CRYSTALLINE FORM OF INDAZOLYL AMIDE DERIVATIVES FOR THE TREATMENT GLUCOCORTICOID RECEPTOR MEDIATED DISORDERS

Field of the invention

The present invention relates to new solid state forms of a drug, to pharmaceutical compositions containing them, to processes for obtaining them and to the use of the new solid state forms and compositions containing them in medical treatment.

Background of the invention

In the formulation of drug compositions, it is desirable for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound. In particular, pharmaceutical compositions which are formulated for inhaled administration must be in a form which enables appropriate processing techniques, such as micronisation, and which enables delivery using a suitable delivery device, for example a dry powder inhaler, a metered dose inhaler, a nebuliser or a nasal delivery device.

Chemical stability, solid state stability and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, melting point, hygroscopicity and solubility).

Moreover, it is desirable to be able to provide the drug in a form which is as chemically pure as possible.

Furthermore, crystalline drug compounds have been shown to provide more reliable and reproducible plasma concentration profiles following administration to a patient.

Moreover, different crystalline forms of a compound may exhibit different physico-chemical properties, such as melting point, solubility and hygroscopicity.

Furthermore, different crystalline forms of a compound may exhibit different pharmacokinetic characteristics, such as total lung exposure, total lung retention, total blood exposure, peak plasma exposure and oral bioavailability.

Additionally, it is desirable for the drug substance to be in a thermodynamically stable form in order to prevent or minimize the risk of conversion to another alternative form during the manufacturing or formulation process, or during or following administration to a patient.

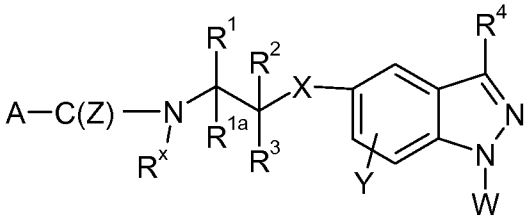
Amorphous, or semi-amorphous materials may present significant problems in this regard. For example, such materials are typically difficult to handle and to formulate, provide for an unreliable solubility, and are often found to be unstable and chemically impure.

The skilled person will appreciate that, if a drug can be found in a stable crystalline form, the above problems may be solved.

Thus, in the manufacture of commercially viable, and pharmaceutically acceptable, drug compositions, it is desirable, wherever possible, to provide the drug in a substantially crystalline, and stable, form.

It is to be noted, however, that this goal is not always achievable. Indeed, typically, it is not possible to predict, from molecular structure alone, what the crystallization behaviour of a compound will be. This can usually only be determined empirically.

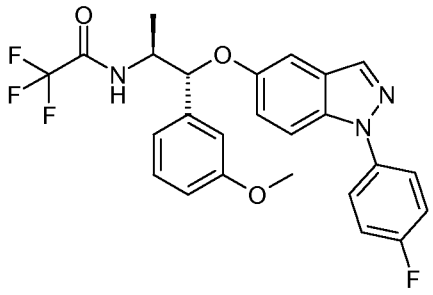
International patent application WO 2008/076048 discloses a number of compounds, which have been found to be useful as modulators of the glucocorticoid receptor, which modulators are of the general formula (I):



(I)

(wherein R^1, R^{1a}, R^2, R^3, R^4, R^x, A, W, X, Y and Z have meanings given in the description of WO 2008/076048) and pharmaceutically acceptable salts thereof.

WO 2008/076048 also discloses, as Example 6, the specific compound 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide (referred to hereinafter as Compound (I)). The Compound (I) obtained by following the procedure described therein is non-crystalline.



Compound (I)

Disclosure of the invention

We have now found the Compound (I) may be prepared in crystalline form, including a new, thermodynamically stable, crystalline form of Compound (I), or a pharmaceutically acceptable salt thereof.

Thus, according to one aspect of the invention, there is provided a substantially crystalline form of Compound (I), or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, there is provided a substantially crystalline form of Compound (I).

In another aspect of the invention, there is provided Form A of Compound (I).

In one aspect of the invention, Form A of Compound (I) is substantially crystalline.

In another aspect of the invention, Form A of Compound (I) is crystalline.

In another aspect of the invention, there is provided Form B of Compound (I).

In one aspect of the invention, Form B of Compound (I) is substantially crystalline.

In another aspect of the invention, Form B of Compound (I) is crystalline.

Forms A and B of Compound (I) are described in further detail hereafter.

In so far as any of the cystalline forms of Compound (I) may exists as solvate, such solvates form a part of the present invention. Solvates of Compound (I) include hydrates and alcoholates (such as propanol and iso-propanol solvates).

According to a further aspect of the invention, there is provided a substantially crystalline anhydrate form of Compound (I). In a still further aspect, Compound (I) is not in the form of a salt. In a yet still further aspect, Compound (I) is not in the form of a solvate, i.e. it is an "ansolvate". Hence, the term "anhydrate" encompasses "ansolvate".

We have found that Compound (I) may be obtained in forms that are substantially crystalline in nature. When herein reference is made to compounds of the invention being 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%, 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.

It is stated hereinbefore that Compound (I) may be produced in a crystalline form that is an anhydrate. By this we mean that the crystalline form contains less than 10% of hydrate form(s) (e.g. a monohydrate) of Compound (I).

In a further aspect of the invention Form A and Form B of Compound (I) are anhydrate crystalline forms.

Form B of Compound (I)

In another aspect, Form B of Compound (I) is characterised by an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) of 9.2, 17.4 and 21.5.

In a further aspect, Form B of Compound (I) is characterised by an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) of 9.2, 11.8, 15.7, 17.4 and 21.5.

In a yet still further aspect, Form B of Compound (I) is characterised by an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) as shown in Table 1 hereafter.

In a yet still further aspect, Form B of Compound (I) is characterised by and hence the form may be characterized by the X-ray powder diffraction pattern substantially as shown in Figure 1, when measured using a wavelength of X-rays 1.5418 Å. .

In a further aspect, Form B of Compound (I) is characterized by a differential scanning calorimetry curve, at a heating rate of 5°C per minute in a closed aluminium cup under a nitrogen atmosphere, exhibiting an onset temperature of the melting endotherm of about 109°C.

In a further aspect, Form B of Compound (I) is characterized by the differential calorimetry curve substantially as shown in Figure 2.

In another aspect, Form B of Compound (I) is characterized by a differential scanning calorimetry curve, at a heating rate of 5°C per minute in a closed aluminium cup under a nitrogen atmosphere, exhibiting an onset temperature of the melting endotherm of

about 109°C and/or an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) of 9.2, 11.8, 15.7, 17.4 and 21.5.

In another aspect, Form B of Compound (I) is characterized by the differential calorimetry curve substantially as shown in Figure 2 and/or an X-ray powder diffraction pattern substantially as shown in Figure 1.

Suitably a crystalline modification of a compound according to the invention is substantially free from other crystalline modifications of the compound. For example in one embodiment Form B of Compound (I) is substantially free of Form A of Compound (I). Suitably, a described crystalline modification of Compound (I) that is substantially free from other crystalline modifications of the compound includes less than, for example, 20%, 15%, 10%, 5%, 3% or particularly, less than 1% by weight of other crystalline forms of that compound.

Crystalline anhydrates of Compound (I) may be prepared as described herein by crystallizing Compound (I) from one or more suitable solvents or mixtures thereof. Anhydrate may be produced by crystallization from a solvent system which is substantially free of water (which may have been dried, and/or may be dried during the crystallization process). Solvent may be dried during the crystallization process, for example by decreasing the water content of a mixture of the compound to be crystallized in a suitable organic solvent / aqueous solvent system (e.g. by increasing the amount of organic solvent that is present and/or removal of water by formation of an azeoptrope, with successive distillations). However, crystalline anhydrates of Compound (I) may also be prepared from water and/or water/alcohol mixtures.

Compounds of the invention that are anhydrates typically contain no more than 2%, particularly 1%, more particularly 0.5% and more particularly 0.2% (w/w) water, whether such water is bound (crystal water or otherwise) or not.

In order to ensure that crystalline forms as described herein are prepared in the absence of other crystalline forms, crystallisations may be carried out by seeding with nuclei and/or seed crystals of the desired crystalline form in the absence of nuclei and/or seed crystals of other crystalline forms.

The skilled person will appreciate that the concentration in solution of the compound that is to be crystallised, and the solvent system that is used, may influence crystallisation temperatures and crystallisation times.

Different crystalline forms may have different solubility in different organic solvents at any given temperature. In this respect, above-mentioned, or other, solvents may be employed as "antisolvents" (i.e. a solvent in which compounds of the invention are poorly soluble, but which is miscible with another solvent, in which compounds of the invention are more soluble), and may thus aid the crystallisation process.

As may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallisation process. Under certain thermodynamic conditions (solvent system, temperature, pressure and concentration of the compound of the invention), one crystalline form may be more stable than another (or indeed any other). However, other crystalline forms that may have, in comparison, a relatively low thermodynamic stability, may be kinetically-favoured. Thus, in addition, kinetic factors, such as time, impurity profile, agitation, the presence of seeds, etc. may also influence which forms appear. Thus, the procedures discussed herein may be adapted by the skilled person as appropriate in order to obtain the particular crystalline form of Compound (I).

Compounds of the invention may be dried using standard techniques. It will be appreciated by the skilled person that drying temperature and drying time may affect the solid state properties and/or the solid state form of compounds of the invention. For example, dehydration may occur at low humidity and/or elevated temperatures and/or reduced pressure. Hence, the crystalline anhydrates of compounds of the invention may also be formed by dehydration of a hydrate.

Preparation of Crystalline Forms of Compound (I)

According to a further aspect of the invention there is provided a process for the production of a compound of the invention which comprises crystallizing Compound (I) from a solution, suspension or slurry of Compound (I) with a suitable solvent system. In such a process it is important to leave the solution, suspension or slurry mixed for a sufficient period of time. The length of time depends on the level of saturation so that highly saturated solutions may crystallize within hours or a day or two, whereas less saturated solutions may require longer (for example a week or more).

Suitable mixing, for example by stirring, is believed to be important, possibly since it creates sites for primary, as well as secondary nucleation, thus speeding up the crystallisation process. Once available, the addition of seed crystals (of the form to be

crystallised) to the solution, suspension or slurry will speed up the crystallisation process since the time for primary nucleation will then be shortened. Thus, a further process of the invention provides the production of a compound of the invention which comprises crystallising Compound (I) from a solution, suspension or slurry of the compound with a suitable solvent using seeds of the relevant compound to initiate and/or facilitate crystallisation. Suitable solvents include alcohols (such as ethanol, propanol and isopropanol), ethyl acetate, isopropyl acetate, aqueous systems and suitable mixtures thereof (for example, water/propanol, water/isopropanol). Other suitable solvents include ethereal solvents (such as methyl *tert*-butyl ether). Antisolvents (such as heptanes) may also be used as appropriate. A particular process of the invention comprises the use of a two solvent system that favours aggregation of crystals, i.e use of a good solvent and an antisolvent, such as the good solvent 1-propanol and the antisolvent n-heptane or the good solvent methyl *tert*-butyl ether and the anti-solvent n-heptane.

Form B of Compound (I) may be prepared by crystallization of Compound (I) in amorphous form in a suitable solvent system. Thus in one aspect of the invention, Compound (I) in amorphous form is suspended or slurried (or partially dissolved) in a suitable solvent system and thereafter the suspension or slurry is heated and then allowed to cool. In another aspect the suspension or slurry is heated to a sufficient temperature to afford dissolution of compound (I) before being allowed to cool. In a further aspect the suspension or slurry is heated to at least 75°C (such as at least 80°C for example about 87°C). In another aspect the solvent system includes any suitable solvent, or mixture of solvents, that do not result in the formation of a solvate of Compound (I) at room temperature. In another aspect, the solvent system may include those in which Compound (I) is only partially (or is at least partially) soluble. In a further aspect, the solvent system comprises a two solvent system comprising a good solvent and an antisolvent. In a still further aspect, the solvent system comprises an organic solvent that is polar, e.g. alcohols (such as lower alkyl alcohols, e.g. a C_{1-6} alcohol for example 1-propanol or isopropanol) or acetates (such as isopropyl acetate) and an alkyl antisolvent such as heptanes. In a yet further aspect the solvent system comprises isopropyl acetate and n-heptane. In a still further aspect, n-heptane constitutes at least 75% w/w (e.g. at least 85% such as about 90%) of the total solvent employed in the solvent system. That is, the solvent system may contain up to 25% w/w (e.g. up to 15%, or about 10%) of isopropyl acetate.

