
</tr>
<tr>
<td>7-9⁺</td>
<td>0.92</td>
<td>0.061</td>
</tr>
</tbody>
</table>
* The compounds were tested in the assay using solutions of the compounds as described above. As such, the crystalline form of the solid compounds in Preparations 5 and 6, and Preparations 7 to 9 are not expected to affect the measured Ic50 value in this assay.

Protocols for Combination Experiments

The effect of the glucocorticoid receptor modulator (the first active ingredient), the second active ingredient defined herein, and their combination together in the pharmaceutical product according to the invention can be measured using the following examples of suitable assays.

Example 1

Inhibition of lipopolysaccharide (LPS)-induced TNFa production in human peripheral blood mononuclear cells.

Human isolated peripheral blood mononuclear cells (PBMCs) are pre-incubated with a range of concentrations of the inhibitor compound (or combination of compounds) for 45 minutes at 37°C. After the pre-incubation period, the cells are then incubated with LPS (0.5ng/mL) for 18 hours at 37°C to induce TNFa production. The total assay volume is 200 µL. Analysis of TNF-a release is measured by an AlphaLISA immunoassay® from PerkinElmer. In brief, 10 µL/sample of culture supernatant are diluted in assay and added to a 384 well OptiPlate (PerkinElmer) and incubated in the dark. TNF-a is measured according to the manufacturer's instructions. The plates are then read on an Envision® multilabel plate reader. The fluorescent values are then translated to absolute concentrations by reading off a standard curve.

As a control of the hPBMC assay Dexamethasone is run in every experiment at the same concentrations as test compound(s).

Example 2

Evaluation on the effect of compound on BAL-neutrophilia following acute smoke exposure in the mouse

Smoke exposure is performed using an automated whole body box exposure system SIU 48 (ProMech Lab AB, Malmo, Sweden). Animals were positioned group wise in a randomized way in an exposure box divided into eight compartments. The exposure box is connected to the smoke generator and a vacuum flow of approximately 10 L/min, connected to the bottom of the exposure box. Smoke from 12 Kentucky research cigarettes 1R3F and fresh air are then alternately drawn into the exposure box for 50 min.
BALB/c mice undergo whole body exposure to main stream smoke (50 min/12 cigarettes) and fresh air twice a day for 4 days. Mice are dosed via the appropriate route with vehicle, standard compound or test compounds (alone or in combination) at various time points before and after challenge depending upon the experimental protocol. Animals are terminated 16 hrs after the last smoke exposure by an overdose of sodium pentobarbital intraperitoneally. After tracheal cannulation, lungs are lavaged with Phosphate Buffered Saline (PBS) at a hydrostatic pressure of 23 cm H$_2$O. PBS is allowed to flow in to the lungs for two minutes followed by an outflow for one minute, and repeated once more in all animals. The Bronchoalveolar lavage (BAL) fluid is collected in ice- cold tubes and centrifuged at 1200 rpm for 10 min, 4°C (Sorvall RT 6000D, 46R). The supernatant is aliquoted and stored at -70°C until further analysis. The pellet is resuspended in 250 µL PBS and the total numbers of leukocytes are determined using an automated cell counter (SYSMEX F820, TOA Medical Electronics Co. Kobe, Japan).

**Example 3**

**Evaluation on the effect of compound on lung oedema in the rat Sephadex model**

Male Sprague Dawley rats are challenged via intratracheal instillation with Sephadex beads, and due to the inborn hypersensitivity of the rats towards dextran, an eosinophilic-driven inflammation develops over time in the lungs. The inflammatory response can be followed by monitoring the increase in lung weight (oedema), which peaks at 24 to 48 hours and is maintained for more than 7 days after provocation. To determine potency, test compounds (alone or in combination) or vehicle are administered to rats as a nose-only inhaled dry powder, where the first administration was given 2 hours prior to challenge with Sephadex, and is followed by 3 once daily treatments prior to termination. The most common method to determine mechanistic side-effects for inhaled GR agonists in animal models is to quantify thymic involution (thymus weight decrease compared to vehicle treated animals), expressed as ED$_{25}$. This value is then used to determine the therapeutic ratio for the compound (the ratio between mechanistic side-effects [ED$_{25}$ thymus involution] and potency [ED$_{50}$ lung oedema]). Animals are terminated 24 hrs after the last vehicle or compound exposure by an overdose of sodium pentobarbital intraperitoneally. The animals are weighed, and then the thymus and left lung lobe dissected out and weighed.
Example 4
Evaluation on the effect of compound on BAL-neutrophilia following LPS exposure in the mouse

Exposure to significant levels of LPS is reported to be associated with the development and/or progression of many types of lung disease. These can be characterised by inflammatory processes in the lung, including neutrophilic inflammation, increase of cytokine release and increase of capillary permeability in the lungs causing pulmonary oedema. In mice, challenge with LPS results in an inflammatory cell response that can be detected after 4 hours, peaking at 48 hours and which lasts for up to 5 days.