The crystallization of Form B of Compound (I) may also be promoted by the addition of seed crystals of Form B (once available). Thus in one aspect of the invention there is provided a crystalline form obtainable by such a seeding process. In order to obtain Form B by this process, Compound (I) in amorphous form may be suspended or slurried (or at least partially dissolved) in a suitable solvent system (solvent system V) and thereafter seeds of Form B (for example 0.2 to 1.5% w/w, e.g. 0.5 to 1.0% w/w, such as 0.5% w/w) added optionally followed by the addition of an anti-solvent (anti-solvent W). In a further aspect of the invention, solvent system V includes any suitable solvent, or mixture of solvents, that do not result in the formation of a solvate of Compound (I). In another aspect, solvent system V may include those in which Compound (I) is only partially (or is at least partially) soluble. In a further aspect, solvent system V comprises a two solvent system comprising a good solvent and an antisolvent.

In one embodiment, solvent system V comprises an organic solvent that is polar, e.g. alcohols (such as lower alkyl alcohols, e.g. a C_{1-6} alcohol) and an alkyl antisolvent such as heptanes. In a further aspect solvent system V comprises 1-propanol and n-heptane. In a further aspect, n-heptane constitutes at least 50% w/w (e.g. at least 60% such as about 70%) of the total solvent system employed in solvent system V. That is, solvent system V may contain up to 50% w/w (e.g. up to 40%, or about 30%) of 1-propanol. In a further aspect, antisolvent W is an alkyl antisolvent such as n-heptane. In a still further aspect of the invention, solvent system V is heated and then cooled before the seed crystals are added and the mixture is allowed to cool further before antisolvent W is added. In a further aspect, solvent system V is heated to at least 55°C (such as at least 60°C for example about 65°C) then allowed to cool to 40°C to 50°C (such as 45°C to 50°C for example about 50°C) then the seed crystals of Form B are added (for example 0.2 to 1.5% w/w, e.g. 0.5 to 1.0% w/w, such as 0.5% w/w) and the mixture gradually cooled to at least room temperature (such as at least 25°C for example at least 15°C such as at least 8°C).

In a further embodiment of the invention, solvent system V comprises an organic solvent that is ethereal and an alkyl antisolvent such as a heptane. In a further aspect solvent system V comprises methyl *tert*-butyl ether and n-heptane. In a further aspect, n-heptane constitutes at least 20% w/w (e.g. such as about 30%) of the total solvent system employed in solvent system V. That is, solvent system V may contain up to 80% w/w (e.g. up to about 70%) of methyl *tert*-butyl ether. In a further aspect, antisolvent W is an alkyl antisolvent such as n-heptane. In a still further aspect of the invention, solvent system V is

heated and then cooled before the seed crystals are added. In a further aspect, solvent system V is heated to at least 30°C (such as about 35°C) then allowed to cool to 20°C to 25°C (such as about 21°C) then the seed crystals of Form B added.

In a further embodiment of the invention, the amorphous form of Compound (I) referred to herein is synthesised via the route described in Example 1, steps (ii) to (vii).

The terms "suspended" and "slurried" (or "partially dissolved") are well understood by the skilled person. For instance to form a suspension or slurry, an excess of the solid substance, relative to the solubility in the solvent, is added such that there is (undissolved) solid in the solvent system throughout the "suspension" or "slurrying" procedure.

Crystalline Form B of Compound (I) may also be prepared by seeding a suspension of an alternative form of Compound (I) (hereinafter referred to as "Form A") in a solvent system with seeds of Form B of Compound (I). The preparation of Form A of Compound (I) is described below at Example 4 and Example 5. The characteristic X-ray powder diffraction pattern peaks of Form A are tabulated in Table 2 below and the X-ray powder diffraction diffractogram shown in Figure 3 below. The characteristic differential calorimetry curve of Form A of Compound (I) is shown in Figure 4 below.

There is further provided a crystalline form of Compound (I) obtainable by such a (crystallisation) conversion process. The skilled person will understand that a suspension process is essentially a "slurrying" process or a process that involves at least partial (but not complete) dissolution in a solvent system.

In an aspect of the invention therefore, there is provided the conversion of one crystalline form (e.g. one anhydrate form) of Compound (I) to another. In particular Form A may be converted to Form B. There is therefore provided a crystalline form obtainable by such a (crystallisation) conversion process.

In order to obtain Form B of Compound (I) by this process, Form A may be suspended or slurried (or at least partially dissolved) in a suitable solvent system and thereafter seeds of Form B (for example 1.0 to 2.5% w/w, e.g. 2 % w/w) added. In one aspect of the invention, solvent systems employed to obtain Form B of Compound (I) by suspension or slurrying (i.e. to achieve the conversion of Form A of Compound (I) to Form B) include any suitable solvent, or mixture of solvents, that do not result in the formation of a solvate of Compound (I). In another aspect, solvent systems may include those in which Compound (I) is only partially (or is at least partially) soluble. In a further aspect, the solvent system comprises a two solvent system comprising a good solvent and a

moderate solvent. In a still further aspect, the solvent system comprises an organic solvent that is polar, e.g. alcohols (such as lower alkyl alcohols, e.g. a C_{1-6} alcohol) and water. In a yet further aspect the solvent system comprises isopropanol and water. In a further aspect, water constitutes at least 60% w/w (e.g. at least 75% such as about 80%) of the total solvent system employed to obtain Form B. That is, the solvent system may contain up to 40% w/w (e.g. up to 25%, or about 20%) of isopropanol.

The phase conversion in the solvent system to obtain Form B of Compound (I) may take a number of hours or days (e.g. 4 days, see Example 3 hereinafter), but the length of time may be reduced depending on for example the temperature of the process (or it may take longer if performed at lower temperatures) or the concentration of the solution, etc. However, the skilled person can easily determine the length of time taken for conversion to Form B.

We have found that Form B of Compound (I) has improved physical properties when compared with other forms of Compound (I) which may have previously been prepared (for example compared with the amorphous free-base form or with Form A). Form B of Compound (I) has, for example, a different hygroscopicity profile compared to the amorphous free-base form which may be useful in formulations comprising the compounds of the invention. Furthermore, Form B of Compound (I) has a different solubility profile and/or dissolution rate compared to Form A (in various solvents, for example buffered aqueous systems or propanol/heptane systems) and a different melting point compared to Form A which may be useful in the manufacturing process and in formulations comprising the compounds of the invention. Furthermore, we have found that by employing the crystallisation or conversion processes described herein, it is possible to produce Form B of Compound (I) with a high chemical purity.

Moreover, we have found that Form A of Compound (I) is converted to Form B in the conversion processes described herein, showing that Form B is a thermodynamically more stable form of Compound (I), at least at the relevant temperature range, and may be particularly advantageous for use as a medicament.

Furthermore, we have found that Form B of Compound (I) exhibits different pharmacokinetic properties compared with other forms of Compound (I) (such as Form A). Form B of Compound (I) exhibits an increased level of total lung exposure (expressed as "Area Under the Curve" or AUC) when compared with Form A. Moreover, Form B of Compound (I) exhibits a reduced level of peak blood level (expressed as Cmax) when

compared with Form A. Differences in pharmacokinetic properties may lead to differences in the pharmacological efficacy and may provide improved safety margins.

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

By "solid state stability", we include that the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, loss of crystallinity, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably ambient temperature, such as between 15 and 30°C), pressures of between 0.1 and 2 bars (preferably atmospheric pressure), and/or exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months). Under such conditions, compounds of the invention may be found to be less than about 15%, more preferably less than about 10%, and especially less than about 5%, chemically degraded/decomposed, or solid-state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature and pressure represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

The term "normal storage conditions" may also include relative humidities of between 5 and 95% (preferably 10 to 60%). However, in the case of certain crystalline forms according to the invention, changes in conformation or crystal structure by hydration and/or dehydration may occur as a result of prolonged exposure to certain extremes of relative humidities, at normal temperatures/pressures.

Although compounds of the invention (i.e. the crystalline forms) are preferably not in the form of salts, salts that may be mentioned include acid addition salts and base addition salts.

The preparation and characterisation of compounds of the invention are described hereinafter. Different crystalline forms of the compounds of the invention may be readily characterised using X-ray powder diffraction (XRPD) methods, for example as described hereinafter. Standard DSC techniques may also be used.

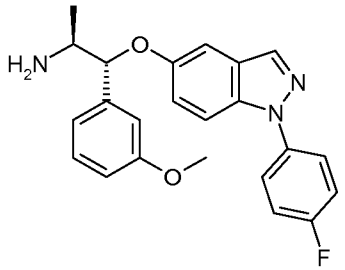
As may also be appreciated by the skilled person, the crystalline form that is obtained may be significantly influenced by the synthetic process undertaken to produce the compound to be crystallised. In particular factors such as the nature of reactants, the nature of the reagents, the nature of the solvents and the nature of the purification techniques (if any) utilised in any previous steps (and in particular in the penultimate and/or immediately preceeding step) may all affect the crystalline form that is obtained.

We have found that an alternative synthetic process for the preparation of Compound (I) (not disclosed in WO 2008/076048) enables reliable production of Form B. In a further embodiment of the invention therefore, there is provided an alternative process for the preparation of Compound (I).

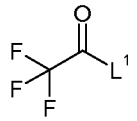
In one aspect of the invention, therefore, there is provided a process for the preparation of Form B of Compound (I).

Preparation of Compound (I)

In another aspect there is provided a process for the preparation of Compound (I) which comprises coupling a compound of formula (II) with an acylating agent of formula (III)



(II)



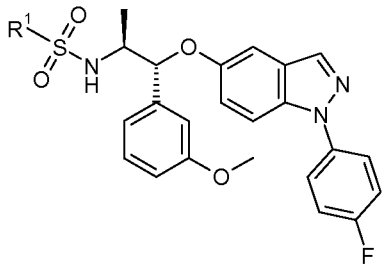
(III)

wherein L^1 is an alkoxy or trifluoroacetoxy group. In a further aspect the acylating agent is ethyl trifluoracetate. In a still further aspect compound (II) is in the hydrochloride salt-form.

The compound of formula (III) is either commercially available or it may be prepared using well-known chemistry from commercially available starting materials. The methods which may be utilized to couple compounds of formula (II) and formula (III) are well known in the art. For example, the coupling reaction may be carried out by mixing

compounds of formula (II) and (III) in a suitable solvent (e.g. an ethereal solvent such as methyl tert-butyl ether) in the presence of a suitable base (e.g. an organic base such as triethylamine) at a suitable temperature (e.g. ambient temperature) for a suitable time (e.g. 24 hours).

In a further aspect, there is provided a process for the preparation of a compound of formula (II), which comprises the deprotection of a compound of formula (IV):

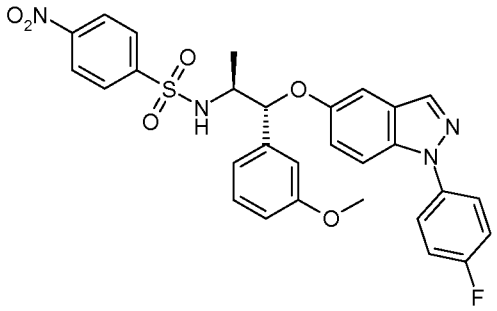


(IV)

wherein R^1 is alkyl (unsubstituted or substituted by silylalkyl), dialkylamino, aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2) or heteroaryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2). In a still further aspect R^1 is aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2).

The methods which may be utilized to deprotect compounds of formula (IV) are well known in the art. For example, where R^1 is aryl, the deprotection may be carried out by mixing a compound of formula (IV) in a suitable solvent (e.g. an organic solvent such as acetonitrile) in the presence of a suitable base (e.g. an inorganic base such as potassium carbonate) with a suitable deprotecting agent such as a thiol nucelophile (e.g. thioglycolic acid) at a suitable temperature (e.g. 60-100°C such as 75°C) for a suitable time (e.g. 18 hours). Alternatively, the deprotection may be carried out using other well-known deprotecting agents, for example strong acids (such as hydrobromic acid or sulphuric acid), strong reducing agents (such as ground magnesium or sodium in liquid ammonia or sodium naphthalene or tributyl tin hydride) or samarium iodide. Alternative methods for carrying out this deprotection are described in standard chemistry texts, for example Greene, T.W. & Wuts, P.G.M. (2006), *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience; or Kocienski, P. (2005), *Protecting Groups*, Thieme.

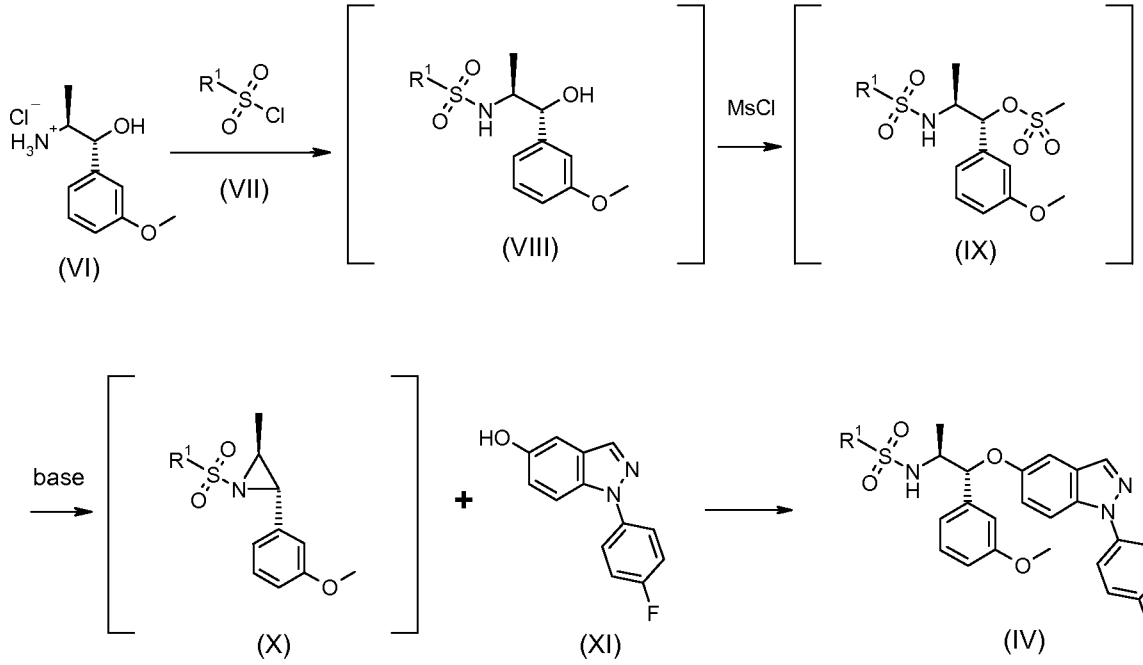
In a yet further aspect, there is provided a process for the preparation of a compound of formula (II), which comprises the deprotection of a compound of formula (V):



(V)

using methods well-known in the art, for example those described above and in the Examples herein.

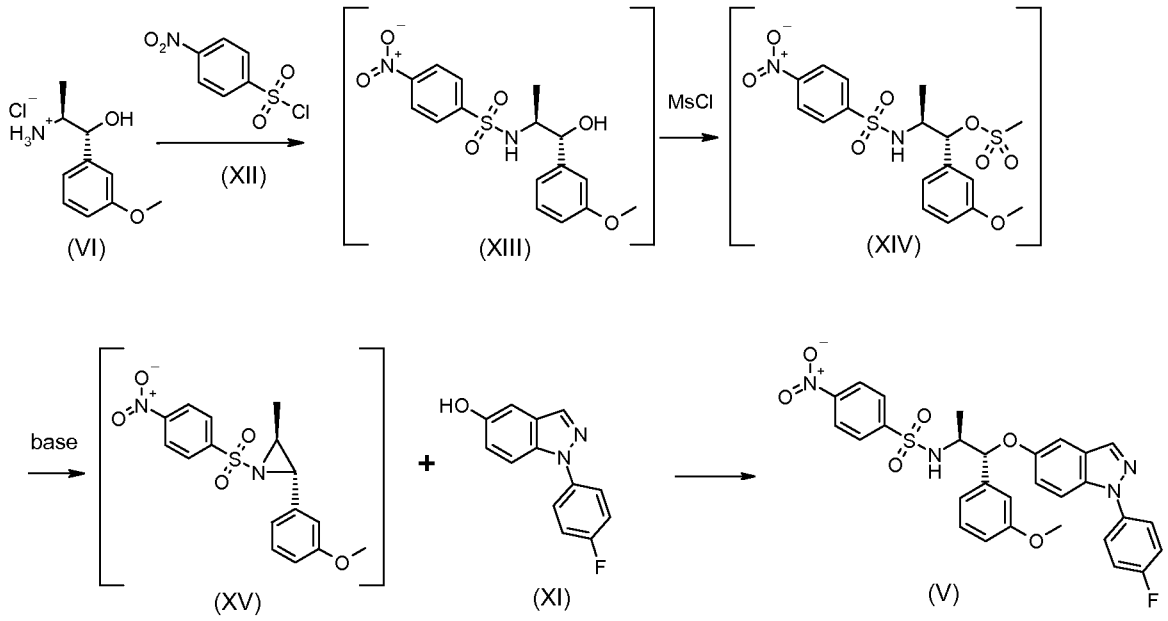
In a further aspect of the invention there is provided a process for the preparation of compounds of formula (IV), which comprises the in-situ formation of a protected aziridine (X) from amino-alcohol (VI) followed by in-situ aziridine ring-opening with hydroxyindazole (XI):



wherein R^1 is alkyl (unsubstituted or substituted by silylalkyl), dialkylamino, aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2) or heteroaryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2). In a still further aspect R^1 is aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2).

The process to the free-base form of the compound of formula (VI) (ie. not in salt-form) is described in WO 2008/076048 (example 6b). The formation of the hydrochloride salt of the compound of formula (VI) is described in the Examples herein. The compound of formula (VII) is either commercially available or it may be prepared using well-known chemistry from commercially available starting materials. Processes to compound of formula (XI) are described in WO 2008/079073 (example 1) and in the Examples herein. The methods which may be utilized to form compounds of formula (IV) are well known in the art, for instance those described in the Examples herein.

In a still further aspect of the invention there is provided a process for the preparation of compounds of formula (V), which comprises the in-situ formation of a protected aziridine (XV) from amino-alcohol (VI) followed by in-situ aziridine ring-opening with hydroxyindazole (XI):



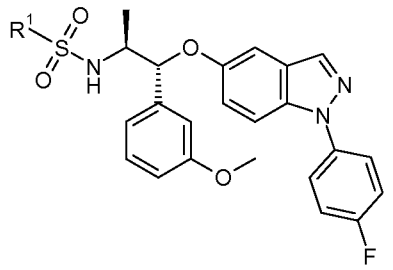
The process to the free-base form of the compound of formula (VI) (ie. not in salt-form) is described in WO 2008/076048 (example 6b). The formation of the hydrochloride salt of the compound of formula (VI) is described in the Examples herein. The compound of formula (XII) is commercially available. Processes to compound of formula (XI) are described in WO 2008/079073 (example 1) and in the Examples herein.

The methods which may be utilized to form compound of formula (V) are well known in the art. For example, compound of formula (XIII) may be prepared by mixing

compounds of formula (VI) and formula (XII) in a suitable solvent (for example an organic solvent such as 2-methyltetrahydrofuran) in the presence of a suitable base (for example an organic base such as N-methylmorpholine) at a suitable temperature (e.g. ambient temperature) for a suitable time (e.g. 1 hour). Compound of formula (XIV) may be prepared by adding methanesulfonyl chloride directly to the reaction mixture containing compound of formula (XIII) and a suitable base (for example an organic base such as N-methylmorpholine) at a suitable temperature (e.g. 40°C) for a suitable time (e.g. 16 hours). Compound of formula (XV) may be prepared by adding a suitable base (such as an inorganic base, e.g. sodium hydroxide) to a compound of formula (XIV) in a suitable solvent (such as an organic solvent e.g. 2-methyltetrahydrofuran) at a suitable temperature (e.g. ambient temperature). Alternatively the suitable base (such as an inorganic base, e.g. sodium hydroxide) can be added directly to the reaction solution containing the compound of formula (XIV) after a method of work-up well-known to those skilled in the art (for example washing with an aqueous acidic solution such as aqueous hydrochloric acid followed by washing with water). Compound of formula (V) may be prepared by adding compound of formula (XI) directly to the reaction mixture containing compound of formula (XV) and a suitable base (such as an inorganic base, e.g. sodium hydroxide) at a suitable temperature (e.g. 40°C) for a suitable time (e.g. 17 hours).

Further information on the processes of the invention and the products obtainable therefrom are described in the Examples herein.

In a further embodiment of the invention there is provided a compound of formula (IV):



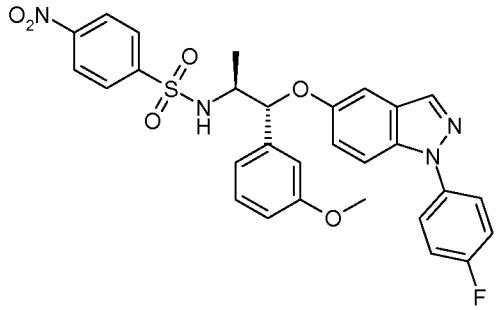
(IV)

wherein R^1 is alkyl (unsubstituted or substituted by silylalkyl), dialkylamino, aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2) or heteroaryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or

NO_2). In a further aspect there is provided the use of compound (IV), or a salt thereof, as defined herein, as a pharmaceutical intermediate.

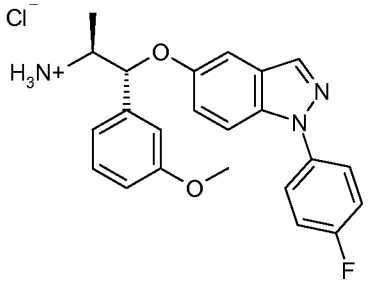
In a still further aspect R^1 is aryl (unsubstituted or substituted by one or more of halogen, haloalkyl, alkyl or NO_2).

In another embodiment of the invention there is provided a compound of formula (V). In a further aspect there is provided the use of compound (V), or a salt thereof, as defined herein, as a pharmaceutical intermediate.



(V)

In a further embodiment of the invention there is provided a compound of formula (II) in the hydrochloride salt-form (compound (XVI)). In a further aspect there is provided the use of the compound (XVI), as defined herein, as a pharmaceutical intermediate.



(XVI)

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Aryl groups and moieties are monocyclic or multicyclic aromatic carbocycles comprising, for example, 6 to 14 (such as 6 to 10) carbon atoms. Examples of aryl groups are phenyl or napthyl.

Dialkylamino means a $-N(alkyl)_2$ group in which alkyl is defined as above. Examples of dialkylamino groups are dimethylamino or diethylamino.

Haloalkyl means an alkyl group as defined above which is substituted by one or more halo atoms. Examples of haloalkyl are trifluoromethyl and trifluoroethyl.

Silylalkyl means a $-Si(alkyl)_3$ group in which alkyl is defined as above. Examples of silylalkyl groups are trimethylsilyl, triethylsilyl and tert-butyl dimethylsilyl.

We have found that this new synthetic process to Compound (I) has a number of advantages over the process previously described in WO 2008/076048. The need for large-scale chromatography is removed, avoiding significant time, resource allocation and costs in purification. The formation of intermediates in-situ without the need for additional isolation reduces the need for significant work-up and reaction mixture manipulations. Furthermore, the relatively low-yielding copper-promoted coupling step described in WO 2008/076048 is avoided, providing enhanced selectivity of nitrogen over oxygen and better overall reaction control. Furthermore, we have found that this new synthetic process and the crystallisation step described herein reliably provide Form B of Compound (I).

Medical Use

Because of their ability to bind to the glucocorticoid receptor the compounds of the invention are useful as anti-inflammatory agents, and can also display antiallergic, immunosuppressive and anti-proliferative actions. Thus, compounds of the invention, or a pharmaceutically acceptable salt thereof can be used as a medicament for the treatment or prophylaxis of one or more of the following pathologic conditions (disease states) in a mammal (such as a human):

(i) Lung diseases, which coincide with inflammatory, allergic and/or proliferative processes:

chronically obstructive lung diseases of any origin, mainly bronchial asthma, chronic obstructive pulmonary disease (COPD)

bronchitis of different origins

Adult respiratory distress syndrome (ARDS), acute respiratory distress syndrome

Bronchiectases

all forms of restructive lung diseases, mainly allergic alveolitis

all forms of pulmonary edema, mainly toxic pulmonary edema

sarcoidoses and granulomatoses, such as Boeck's disease

(ii) Rheumatic diseases/auto-immune diseases/degenerative joint diseases, which coincide with inflammatory, allergic and/or proliferative processes:

all forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, polymyalgia rheumatica, collagenoses, Behçet's disease

reactive arthritis

inflammatory soft-tissue diseases of other origins

arthritic symptoms in degenerative joint diseases (arthroses)

traumatic arthritides

collagen diseases of other origins, for example systemic lupus erythematodes, discoid lupus erythematosus, sclerodermia, polymyositis, dermatomyositis, polyarteritis nodosa, temporal arteritis

Sjögren's syndrome, Still syndrome, Felty's syndrome

Vitiligo

Soft-tissue rheumatism

(iii) Allergies, which coincide with inflammatory, allergic and/or proliferative processes:

All forms of allergic reactions, for example Quincke's edema, insect bites, allergic reactions to pharmaceutical agents, blood derivatives, contrast media, etc., anaphylactic shock, urticaria, allergic vascular diseases

Allergic vasculitis

inflammatory vasculitis

(iv) Vascular inflammations (vasculitides)