Mice are treated intratracheally with vehicle or compounds (alone or in combination) 1 hour before challenge with nebulised LPS (1 mg/ml of Pseudomonas aeruginosa LPS). Twenty-four (24) hours after LPS challenge animals are terminated by an overdose of sodium pentobarbital (intraperitoneally) and inflammatory cell numbers in BAL are determined using an automated cell counter (SYSMEX F820, TOA Medical Electronics Co. Kobe, Japan) as described previously.
CLAIMS

1. A pharmaceutical product comprising, in combination:
   i) a first active ingredient which is a glucocorticoid receptor modulator selected from:
   5 3-[[lR,2S]-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-
     yl)propyl]oxy]-lH-indazol-1-yl)-N-[(3R)-1,1-dioxidotetrahydrothiophen-3-
yl]benzamide;
   3-[[lR,2S]-l-(4H-l,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy]-
   lH-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide;
   3-[[lR,2S]-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-
   yl)propyl]oxy]-lH-indazol-1-yl)-N-[(3S)-1,1-dioxidotetrahydrothiophen-3-yl]benzamide;
   3-[[lR,2S]-l-(4H-l,3-Benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy]-
   lH-indazol-1-yl]-N-[(3R)-1,1-dioxidotetrahydrothiophen-3-yl]benzamide;
   3-[[lR,2S]-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-
   yl)propyl]oxy]-lH-indazol-1-yl)-N-[(3R)-tetrahydrofuran-3-yl]benzamide; and
   3-[[lR,2S]-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-
   yl)propyl]oxy]-lH-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide;
   or a pharmaceutically acceptable salt thereof; and

   ii) a second active ingredient selected from:
   an Adenosine A2A receptor antagonist;
   an anti-infective;
   an antioxidant;
   a $\beta_2$ adrenoceptor agonist;
   a CCR1 antagonist;
   a chemokine antagonist (not CCR1);
   a glucocorticostroid;
   a CRTh2 antagonist;
   a DPI antagonist;
   a formyl peptide receptor antagonist;
   a Histone Deacetylase activator;
   a chloride channel hCLCA1 blocker
   an Epithelial sodium channel blocker (ENAC blocker)
   an Inter-cellular adhesion molecule 1 blocker (ICAM blocker);
an IKK2 kinase inhibitor;
a INK kinase inhibitor;
a cyclooxygenase inhibitor (COX inhibitor);
a lipoxygenase inhibitor;
a leukotriene receptor antagonist;
a MEK-1 kinase inhibitor
a myeloperoxidase inhibitor (MPO inhibitor);
a muscarinic antagonist;
a dual muscarinic antagonist adrenoceptor agonist (MABA compound);
a phosphodiesterase PDE4 inhibitor;
a phosphatidylinositol 3 (PD)-kinase γ inhibitor (PI 3 kinase γ inhibitor)
a peroxisome proliferator activated receptor agonist (PPARγ agonist);
a protease inhibitor;
a p38 inhibitor;
a retinoic acid receptor modulator (RAR γ modulator)
a Statin;
a thromboxane antagonist; and
a vasodilator.

2. A pharmaceutical product according to claim 1, wherein the second active ingredient selected from:
a β2 adrenoceptor agonist;
a CCR1 antagonist;
a muscarinic antagonist;
a PDE4 inhibitor; and
a p38 inhibitor.