Panarteritis nodosa, temporal arteritis, erythema nodosum

Polyarteris nodosa

Wegner's granulomatosis

Giant-cell arteritis

(v) Nephropathies, which coincide with inflammatory, allergic and/or proliferative processes:

nephrotic syndrome

all nephritides, such as, for example, glomerulonephritis

(vi) Liver diseases, which coincide with inflammatory, allergic and/or proliferative processes:

acute liver cell decomposition

acute hepatitis of different origins, for example virally-, toxically- or pharmaceutical agent-induced

chronically aggressive and/or chronically intermittent hepatitis

(vii) Gastrointestinal diseases, which coincide with inflammatory, allergic and/or proliferative processes:

regional enteritis (Crohn's disease)

Gastritis

Reflux esophagitis

ulcerative colitis

gastroenteritis of other origins, for example native sprue

(viii) Proctological diseases, which coincide with inflammatory, allergic and/or proliferative processes:

anal eczema

fissures

haemorrhoids

idiopathic proctitis

(ix) Eye diseases, which coincide with inflammatory, allergic and/or proliferative processes:

allergic keratitis, uvenitis iritis

conjunctivitis

blepharitis

optic neuritis

chorioiditis

sympathetic ophthalmia

(x) Diseases of the ear-nose-throat area, which coincide with inflammatory, allergic and/or proliferative processes:

allergic rhinitis, hay fever

otitis externa, for example caused by contact dermatitis, infection, etc.

otitis media

(xi) Neurological diseases, which coincide with inflammatory, allergic and/or proliferative processes:

cerebral edema, mainly tumor-induced cerebral edema

multiple sclerosis

acute encephalomyelitis

different forms of convulsions, for example infantile nodding spasms

Meningitis

spinal cord injury

Stroke

(xii) Blood diseases, which coincide with inflammatory, allergic and/or proliferative processes:

acquired haemolytic anemia

thrombocytopenia such as for example idiopathic thrombocytopenia

M. Hodgkins or Non-Hodgkins lymphomas,

thrombocythemias,

erythrocytoses

(xiii) Tumor diseases, which coincide with inflammatory, allergic and/or proliferative processes:

acute lymphatic leukaemia

malignant lymphoma

lymphogranulomatoses

lymphosarcoma

extensive metastases, mainly in breast and prostate cancers

(xiv) Endocrine diseases, which coincide with inflammatory, allergic and/or proliferative processes:

endocrine orbitopathy

thyrotoxic crisis

de Quervain's thyroiditis

Hashimoto's thyroiditis

Hyperthyroidism

Basedow's disease

Granulomatous thyroiditis

Lymphadenoid goiter

(xv) Transplants, which coincide with inflammatory, allergic and/or proliferative processes;

(xvi) Severe shock conditions, which coincide with inflammatory, allergic and/or proliferative processes, for example anaphylactic shock

(xvii) Substitution therapy, which coincides with inflammatory, allergic and/or proliferative processes, with:

innate primary suprarenal insufficiency, for example congenital adrenogenital syndrome
acquired primary suprarenal insufficiency, for example Addison's disease, autoimmune adrenalitis, meta-infective, tumors, metastases, etc.
innate secondary suprarenal insufficiency, for example congenital hypopituitarism
acquired secondary suprarenal insufficiency, for example meta-infective, tumors, etc.

(xviii) Emesis, which coincides with inflammatory, allergic and/or proliferative processes: for example in combination with a 5-HT_3-antagonist in cytostatic-agent-induced vomiting.

(xix) Pains of inflammatory origins, e.g., lumbago

Without prejudice to the foregoing, the compounds of the invention can also be used to treat disorders such as: diabetes type I (insulin-dependent diabetes), Guillain-Barré syndrome, restenoses after percutaneous transluminal angioplasty, Alzheimer's disease, acute and chronic pain, arteriosclerosis, reperfusion injury, thermal injury, multiple organ injury secondary to trauma, acute purulent meningitis, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, granulocyte transfusion, Conies Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, oesophageal varicies, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, rheumatic fever, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Thl/Th2 cytokine balance, chronic kidney disease, hypercalcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, Little's syndrome, systemic inflammation, inflammatory bowel disease, Wegener's granulomatosis, giant cell arthritis, osteoarthritis, angioneurotic edema, tendonitis, bursitis, autoimmune chronic active hepatitis, hepatitis, cinhosis, panniculitis, inflamed cysts, pyoderma gangrenosum, eosinophilic fasciitis, relapsing polychondritis, sarcoidosis Sweet's disease, type 1 reactive leprosy, capillary

hemangiomas, lichen planus, erythema nodosum acne, hirsutism, toxic epiderrnal necrolysis, erythema multiform, psychoses, cognitive disorders (such as memory disturbances) mood disorders (such as depression and bipolar disorder), anxiety disorders and personality disorders.

As used herein the term "congestive heart failure" (CHF) or 'congestive heart disease" refers to a disease state of the cardiovascular system whereby the heart is unable to efficiently pump an adequate volume of blood to meet the requirements of the body's tissues and organ systems. Typically, CHF is characterized by left ventricular failure (systolic dysfunction) and fluid accumulation in the lungs, with the underlying cause being attributed to one or more heart or cardiovascular disease states including coronary artery disease, myocardial infarction, hypertension, diabetes, valvular heart disease, and cardiomyopathy. The term "diastolic congestive heart failure" refers to a state of CHF characterized by impairment in the ability of the heart to properly relax and fill with blood. Conversely, the term "systolic congestive heart failure" refers to a state of CHF characterized by impairment in the ability of the heart to properly contract and eject blood. As will be appreciated by one of skill in the art, physiological disorders may present as a "chronic" condition, or an "acute" episode. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of physiological disorders contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear.

In another aspect the present invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in therapy (such as a therapy described above).

In yet another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a glucocorticoid receptor mediated disease state (such as a disease state described above).

In a further aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of an inflammatory condition (such as an arthritic).

In a further aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a respiratory condition (for example a lung disease as described above).

In a still further aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of asthma.

In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of COPD.

In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of allergic rhinitis.

In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of irritable bowel syndrome.

In another aspect the present invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in treating an inflammatory condition, asthma, COPD, allergic rhinitis or irritable bowel syndrome.

In yet another aspect the present invention provides a method of treating a glucocorticoid receptor mediated disease state (such as a disease state described above) in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides a method of treating an inflammatory condition (such as an arthritic) in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides a method of treating a respiratory condition (such as a lung disease described above) in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In a still further aspect the invention provides a method of treating asthma in a mammal (such as man), which comprises administering to a mammal in need of such

treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In a still further aspect the invention provides a method of treating COPD in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In a still further aspect the invention provides a method of treating allergic rhinitis in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In a still further aspect the invention provides a method of treating irritable bowel syndrome in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of treating a glucocorticoid receptor mediated disease state (such as a disease state described above), an inflammatory condition, asthma, COPD, allergic rhinitis and/or irritable bowel syndrome, in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

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

In this specification, unless stated otherwise, the terms “inhibitor” and “antagonist” mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the agonist. An agonist may be a full or partial agonist.

The term “disorder”, unless stated otherwise, means any condition and disease associated with glucocorticoid receptor activity.

Pharmaceutical composition

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a mammal, said active ingredient is normally

formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, (active ingredient) and a pharmaceutically acceptable adjuvant, diluent or carrier. One embodiment relates to the use of a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, for treating a glucocorticoid receptor mediated disease state (such as a disease state described above), an inflammatory condition, asthma and/or COPD.

A further aspect the present invention provides a process for the preparation of said composition comprising mixing the active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition can comprise from 0.05 to 99 %w (per cent by weight), for example from 0.05 to 80 %w, such as from 0.10 to 70 %w (for example from 0.10 to 50 %w), of active ingredient, all percentages by weight being based on total composition.

A pharmaceutical composition of the present invention can be administered in a standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. Thus, a compound of the invention or a pharmaceutically acceptable salt thereof, may be formulated into the form of, for example, an aerosol, a powder (for example dry or dispersible), a tablet, a capsule, a syrup, a granule, an aqueous or oily solution or suspension, an (lipid) emulsion, a suppository, an ointment, a cream, drops, or a sterile injectable aqueous or oily solution or suspension.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule containing between 0.1 mg and 10 g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous, intraarticular or intramuscular injection.

In one embodiment the compounds of the invention or a pharmaceutically acceptable salt thereof, are administered orally.

In another embodiment the compounds of the invention, or a pharmaceutically acceptable salt thereof, are administered by inhalation.

In another embodiment the compounds of the invention, or a pharmaceutically acceptable salt thereof, are administered nasally.

Inhalation (particularly oral inhalation) is a particularly useful method for administering a compound of the invention (or a pharmaceutically acceptable salt thereof) when treating respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma. When administered by oral inhalation, a compound of the invention (or a pharmaceutically acceptable salt thereof) may be used effectively at a daily dose in the μg range, for example up to 500 μg, such as from 0.1 to 50 µg, from 0.1 to 40 µg, from 0.1 to 30 µg, from 0.1 to 20 µg or from 0.1 to 10 µg, of a compound of the invention (or a pharmaceutically acceptable salt thereof) as active ingredient.

A pharmaceutical composition of the invention may be administered by oral inhalation in any suitable form and using any suitable inhaler device. Suitable inhaler devices are known to persons skilled in the art and may be manual or breath actuated. The pharmaceutical composition may be formulated as a dry powder, as a suspension (in a liquid or gas) or as a solution (in a liquid) for administration by oral inhalation by means of a suitable inhaler device.

Inhaler devices suitable for pulmonary administration include metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebulisers and soft mist inhalers. Multi-chamber devices may be used to allow for delivery of a compound of the invention (or a pharmaceutically acceptable salt thereof) and one or more further active ingredients (when present).

A preferred metered dose inhaler device is a pressurised metered dose inhaler (pMDI).

A pharmaceutical composition for use in a pMDI may be provided in the form of a solution or suspension comprising the active ingredient and one or more excipients, the excipients including a suitable propellant in which the active ingredient is dissolved or dispersed. Suitable propellants are known to persons skilled in the art and include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane propellants, or mixtures of any such propellants. Examples of propellants are 1,1,1,2,-tetrafluoroethane (HFA or HFC 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA or HFC 227), each of which may be used alone or in combination with other propellants and/or other excipients.

A pMDI device contains the pharmaceutical composition in a pressurised container. The active ingredient is delivered by actuating a valve of the container of the pMDI device.

Actuation may be manual or breath actuated. In a manually actuated pMDI, the device is actuated by a user as they inhale, for example by pressing a suitable release mechanism on the pMDI device. A breath actuated pMDI device is actuated automatically when the user inhales through a mouthpiece of the pMDI. Examples of pMDI devices include for example Rapihaler®, Vannair®, Ventolin® HFA, Evohaler®, Maxair®, Autohaler® and Easi-Breathe®.

A metered dose inhaler device (such as a pMDI) may be used in combination with a spacer device. Suitable spacer devices are well known to persons skilled in the art and include Nebuchamber® or Volumatic®.

A pharmaceutical composition for use in a dry powder inhaler device is provided in the form of a dry powder comprising the active ingredient and one or more excipients, the excipients typically including a suitable carrier and/or diluent and/or coating agent. The active ingredient is provided in an inhalable form and preferably the particles of the active ingredient have a mass median aerodynamic diameter of less than about 10μm, more preferably of less than about 5μm, for example from 1 to 5μm. Persons skilled in the art may measure the mass median aerodynamic diameter using standard techniques known to them. Inhalable forms of the active ingredient may be may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation.

The dry powder composition may take the form of a powder agglomerate or an ordered mixture.

When the dry powder composition takes the form of an ordered mixture the mixture may comprise inhalable particles of the active ingredient formulated with carrier particles that aid flow from the dry powder inhaler device into the lung. The particles of the active ingredient adhere to the carrier particles to form an ordered (interactive) powder mixture. Suitable carrier particles for inclusion in such dry powder compositions are known, and include sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol and starch. Suitable carriers are lactose particles and they may have a mass median aerodynamic diameter of greater than 90μm.

When the dry powder composition takes the form of a powder agglomerate the agglomerate may comprise the active ingredient in the form of microparticles formulated with one or more diluents. Suitable diluents include sugars, for example lactose, mannitol and sucrose.

The active ingredient and/or excipients used in powder compositions for inhalation may be conditioned before, during or after formulation. Conditioning may be useful in, for example, restoring crystallinity and maintaining aerodynamic properties of the particles. Conditioning processes are well known and include exposure of particles to controlled temperature and humidity/solvent vapour. Examples of conditioning processes include those described in WO92/018110 and WO95/05805.

Dry powder inhaler devices may be single dose, multiple unit dose or multi-dose (reservoir) inhalers, and may utilise a dry powder or a powder-containing capsule.

In single-dose dry powder inhaler devices, individual doses are provided, usually in capsules (such as gelatine capsules), and are loaded into the device before use. Examples of these devices include Spinhaler®, Rotahaler®, Aeroliser™, Inhalator® and Eclipse devices. Multiple unit dose dry powder inhaler devices contain a number of individually packaged doses, either as multiple capsules (such as gelatine capsules) or in blister packs. Examples of these devices include Diskhaler®, Diskus® and Aerohaler® devices and breath-actuated, dry-powder inhaler devices having multiple cavities for powder arranged in a disc or ring, such as is disclosed in WO2005/002654, WO2012/010877, or WO2012/010878. In multi-dose (reservoir) dry powder inhaler devices, the active ingredient is stored in a bulk powder reservoir from which individual doses are metered. Examples of these devices include Turbuhaler®, Easyhaler®, Novolizer®, Clickhaler®, Spiromax®, Airmax® and Pulvinal® devices.

Nebuliser devices may for example be used to administer the active ingredient as an aqueous suspension or, preferably, solution, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulation. Suitable nebulisers are well known to persons skilled in the art and include the eFlow®.

Nasal administration of a compound of the invention (or a pharmaceutically acceptable salt thereof) may be provided by means of a spray from a suitable nasal delivery device, such as a spray pump or an MDI nasal delivery device, for example Rhinocort Aqua®. Alternatively, the compound of the invention (or a pharmaceutically acceptable salt thereof) may be administered nasally as a powder using a suitable DPI device, for example Rhinocort® or Turbuhaler®.

A pharmaceutical composition for use in a spray pump or MDI nasal delivery device may comprise a compound of the invention (or a pharmaceutically acceptable salt thereof) dispersed or preferably dissolved in a suitable aqueous medium. Where it is

desirable to limit the penetration of the active ingredient into the lung and to retain the active ingredient in the nasal cavity, it may be necessary to use particles of the active ingredient having a mean mass aerodynamic diameter greater than about 10μm, for example from 10 μm to 50 μm.

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. Tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention further relates to combination therapies or compositions wherein the compounds of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compounds of the invention, or a pharmaceutically acceptable salt thereof, is administered concurrently (possibly in the same composition) or sequentially with one or more agents for the treatment of any of the above disease states.

For example, for the treatment of rheumatoid arthritis, osteoarthritis, COPD, asthma, irritable bowel syndrome or allergic rhinitis a compound of the invention, or a pharmaceutically acceptable salt thereof, can be combined with one or more agents for the treatment of such a condition. Where such a combination is to be administered by inhalation, then the one or more agents is selected from the list comprising:

- a PDE4 inhibitor including an inhibitor of the isoform PDE4D;
- a selective β_2 adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, indacaterol, olodaterol, milveterol or vilanterol;
- a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, telenzepine, aclidinium bromide or glycopyrronium bromide;
- a steroid (such as budesonide);
- a modulator of chemokine receptor function (such as a CCR1 receptor antagonist);

- an inhibitor of p38 kinase function;
- an inhibitor of matrix metalloproteases, most preferably targeting MMP-2, -9 or MMP-12; or,
- an inhibitor of neutrophil serine proteases, most preferably neutrophil elastase or proteinase 3.

In another embodiment of the invention where such a combination is for the treatment of COPD, asthma or allergic rhinitis, the compounds of the invention, or a pharmaceutically acceptable salt thereof, can be administered by inhalation or by the oral route and the other agent, e.g. xanthine (such as aminophylline or theophylline) can be administered by inhalation or by the oral route. The compounds of the invention, or a pharmaceutically acceptable salt thereof, and the other agent, e.g xanthine may be administered together. They may be administered sequencially. Or they may be administered separately.

Examples

The invention is illustrated, but in no way limited, by the following Examples and with reference to the enclosed Figures.

The following abbreviations may be used:

DSC	Differential scanning calorimeter
HPLC	High-performance liquid chromatography
MTDSC	Modulated temperature differential scanning calorimeter
NMR	Nuclear magnetic resonance
UV	Ultraviolet
XRPD	X-Ray powder diffraction
PS80	Polysorbate 80
LOD	Loss on drying
LC	Liquid chromatography
GC	Gas chromatography

General Procedures

X-Ray powder diffraction analysis (XRPD) were performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L.

(1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), *X-ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using a Panalytical X´Pert PRO MPD instrument with the following parameters:

- CuK_α (1.5418Å)
- 45 kV and 40 mA
- $2° \leq 2\theta \leq 40°$
- 4 °/min, 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.

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, sample preparation 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 intensities of the peaks may vary according to the orientation of the sample under test and on the type and setting of the instrument used. 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 and any crystalline form that provides a powder diffraction pattern substantially identical to those disclosed herein fall within the scope of the present disclosure. Generally, a measurement error of a diffraction angle in an X-ray powder diffraction pattern is about 5% or less, typically plus or minus 0.2° 2-theta.

Melting point was determined by Differential Scanning Calorimetry (DSC) using standard methods, for example those described in Höhne, 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.

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. 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.

A person skilled in the art will further appreciate that slight variations in the measurements of solubility given in the examples herein may occur as a result of sample purity, polymorph purity, sample preparation and the measuring conditions (e.g. temperature, time and degree of agitation). It will be appreciated that alternative measurements of solubility may be given by using conditions different to those described hereinafter. Hence the measurements of solubility quoted herein are not to be taken as absolute values.

It will be further appreciated by a person skilled in the art that slight variations in the measurements of hygroscopicity given in the examples herein may occur as a result of sample purity, polymorph purity, sample preparation and the measuring conditions (e.g. equipment and parameters used). It will be appreciated that alternative measurements of hygroscopicity may be given by using conditions different to those described hereinafter.

Hence the measurements of hygroscopicity quoted herein are not to be taken as absolute values.

Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were acquired using Varian (Inova 400 MHz) or Bruker (Avance 500 or DPX 300) spectrometers, at 25 °C or 300 K. Samples were prepared as solutions in a suitable deuterated solvent (d_6-DMSO – d_6-dimethyl sulfoxide, $CDCl_3$ – d-chloroform, or d_6-acetone), optionally containing trimethylsilane (TMS). Sample solutions may also contain an internal standard (either maleic acid or 2,3,5,6-tetrachloronitrobenzene) for assay determination and/or added trifluoroacetic acid, to move exchangeable proton signals (e.g. from maleic acid) away from analyte resonances. Spectral data is reported as a list of chemical shifts (δ, in ppm) with a description of each signal, using standard abbreviations (s = singlet, d = doublet, m = multiplet, t = triplet, q = quartet, br = broad, etc.). Spectra were referenced relative to TMS (δ = 0.00 ppm), d_5-DMSO (δ = 2.50 ppm), chloroform (δ = 7.24 ppm) or d_5-acetone (δ = 2.05 ppm). *J*-Coupling constants are listed, where measured, in the descriptions of the resonances. Slight variation of chemical shifts and *J*-coupling constants may occur, as is well known in the art, as a result of variations in sample preparation, such as analyte concentration variations and including or omitting additives (for example NMR assay standards or trifluoroacetic acid).

Loss-on-drying analysis was performed using a Mettler Toledo HR83 Moisture Analyser or Perkin-Elmer TGA7 Thermogravimetric Analyzer.

Large scale reactions were carried out in glass-lined steel reactors fitted with heat transfer jackets and serviced with appropriate ancillary equipment. Large scale preparative chromatography was performed using a Novasep LC150 preparative HPLC system, equipped with a dynamic axial compression column, of internal diameter 15 cm. Standard laboratory glassware and equipment was used for small scale processes. Starting materials, solvents and reagents were purchased commercially and used as supplied.

Liquid chromatography (LC) was performed on reversed phase columns packed with octadecyl or phenyl bonded silica. Agilent 1100 HPLC instruments equipped with UV detectors (λ = 230 nm unless stated otherwise) were used. Stationary phase particle size, column dimensions, mobile phases (acetonitrile and water, pH adjusted with trifluoroacetic acid or ammonium formate/ammonia), gradient timetables, flow rates and temperature suitable for the specific analyses were used. Sample solutions were prepared at a main analyte concentration of approximately 0.5 mg mL^{-1} using suitable diluents.

Gas chromatography (GC) was performed using helium as carrier gas on a DB-624 capillary column. Agilent 6890 GC instruments equipped with flame-ionisation detectors were used.

Water analysis was performed by coulometric Karl-Fischer titration using a Metrohm 756 KF coulometer.

Summary of XRPD Analysis of Form A and Form B of Compound (I)

Crystals of Compound (I) Form A and Form B obtained as described herein were analysed by XRPD and the results are tabulated below (RI represents relative intensity) and are shown in the respective Figures.

Table 1 shows the most significant peaks in the XRPD-diffractogram of crystalline Form B of Compound (I). **Table 2** shows the most significant peaks in the XRPD-diffractogram of crystalline Form A of Compound.

A number of weak and very weak peaks have been omitted. Due to preferred orientation effects some of the weak omitted peaks may become more significant.

Table 1 (Form B)

Position °2-Theta	**RI**
21.5	vs
20.6	s
20.3	s
19.9	s
17.4	vs
15.7	vs
14.4	s
11.8	vs
9.9	s
9.2	vs

Table 2 (Form A)

Position °2-Theta	**RI**
18.7	vs
18.1	vs
17.8	vs
16.7	s
14.9	vs
13.3	vs
11.9	s
10.7	s
9.7	vs
8.4	s

Abbreviations

vs = very strong; s = strong

Summary of Figures

Figure 1 shows the XRPD-diffractogram of crystalline Form B of Compound (I).

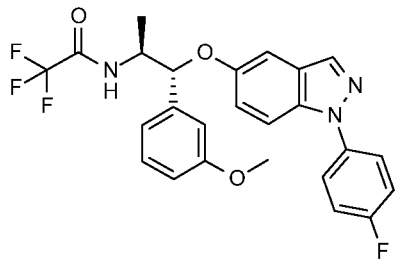
Figure 2 shows the differential scanning calorimetry profile of crystalline Form B of Compound (I).

Figure 3 shows the XRPD-diffractogram of crystalline Form A of Compound (I).

Figure 4 shows the differential scanning calorimetry profile of crystalline Form A of Compound (I).

Example 1: Preparation of Form B of Compound (I)

(i) 2,2,2-Trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide (Form B)



The solution obtained from Example 1, step (ii) was further diluted with 1-propanol (17.0 kg) and adjusted to 60 °C. *n*-Heptane (50.4 kg) was charged gradually whilst maintaining the temperature at 60 °C. The solution was cooled to 50 °C, charged with seeds of Form B of Compound (I) (50 g) to initiate crystallisation, and gradually cooled to 8 °C. Additional n-heptane (25.5 kg) was charged over 20 minutes before analysing a sample of the filtered crystals by XRPD, confirming crystallisation of Form B. The batch was filtered in two roughly equal parts, diluting the second part with further additional n-heptane (3.5 kg) before filtering. The filter cake was washed with a cold mixture of 1-

propanol (7.2 kg) and n-heptane (18.0 kg) and dried under vacuum. Yield 9.15 kg (18.7 mol, 77%). 99.8% Assay (NMR) and 0.2% LOD, both by mass.

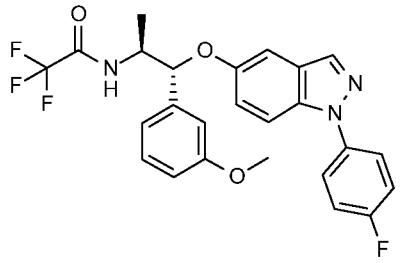
^{1}H NMR (400 MHz, d_6-DMSO) δ 9.50 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.73 (m, 2H), 7.69 (d, J = 9.1 Hz, 1H), 7.39 (m, 2H), 7.26 (dd, J = 8.2, 7.7 Hz, 1H), 7.20 (dd, J = 9.1, 2.4 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.95 (m, 1H), 6.83 (dd, J = 8.2, 2.6 Hz, 1H), 5.27 (d, J = 6.4 Hz, 1H), 4.25 (m, 1H), 3.72 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H).

The XRPD diffractogram of the form of Compound (I) obtained by way of Example 1 (Form B) is shown in Figure 1 below and is tabulated in Table 1 above.

The DSC profile of the form of Compound (I) obtained by way of Example 1 (Form B) is shown in Figure 2 below. The compound exhibited an onset temperature of the melting endotherm of 109 °C.

The starting material used in step (i) was prepared as follows.

(ii) 2,2,2-Trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide

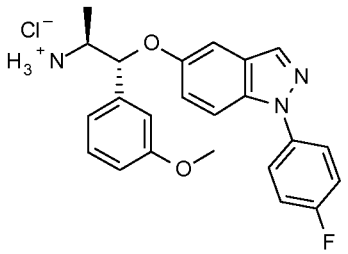


Ethyl trifluoroacetate (14.3 kg, 101 mol) followed by a methyl *tert*-butyl ether (11.2 kg) line wash was charged to a stirring suspension of (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride (14.15 kg, 25.1 mol; assay = 75.9% by mass) in methyl *tert*-butyl ether (35.9 kg) and triethylamine (7.6 kg, 75 mol). The mixture was stirred at 22 °C for 24 hours, by which time LC analysis showed that there was 0.8% residual starting material.