3. A pharmaceutical product according to claim 1, wherein the second active ingredient is N-[(2-(Diethylamino)ethyl)N-(2-[[2-(4-hydroxy-2-oxo-2,3-dihydro-1,3-benzothiazol-7-yl)ethyl]amino]ethyl)-3-[2-(3-chlorophenyl)ethoxy]propanamide or a pharmaceutically acceptable salt thereof.
4. A pharmaceutical product according to claim 1, wherein the second active ingredient is N-Cyclohexyl-3-[2-(3-fluorophenyl)ethylamino]-N-[2-{2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]ethyl}propanamide, or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical product according to claim 1, wherein the second active ingredient is N-{2-[[2S]-3-[[1-(4-chlorobenzyl)piperidin-4-yl]amino]-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide, or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical product according to claim 1, wherein the second active ingredient is 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, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical product according to claim 1, wherein the second active ingredient is 6-fluoro-N-((1S,4S)-4-(6-fluoro-2,4-dioxo-1-(4'-sulfonyl)benzofuran-3-yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl]imidazo[1,2-a]pyridine-2-carboxamide, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical product according to claim 1, wherein the second active ingredient is N-cyclopropyl-3-fluoro-4-methyl-5-[3-[1-{2-[2-(methylamino)ethoxy]phenyl}cyclopropyl] amino]-2-oxo-1(2 H)-pyrazinyl]benzamide, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical product according to claim 1, wherein the second active ingredient is (IR,3aS,3bS,10aR,10bS,11S,12aS)-1-{[(cyanomethyl)sulfanyl]carbonyl} -7-(4-fluorophenyl)-1-1-hydroxy-10a,12a-dimethyl-1,2,3,3a,3b,4,5,7,10,10a,10b,1,12,12a-tetradecahydropenta[5,6]naptho[1,2-f]imidazol-1-yl furan-2-carboxylate, or a pharmaceutically acceptable salt thereof.
10. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-(5-{[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy} -IH-indazol-1-yl)-N-{(3S)-l,1-dioxidotetrahydrothiophen-3-yl}benzamide, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-(5-{[(lR,2S)-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy} -IH-indazol-1-yl)-N-{(3R)-1,1-dioxidotetrahydrothiophen-3-yl}benzamide, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-[5-{[(IR,2S)-l-(4H-1,3-Benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy}-IH-indazol-1-yl]-N-{(3R)-1,1-dioxidotetrahydrothiophen-3-yl]benzamide, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-(5-{[(IR,2S)-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy}-IH-indazol-1-yl)-N-{(3R)-tetrahydrofuran-3-yl]benzamide, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-(5-{[(IR,2S)-2-[(2,2-difluoropropanoyl)amino]-l-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy}-IH-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide, or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical product according to any one of claims 1 to 9 wherein the first active ingredient is 3-[5-{[(IR,2S)-l-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy}-IH-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide, or a pharmaceutically acceptable salt thereof.

16. Use of a product according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment of a respiratory disease.
17. Use according to claim 16, wherein the respiratory disease is chronic obstructive pulmonary disease.

18. 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 as defined in any one of claims 1 or 9 to 15; and
(b) a (therapeutically effective) dose of a second active ingredient as defined in claim 1; to a patient in need thereof.

19. A kit comprising a preparation of a first active ingredient as defined in any one of claims 1 or 9 to 15, and a preparation of a second active ingredient as defined in claim 1 and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

20. A pharmaceutical composition comprising, in admixture, a first active ingredient as defined in any one of claims 1 or 9 to 15 and a second active ingredient as defined in claim 1.
Figure 1

XRPD pattern for 3-[[1R,2S]-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form A
Figure 2

DSC Thermogram for 3-[(1R,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form A
Figure 3

XRPD pattern for 3-[5-((1R,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl)oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form B
Figure 4

DSC Thermogram for 3-[(1R,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy)-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form B and Form C hydrate
Figure 5

XRPD pattern for 3-[(1R,2S)-1-(4H-1,3-benzodioxin-7-yl)-2-[(2,2-difluoropropanoyl)amino]propyl]oxy]-1H-indazol-1-yl]-N-(pyridin-3-ylmethyl)benzamide Form C Hydrate
Figure 6

XRPD pattern for 3-((1R,2S)-2-((2,2-difluoropropanoyl)amino)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl)oxy)-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide

Form A
Figure 7

XRPD pattern for 3-(5-[(1R,2S)-2-[(2,2-difluoropropanoyl)amino]-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propyl]oxy]-1H-indazol-1-yl)-N-(pyridin-3-ylmethyl)benzamide Form B
INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/051905

A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

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

B. FIELDS SEARCHED

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search
4 March 2011

Date of mailing of the international search report
10/03/2011

Name and mailing address of the ISA
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See patent family annex.

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