Aqueous sodium hydroxide (53 kg, 45 mol) was charged, the mixture stirred for 30 minutes (excess ethyl trifluoroacetate is hydrolysed to trifluoroacetic acid during this time) and then allowed to separate into layers before discarding the lower (aqueous) phase. The upper (organic) phase was washed successively with aqueous hydrochloric acid (50 kg, 50 mol) and then water (54 kg), and then screened through a 0.6 μm filter into a clean vessel.

The solution was concentrated by distilling off solvent (31 kg) at < 70 °C (atmospheric pressure). Further solvent (37 kg) was distilled off at < 70 °C under reduced pressure (900-100 mbar) whilst continuously replacing with 1-propanol (35 kg). Analysis showed that there was 11.8 kg (24.2 mol) of 2,2,2-trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide and 7.1 kg of 1-propanol, with < 0.05% methyl *tert*-butyl ether and < 0.1% water by volume. The solution was used directly in the crystallisation step. Yield 96%.

(iii) (1*R*,2*S*)-1-[1-(4-Fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride



N-[(1*S*,2*R*)-2-[1-(4-Fluorophenyl)indazol-5-yl]oxy-2-(3-methoxyphenyl)-1-methyl-ethyl]-4-nitro-benzenesulfonamide (23.3 kg, 35.6 mol; assay = 88.1% by mass) and potassium carbonate (19.90 kg, 144 mol; 325-mesh sieved grade) were added to stirring acetonitrile (322 kg). After sparging the reaction mixture to remove oxygen for one hour, thioglycolic acid (7.10 kg, 77.1 mol) was added before heating to 75 °C. After 24 hours, extra thioglycolic acid (1.75 kg, 19.0 mol) and potassium carbonate (4.92 kg, 35.6 mol) were charged. After a further 18 hours, LC analysis showed 98.7% conversion of the 4-nitro-benzenesulfonamide starting material to the amine product by area.

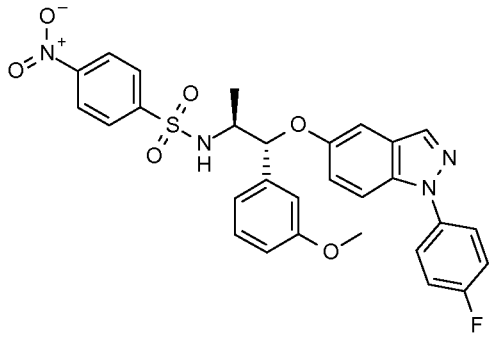
Water (203.6 kg) was charged and then the mixture concentrated by distilling off solvent (126.9 kg) at atmospheric pressure. Methyl *tert*-butyl ether (165.8 kg) was charged, and after allowing the mixture to settle into layers, the lower (aqueous) phase was removed. The organic phase was washed successively with 1M sodium hydroxide (235.6 kg, 225 mol), 1M hydrochloric acid (229.7 kg, 240 mol) and finally saturated aqueous sodium chloride (229.6 kg).

After concentrating the solution by distilling off solvent (151.9 kg) at atmospheric pressure, it was diluted with methyl *tert*-butyl ether (328.1 kg), re-concentrated (327.8 kg solvent distilled off) and diluted again at 40 °C with more methyl *tert*-butyl ether (123.9

kg). (The water content of the resulting mixture was determined as 21 g L^{-1}.) The slurry was cooled to 2 °C, diluted with further methyl *tert*-butyl ether (152.2 kg) and then filtered. The solids were washed with methyl *tert*-butyl ether (34.6 kg) and then dried at 50 °C under vacuum (final LOD analysis 0.2%). Yield 14.3 kg (25.4 mol, 71% by moles). 75.9% Assay and 2.5% residual methyl *tert*-butyl ether, both by mass (NMR). The major part of the remaining mass is sodium chloride.

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.09 (s, 1H), 7.68 – 7.63 (m, 3H), 7.35 – 7.29 (m, 2H), 7.30 (dd, J = 2.4, 9.1 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.84 (dd, J = 2.4, 8.3 Hz, 1H), 5.62 (d, J = 3.1 Hz, 1H), 3.67 (s, 3H), 3.66 (qd, J = 3.1, 6.8 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H). The three exchangeable ammonium protons are coalesced with the exchangeable protons of maleic acid (added to the NMR sample) and water in the recorded spectrum.

(iv) *N*-[(1*S*,2*R*)-2-[1-(4-Fluorophenyl)indazol-5-yl]oxy-2-(3-methoxyphenyl)-1-methyl-ethyl]-4-nitro-benzenesulfonamide



A slurry of (1*R*,2*S*)-2-amino-1-(3-methoxyphenyl)propan-1-ol hydrochloride (12.25 kg, 55.9 mol; 99.4% assay by mass) and 4-nitrobenzenesulfonyl chloride (13.6 kg, 61.4 mol) in 2-methyltetrahydrofuran (260 kg) was heated to 40 °C. A mixture of N-methylmorpholine (28.4 kg, 280 mol) and 2-methyltetrahydrofuran (23.9 kg) was added over 30 minutes, followed by a 2-methyltetrahydrofuran (12.5 kg) line wash. After stirring for one hour, LC analysis showed 99.9% conversion by area (λ = 254 nm) of the amine starting material to *N*-[(1*S*,2*R*)-2-hydroxy-2-(3-methoxyphenyl)-1-methyl-ethyl]-4-nitro-benzenesulfonamide.

Methanesulfonyl chloride (12.6 kg, 110 mol) was added at 40 °C over 10 minutes followed by a 2-methyltetrahydrofuran (12.5 kg) linewash. The reaction mixture was stirred for 16 hours at 40 °C to give [(1*R*,2*S*)-1-(3-methoxyphenyl)-2-[(4-nitrophenyl)sulfonylamino]propyl] methanesulfonate

After sequential washing with 5M hydrochloric acid (61.1 kg, 283 mol) and then water (56.2 kg), 10M Sodium hydroxide (30.4 kg, 223 mol) was added, followed by a line wash with water (12.4 kg), to form (2*S*,3*S*)-2-(3-methoxyphenyl)-3-methyl-1-(4-nitrophenyl)sulfonyl-aziridine.

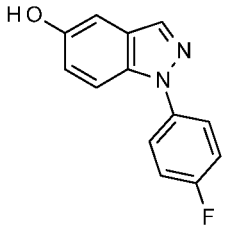
1-(4-Fluorophenyl)indazol-5-ol (14.32 kg, 61.2 mol; 97.5% assay by mass) was added and the reaction mixture stirred for 17 hours at 40 °C to form the subtitle compound. (LC analysis showed 0.8% of the residual aziridine intermediate by area, $\lambda = 254$ nm.)

The lower liquid phase was removed after allowing the mixture to settle and the upper (organic) phase was then washed sequentially with 5M hydrochloric acid (60.7 kg, 284 mol) and then water (56.5 kg). Solvent (200 kg) was distilled off at atmospheric pressure and then toluene (129.2 kg) was added whilst distilling off further solvent (122.0 kg), matching the rate of toluene addition with the rate of distillation. (GC analysis of the solution then showed 5.8% 2-methyltetrahydrofuran by volume.)

The solution was diluted with toluene (109.1 kg), cooled to 50 °C, seeded (approximately 2-5 g of the subtitle compound, slurried in toluene) and further cooled to 0 °C. Finally, the solids were filtered off, washed with toluene (50.5 kg) and dried at 40 °C under vacuum (final LOD analysis 0.6%). Yield 23.30 kg (35.6 mol, 64% by moles). 88.1% Assay and 12.8% toluene, both by mass (NMR).

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.47 (d, $J = 8.3$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 2H), 8.02 (s, 1H), 7.93 (d, $J = 8.9$ Hz, 2H), 7.74 – 7.68 (m, 2H), 7.60 (d, $J = 9.1$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.22 – 7.18 (m, 1H)*, 7.08 (dd, $J = 2.4$, 9.1 Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.76 – 6.72 (m, 3H), 5.01 (d, $J = 4.5$ Hz, 1H), 3.72 (dqd, $J = 4.5$, 6.8, 8.3 Hz, 1H), 3.65 (s, 3H), 1.09 (d, $J = 6.8$ Hz, 3H). The indicated (*) resonance is obscured by toluene signals.

(v) 1-(4-Fluorophenyl)indazol-5-ol



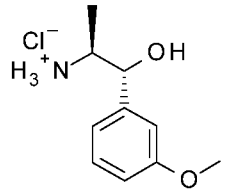
A slurry of 5-hydroxy-1H-indazole (12.4 kg, 91.5 mol; assay 99% by mass), tris(dibenzylideneacetone)dipalladium(0) (1.44 kg, 1.57 mol) and 2-di-tert-

butylphosphino-2',4',6'-triisopropylbiphenyl (1.35 kg, 3.18 mol) in 2-methyltetrahydrofuran (42.5 kg) was prepared. Sodium tert-butoxide (17.45 kg, 182 mol) solution in 2-methyltetrahydrofuran (53.5 kg), 1-chloro-4-fluorobenzene (12.45 kg, 95.4 mol) and then a 2-methyltetrahydrofuran (10.50 kg) line wash were charged sequentially to the stirring mixture. The slurry was heated at 73 °C for 15 hours (LC analysis then showed 0.4% residual 5-hydroxy-1H-indazole by area, with λ = 222 nm).

Water (73.5 kg), heptane (18.9 kg), 10M hydrochloric acid (8.8 kg, 77 mol) and a water (12.3 kg) line wash were then charged after cooling to 50 °C. After phase separation, the subtitle compound was extracted from the organic phase with two portions of aqueous sodium hydroxide (91.5 kg at 0.7 M, 62 mol and then 51.3 kg at 1.0 M, 48 mol). The combined sodium hydroxide extracts were diluted with ethanol (74.6 kg), acetic acid (4.8 kg, 80 mol) and then, gradually over 45 minutes, a solution of acetic acid (5.5 kg, 92 mol) in ethanol (19.5 kg). After cooling to -10 °C, the solids were filtered off, washed with a mixture of water (37.1 kg) and ethanol (19.8 kg) and dried at 40 °C under vacuum (final LOD analysis 0.3%). Yield 15.40 kg (65.8 mol, 72% by moles). 97.5% assay by mass (NMR).

^{1}H NMR (500 MHz, d_6-acetone) δ 8.31 (s, 1H), 8.08 (s, 1H), 7.82 – 7.78 (m, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.20 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 2.0, 9.0 Hz, 1H).

(vi) (1*R*,2*S*)-2-Amino-1-(3-methoxyphenyl)propan-1-ol hydrochloride



To a solution of *tert*-butyl *N*-[(1*S*)-2-(3-methoxyphenyl)-1-methyl-2-oxo-ethyl]carbamate (24.54 kg, 87.8 mol) in toluene (86 kg) and isopropanol (53.5 kg, 890 mol), aluminium isopropoxide (3.7 kg, 18 mol) was added. The reaction was heated up to 50 °C and stirred for 13 hours to give *tert*-butyl *N*-[(1*S*,2*R*)-2-hydroxy-2-(3-methoxyphenyl)-1-methyl-ethyl]carbamate.

1M Hydrochloric acid (50.6 kg, 50 mol) was added over 1 hour, maintaining the temperature between 15-25 °C, followed by a water rinse (2 kg). After phase separation,

the aqueous layer was extracted with two portions of ethyl acetate (34 kg per portion). The combined organics were washed with saturated sodium hydrogen carbonate (50.3 kg) and saturated aqueous sodium chloride (50.3 kg).

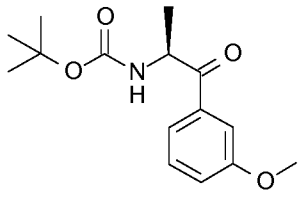
The organic solution was concentrated in vacuo to an oil and ethyl acetate (110 kg) was charged. The organic solution was concentrated in vacuo to an oil and ethyl acetate (110 kg) was charged.

Hydrogen chloride gas (9.7 kg, 266 mol) was charged over 4 hours, maintaining the temperature between 0-5 °C. The reaction contents were heated to 15 °C and stirred for 12 hours.

Methyl *tert*-butyl ether (90 kg) was added and the vessel contents cooled to 0 °C. The slurry was stirred for 2 hours at 0 °C and filtered under vacuum. The damp cake was slurry washed with methyl *tert*-butyl ether (72 kg), stirring for 30 minutes at 0 °C before filtering under vacuum. The filter cake was washed with methyl *tert*-butyl ether (20 kg) and then dried in a vacuum oven at 50 °C. Yield 16.3 kg (74.2 mol, 85% by moles). 99.1% Assay by mass (NMR).

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.09 (s, 3H), 7.28 (t, J = 8.0 Hz, 1H), 6.94 – 6.91 (m, 2H), 6.87 – 6.83 (m, 1H), 6.03 (d, J = 4.2 Hz, 1H), 4.91 (t, J = 3.5 Hz, 1H), 3.75 (s, 3H), 3.38 (qd, J = 3.0, 6.7 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H).

(vii) Tert-butyl *N*-[(1*S*)-2-(3-methoxyphenyl)-1-methyl-2-oxo-ethyl]carbamate



To a cooled (0-5 °C) solution of *N*-(*tert*-butyloxycarbonyl)-L-alanine (45.0 kg, 238 mol) in dichloromethane (596.5 kg) was added 1,1-carbonyldiimidazole (52.5 kg, 324 mol) over 3 hours and the resultant solution maintained at 0-5 °C for 30 minutes. *N*,*O*-Dimethylhydroxylamine hydrochloride (31.5 kg, 323 mol) was added over 1 hour 30 minutes and the resultant solution maintained at 0-5 °C for 30 minutes.

After stirring for 14 hours at 15 °C, the reaction mixture was washed sequentially with two portions of 1M hydrochloric acid (164.5 kg, 163 mol and 166 kg, 164 mol), 10% aqueous sodium hydrogen carbonate (164.5 kg) and then 20% aqueous sodium chloride

solution (199 kg) to give an organic phase solution of *tert*-butyl *N*-[(1*S*)-2-(methoxy (methyl)amino)-1-methyl-2-oxo-ethyl]carbamate (606 kg). Half of the solution (303 kg) was solvent swapped by distillation into tetrahydrofuran (220 kg).

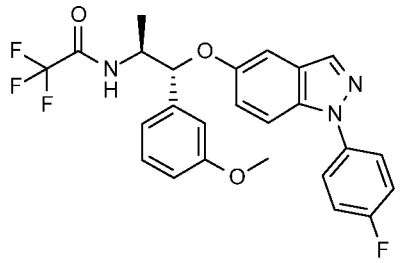
The solution was cooled to below 10 °C and isopropylmagnesium chloride 1.91 M in tetrahydrofuran (54 kg, about 114 mol) added over 1 hour 20 minutes, maintaining the temperature between 10-15 °C, followed by a tetrahydrofuran rinse (3 kg). 3-Methoxy phenylmagnesium bromide 0.86 M in THF (203 kg, about 202 mol) was gradually added, maintaining the temperature between 10-15 °C, followed by a tetrahydrofuran rinse (3 kg).

After warming to 20 °C, 20% aqueous acetic acid (101 kg) was added, maintaining the temperature below 30 °C, followed by a water rinse (5 kg). After phase separation, the aqueous layer was back-extracted with ethyl acetate (91 kg). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (101 kg) and then saturated aqueous sodium chloride solution (100 kg).

The organic layer was solvent swapped into heptane (80 kg) by distillation, then methyl *tert*-butyl ether (6.3 kg) was charged and the slurry stirred at 20 °C for 6 hours. The solids were then filtered off, washed with a mixture of heptane (15.75 kg) and methyl *tert*-butyl ether (4.25 kg), and dried in a 50 °C vacuum oven. Yield 26.2 kg (93.8 mol, 79% by moles).

^{1}H NMR (300 MHz, CDCl3) δ 7.55 (m, 2H), 7.38 (t, J=7.8Hz, 1H), 7.13 (m, 1H), 5.61 (m, 1H), 5.27 (m, 1H), 3.85 (s, 3H), 1.39-1.46 (m, 12H).

Example 2: Preparation of seed crystals of Form B of Compound (I)

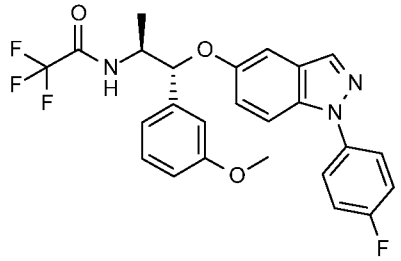


2,2,2-Trifluoro-*N*-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide (7.5 g) in amorphous form (prepared as described in Example 4 steps (i) to (iv) below but without the crystallization step in step (i)) was charged to a solution of 9:1 v:v heptane:isopropyl acetate (75 mL). The solution was heated to 87 °C which afforded dissolution. The solution was allowed to cool to 15 °C.

The resulting product was filtered off and dried at 40 °C in a vacuum oven to constant weight. Yield 6.40 g (85%). XRPD diffractogram consistent with Form B reference (Table 1 and Figure 1). DSC profile consistent with Form B reference (Figure 2).

Example 3: Conversion of Form A to Form B of Compound (I)

(i) Conversion of Form A of Compound (I) to Form B of Compound (I)

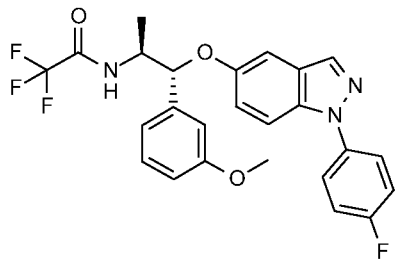


A Form B seed of Compound (I) (28.4 g) was charged to a stirring slurry of Form A of Compound (I) (1.45 kg) in water (101 L) and 2-propanol (22.5 L). The slurry was stirred for 4 days at 20-25 °C, by which time XRPD analysis showed conversion to Form B was complete. The Form B product was filtered off and dried at 40 °C in a vacuum oven to constant weight. Yield 1.41 kg (97%). 98.8% Assay (NMR).

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.50 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 0.9 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.70 (d, J = 9.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.23 (dd, J = 2.4, 9.1 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.00 – 6.98 (m, 1H), 6.85 (ddd, J = 0.8, 2.6, 8.3 Hz, 1H), 5.30 (d, J = 6.4 Hz, 1H), 4.28 (dqd, J = 6.4, 6.8, 8.5 Hz, 1H), 3.74 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H).

Example 4: Preparation of Form A of Compound (I)

(i) 2,2,2-Trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide (Form A)



Trifluoroacetic anhydride (1.14 L, 8.14 mol) was charged to a stirring 20 °C suspension of (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride (2.58 kg, 5.42 mol; 90% assay by mass) in methyl *tert*-butyl ether (9.30 L) and triethylamine (2.80 L, 20.1 mol) over 45 minutes, keeping the temperature below 40 °C. After 5 minutes, LC analysis showed < 0.05% amine starting material remaining by area.

The reaction mixture was washed successively with water (9.28 L), 1M hydrochloric acid (9.28 L, 9.28 mol), 7% aqueous sodium bicarbonate (9.28 L, 8.03 mol) and water (9.30 L). The organic phase was evaporated at 40-50 °C under reduced pressure (500 mbar), dissolved in 2-propanol (9.30 L) and evaporated again at 40-50 °C, 50-500 mbar.

The residue was dissolved in 2-propanol (18.6 L), screened through a 1 μm filter into a clean vessel, and then water was charged until the solution became turbid (11.3 L was required). Two portions of the turbid solution (0.325 and 1.30 L) were removed and the first stirred with a Form A seed of 2,2,2-trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide (1.1 g) in a clean flask until a thick slurry was produced, and then the second portion was added, continuing to stir until the slurry thickened once again. The main crystallisation vessel was heated to about 60 °C to re-dissolve some small deposits of amorphous solids before cooling back to 25 °C. The seed slurry was warmed to about 35 °C for better mobility and then charged to the main crystallisation vessel. The slurry was warmed to 30 °C during a 3 hour stir to reduce viscosity. Water (5.70 L) was then charged over 15 minutes and stirring continued for 16 hours whilst the temperature was slowly varied in the range 30-38 °C. The 30 °C slurry was filtered and washed with a mixture of 2-propanol (2.30 L) and water (3.50 L). The solids were dried to constant mass at 40 °C and reduced pressure. Yield 2.45 kg (93%). 99.4% Assay (NMR), 0.04% water, 0.1% 2-propanol (all by mass).

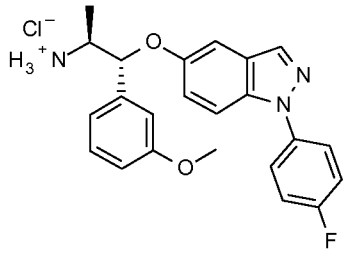
^{1}H NMR (400 MHz, d_6-DMSO) δ 9.52 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.77 – 7.72 (m, 2H), 7.70 (d, J = 9.1 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.21 (dd, J = 2.4, 9.1 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.97 – 6.95 (m, 1H), 6.84 (dd, J = 2.3, 8.1 Hz, 1H), 5.28 (d, J = 6.3 Hz, 1H), 4.26 (dqd, J = 6.3, 6.8, 8.4 Hz, 1H), 3.73 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H).

The XRPD diffractogram of the form of Compound (I) obtained by way of Example 4 (Form A of Compound (I)) is shown in Figure 3 below.

The DSC profile of the form of Compound (I) obtained by way of Example 4 (Form Aof Compound (I)) is shown in Figure 4 below. The compound exhibited an onset temperature of the melting endotherm of 83 °C.

The (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride starting material was prepared as follows.

(ii) (1*R*,2*S*)-1-[1-(4-Fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride

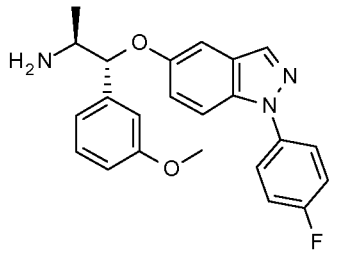


(1*R*,2*S*)-1-[1-(4-Fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine solution (37.8 kg, 7.89 mol; 8.2% assay by mass) obtained using the method of Example 4 step (iii) below, was evaporated to a thick oil then re-dissolved in ethyl acetate (15.5 L). The solution was washed with 1M hydrochloric acid (15.4 L, 15.4 mol) and then aqueous sodium chloride (15.5 L; 10% assay by mass). The solution was evaporated to a thick oil at 40 °C under reduced pressure and re-dissolved in ethanol (6.2 L).

Methyl *tert*-butyl ether (21.6 L) was charged at 50 °C and the solution then cooled to 0 °C. The crystallised (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride was filtered off, washed with four portions of methyl *tert*-butyl ether (6.2 L per portion) and dried at 40 °C to constant mass. Yield 2.98 kg (6.27 mol, 79% by moles). 90.0% Assay by mass (NMR). Contains residual methyl *tert*-butyl ether. 99.9% LC purity.

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.60 (s, 3H), 8.21 (d, J = 0.9 Hz, 1H), 7.79 – 7.73 (m, 3H), 7.44 – 7.38 (m, 2H), 7.36 (dd, J = 2.4, 9.2 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.91 – 6.88 (m, 1H), 5.79 (d, J = 3.0 Hz, 1H), 3.75 (s, 3H), 3.68 (qd, J = 3.0, 6.8 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H).

(iii) (1*R*,2*S*)-1-[1-(4-Fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine

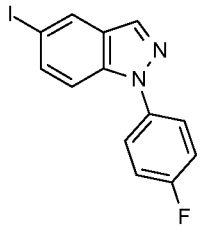


Water was removed from a solution of 1-(4-fluorophenyl)-5-iodo-indazole (2.20 kg, 4.40 mol; 67.6% assay by mass) in butyronitrile (8.5 L) by azeotropic distillation at atmospheric pressure, removing the aqueous phase of the distillate but returning the organic phase to the vessel. (Afterwards, the water content was determined to be 1.3 g L^{-1}). Caesium carbonate (4.65 kg, 14.3 mol) and (1*R*,2*S*)-2-amino-1-(3-methoxyphenyl)propan-1-ol hydrochloride (1.17 kg, 5.29 mol; 98.4% assay by mass) were charged and the mixture sparged with nitrogen for 60 minutes at 50-60 °C. A separately prepared solution, which had been sparged with nitrogen for 40 minutes at 80 °C, of copper (I) iodide (0.21 kg, 1.10 mol), *N,N*-dimethylglycine (0.23 kg, 2.23 mol) and triethylamine (0.31 L, 2.22 mol) in butyronitrile (6.6 L) was then charged. The reaction mixture was heated at 105 °C for 18 hours.

After cooling to 25 °C the reaction mixture was washed with water (two portions, each of 11 L) and 1M hydrochloric acid (11 L, 11 mol). The organic layer was concentrated to a thick oil at 60 °C by solvent evaporation under reduced pressure. Ethyl acetate (11L) was added and then the mixture concentrated at 40 °C by solvent evaporation under reduced pressure to give crude (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine hydrochloride. An additional batch of the crude product was prepared from further 1-(4-fluorophenyl)-5-iodo-indazole (2.14 kg, 4.38 mol; 69.3% assay by mass) by the same method and the two batches were dissolved in ethyl acetate (21.6 L). The solution was washed with a mixture of 0.01N aqueous disodium ethylenediaminetetraacetate (disodium EDTA) (21.6 L) and aqueous sodium chloride (3.6 L; 20% assay by mass) and then diluted with ethyl acetate (1.0 L). The solution was washed twice with a mixture of 0.1N aqueous disodium EDTA (21.6 L for each portion) and sodium chloride (3.6 L for each portion; 20% assay by mass), then with aqueous sodium bicarbonate (21.6 L; 7.0% assay by mass) and then with aqueous sodium chloride (21.6 L; 10% assay by mass).

The solution was chromatographed in portions (0.2 L per cycle, 59 cycles) on Kromasil 60Å 10 μm silica (2.0 kg), eluting with 15:85 v:v ethanol:isohexane (20 L per cycle) containing 1% diethylamine. At the end of each cycle, the column was washed with 1:1 ethanol:ethyl acetate (3 L) and then equilibrated with 15:85 v:v ethanol:isohexane (4 L); both solutions contained 1% diethylamine. Selected fractions were concentrated under reduced pressure to give a solution containing 1.21 kg (3.09 mol) of (1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-amine. Yield 35%, 92.5% LC purity by area (λ = 254 nm).

(iv) 1-(4-Fluorophenyl)-5-iodo-indazole



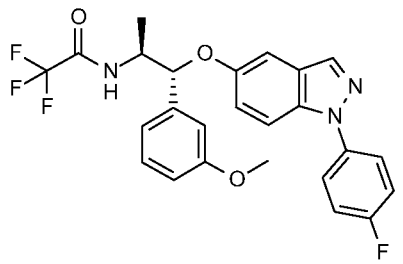
A mixture of 2-fluoro-5-iodobenzaldehyde (3.70 kg, 14.2 mol; 96.1% assay by mass) and 4-fluorophenylhydrazine hydrochloride (2.50 kg, 14.2 mol; 92.4% assay by mass) in *N*-methylpyrrolidone (25 L) was stirred for 5 hours at 20 °C.

Caesium carbonate (13.89 kg, 42.6 mol) was charged and the mixture stirred at 115 °C for 3.5 hours. Water (18.3 L) was charged after adjusting the reaction temperature to 80 °C and once the solids were dissolved, the mixture was allowed to separate into layers. The lower layer was discarded.

The upper layer and an *N*-methylpyrrolidone (2 L) rinse were transferred into stirring water (11.3 L), maintained at 62 °C throughout the addition. After cooling to 20 °C, 1-(4-fluorophenyl)-5-iodo-indazole was filtered off, washed with two portions of water (16.0 L and 17.5 L) followed by 2-methylpentane (16.5 L), and suction dried for around 18 hours at 20 °C. Yield 6.28 kg (11.9 mol, 84% by moles). 64% Assay (LC), 20% water, both by mass. 98.6% LC purity (λ = 254 nm).

^{1}H NMR (400 MHz, d_6-DMSO) δ 8.31 (d, J = 0.9 Hz, 1H), 8.28 (dd, J = 0.7, 1.6 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.70 (dd, J = 1.6, 8.8 Hz, 1H), 7.61 (ddd, J = 0.7, 0.9, 8.9 Hz, 1H), 7.45 – 7.38 (m, 2H).

Example 5: Preparation of seed crystals of Form A of Compound (I)



2,2,2-Trifluoro-*N*-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide in amorphous form (125 mg) (prepared as described in Example 4 above but without the crystallization step in step (i)) was dissolved in dichloromethane (3 ml) and 40 µl of this solution was transferred to an LC-vial. 80 µl of an organic solvent mixture (ethyl acetate:heptane (1:99%)) was then added to the LC-vial and the resulting mixture stirred at 40°C for 7 days. The resulting crystals were analysed via XRPD. The XRPD diffractogram was consistent with Form A reference (Figure 3). The DSC profile was consistent with Form A reference (Figure 4).

Example 6: Alternative Crystallisation Procedure to Form B of Compound (I)

2,2,2-Trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide was prepared according to Example 1, steps (ii) to (vii) but without the exchange of solvent in step (ii) (ie. without distilling off methyl *tert*-butyl ether and thereafter replacing with 1-propanol).

Rather, immediately following the filtration step in Example 1, step (ii), the concentration of the methyl *tert*-butyl ether solution was adjusted to a 5.5 ml solution/g of 2,2,2-trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide through addition of further methyl *tert*-butyl ether. At this point 2.2 ml n-heptane/g was added slowly and the solution was heated to 35°C. The solution was then cooled to 21°C. The solution was seeded with Form B crystals. The formed crystal slurry was stirred overnight. 5 ml n-heptane/g was added and the crystals were filtered off after 5 hours stirring. The crystals were washed with a mixture of 0.4 ml methyl *tert*-butyl ether/g and 0.6 ml n-heptane/g. The crystals were dried at 40°C vacuum. Crystallization yield: 86%. XRPD diffractogram consistent with Form B reference (Table 1 and Figure 1). DSC profile consistent with Form B reference (Figure 2).

Example 7: Solubility of Form B of Compound (I)

Two suspensions of Form B of 2,2,2-trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide in a solution comprising 1.2 mM citric acid buffer, 0.05% PS80 and 9 mg/g sodium chloride were prepared at concentrations of 0.5 mg/g and 0.05 mg/g, and at a pH of 3.8 (adjusting with sodium hydroxide). The suspensions were left standing for two months at 5°C then allowed to warm to room temperature and transferred to 5 mL vials. Each suspension is centrifuged twice (Sigma 2-16KCH, 8000 rpm, 25°C) and the supernatant transferred to a new vial after each centrifuge. The solubility of the supernatant is determined at room temperature using HPLC (Agilent Technologies 1100).

Solubility of Form B = 7 μg/mL.

Example 8: Hygroscopicity of Form B of Compound (I)

The gravimetric response of Form B of 2,2,2-trifluoro-*N*-[(1*R*,2*S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide to changes in humidity was measured using a DVS Advantage (Surface Measurement Systems) Gravimetrical Vapour Sorption (GVS) instrument. Approximately 10 mg of the sample was evaluated using the following conditions: 120 min under dry conditions followed by drying to 90% relative humidity and then at subsequent decreasing levels of humidity in steps of 10%.

Humidity uptake of Form B at 80% relative humidity = 0.07%.

Example 9: Pharmacokinetic Properties of Inhaled Form A and Form B of Compound (I) in Rat Lung and Rat Blood

The level of total lung and blood exposure (expressed as "Area Under the Curve" or AUC) and the level of peak blood level (expressed as Cmax) of Form A and Form B of Compound (I) when administered via the inhaled route were measured using the following protocol.

1. Inhalation

Exposure by the inhalation route was performed using a nose-only "flow-past" exposure chamber (Münster AG, Switzerland). Forms A and B of Compound (I) were administered as a dry powder inhalation (DPI) to the rat (10 min exposure) and compound concentration was measured in plasma up to 24 hours after administration.

Calibration of the inhalation system.

A small animal inhalation system (MIVIS) was used to deliver and measure the inhaled dose. To measure the aerosol concentration a light scattering instrument was used (Casella 950 AMS, London, UK). Before exposure the substance correlation factor was estimated by taking filter samples (AP40 Millipore, n=2+2). The filters were positioned in the inhalation system in the same way as the animals were connected. The amount of Compound (I) Forms A and B on filters were analysed by HPLC. The correlation factor was used in the dose measurement program where particle concentration and tidal volume was used to estimate the inhaled dose. Target concentration on the Casella was 1,5 mg/m^3 (Casella no: 034022, range: 0-2000). The calibration was validated by filter sampling (2+2) at a flow of 0.25 L/min.

Particle size measurements.

The particle size close to the inhalation side was measured using a Mercer Seven Stages Impactor (In-Tox products USA) (n =7+1 filter, flow rate 0.25 L/min). The deposition probability of the inhaled particles was considered similar to that previously reported for the rat (Raabe OG, Yeh HC, Newton GJ, Phalen RF, Velasques DJ. Deposition of inhaled monodisperse aerosols in small rodents. In: Walton WH, editor. Inhaled Particles IV. New York: Pergamon Press; 1977. p 3-21).

Test system (DPI).

Micronized Compound (I) Forms A and B (30% API, 70% lactose) were pressed in medium dust containers (pressure = 1.2 Bar) and aerosol generated by a modified, Wright Dust Feed (WDF) during 10 minutes by scraping of the substance from the pressed tablet. The speed on the WDF (1200 - 1400 rpm) was controlled by a Motomatic II and the flow through WDF was 8.0 L/min. The air supply to each animal port was 0.3 L/min which is approximately two times the respiratory minute volume for a 210 g rat and considered sufficient to cover the oxygen requirement of the animal (Crosfill ML, Widdicombe JG. Physical characteristics of the chest and lungs and the work of breathing in different

mammalian species. J Physiol 1961;158(1):1-14). Breathing volume and particle concentration were monitored during inhalation.

Treatment.

Target lung dose was 50 μg/kg (10 min inhalation). The administration was performed in the morning. The rats were observed continuously during the experiment and up to at least 2 hours after administration.

Calculations of inhaled dose (ID)

Inhaled dose = ((chamber concentration * exposure time * respiratory minute volume) / body weight in kg)

Calculations of Body Dose (BD)

Body Dose = Inhaled dose * fraction deposited in body

Calculations of Lung Dose (LD)

Lung Dose = Inhaled dose * fraction deposited in lung

2. Termination

Animals were terminated periodically during 24 hours after the inhalation of compound. Anaesthetization was performed with an overdose of pentobarbital given intraperitoneally (ip) (60 mg/mL, 10 mL/kg). Animals were weighed and a terminal blood sample was taken. The rib cage was opened and the lung and trachea dissected. The dissected organs were weighed.

3. Bioanalysis

The blood samples were protein precipitated by cold, acidified acetonitrile containing a volume marker. After centrifugation the supernatant was diluted to match the mobile phase and the extracts were quantified using LC-MS/MS. The lung samples were prepared for analysis by first pulverizing in liquid nitrogen and then homogenizing in Ringer solution by adaptive focused acoustic energy (Covaris). The homogenates were protein precipitated by cold, acidified acetonitrile containing a volume marker and after centrifugation the supernatants were diluted to match the mobile phase for analysis by LC-MS/MS (Agilent 6460 triple quadropole with Agilent 1200 binary pump and a CTC autosampler).

4. Calculations

Lung and blood samples from the experiment were analysed by LC-MS/MS. The concentration vs time profiles were analysed by compartmental modelling (2 compartments) using WinNonlin. In this way, parameters were obtained that were used to calculate peak areas (AUC) and C_{max}.

The values for total lung exposure (lung AUC), peak blood level (blood Cmax) and total blood exposure (blood AUC) for Form A and Form B of Compound (I) obtained via this method are tabulated in Table 3 below.

Table 3

	Form A	Form B
Lung AUC (hr*nmol/L)	9110	21289
Blood Cmax (nmol/L)	83	55
Blood AUC (hr*nmol/L)	288	246

CLAIMS

1. A crystalline form which is 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide Form B ("Form B of Compound (I)").

2. Form B of Compound (I) as claimed in claim 1, characterised by an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) of 9.2, 17.4 and 21.5.

3. Form B of Compound (I) as claimed in claim 1, characterised by an X-ray powder diffraction pattern, measured using a wavelength of X-rays 1.5418 Å, with peaks at 2-Theta (in degrees) of 9.2, 11.8, 15.7, 17.4 and 21.5.

4. Form B of Compound (I) as claimed in claim 1, characterised in that said form has an X-ray powder diffraction pattern substantially as shown in Figure 1.

5. A pharmaceutical composition comprising Form B of Compound (I) as defined in any of claims 1 to 4 and a pharmaceutically acceptable adjuvant, diluent or carrier.

6. Form B of Compound (I) as defined in any of claims 1 to 4 for use in therapy.

7. The use of Form B of Compound (I) as defined in any of claims 1 to 4 in the manufacture of a medicament for the treatment of a respiratory condition.

8. The use of Form B of Compound (I) as defined in any of claims 1 to 4 in the manufacture of a medicament for the treatment of COPD.

9. The use of Form B of Compound (I) Form B as defined in any of claims 1 to 4 in the manufacture of a medicament for the treatment of asthma.

10. A method of treating a respiratory condition in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of Form B of Compound (I) as defined in any of claims 1 to 4.

11. A method of treating COPD in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of Form B of Compound (I) as defined in any of claims 1 to 4.

12. A method of treating asthma in a mammal (such as man), which comprises administering to a mammal in need of such treatment an effective amount of Form B of Compound (I) as defined in any of claims 1 to 4.

13. A combination of Form B of Compound (I) Form B as defined in any of claims 1 to 4, and one or more agents selected from the list comprising:

- a PDE4 inhibitor;
- a selective β_2 adrenoceptor agonist;
- a muscarinic receptor antagonist;
- a steroid;
- a modulator of chemokine receptor function;
- an inhibitor of p38 kinase function;
- an inhibitor of matrix metalloproteases, most preferably targeting MMP-2, -9 or MMP-12; or
- an inhibitor of neutrophil serine proteases, most preferably neutrophil elastase or proteinase3.