

POLYMORPHS AND SALTS OF 6-(1H-INDOL-4-YL)-4-(5- { [4-(1-METHYLETHYL)-1-PYRAZOL-5-YL]-1,3-OXAZOL-2-YL)-1H-INDAZOLE AS PI3K INHIBITORS FOR USE IN THE TREATMENT OF E.G. RESPIRATORY DISORDERS

FIELD OF THE INVENTION

The present invention is directed to a polymorph of a compound and salts of the compound and polymorphs thereof, which compound is an inhibitor of kinase activity, more specifically a compound which is an inhibitor of the activity or function of phosphoinositide 3'OH kinase isoform delta (hereinafter PI3K δ), processes for their preparation, pharmaceutical compositions comprising them, and their use in the treatment of various disorders.

BACKGROUND OF THE INVENTION

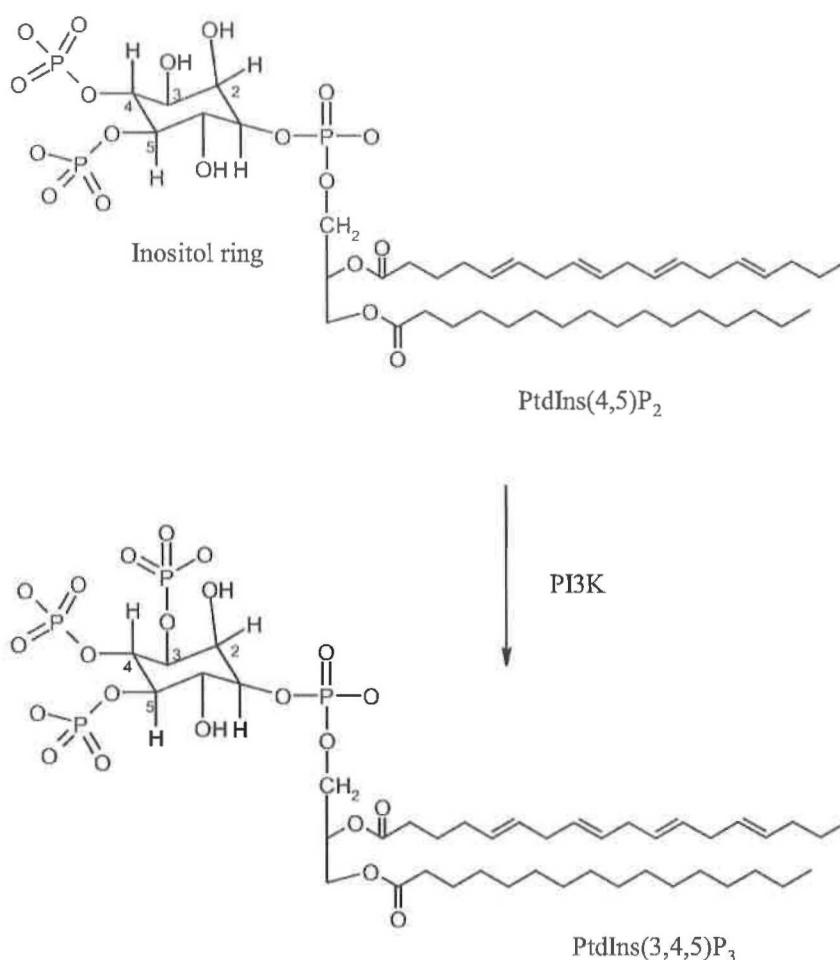
Cellular membranes represent a large store of second messengers that can be enlisted in a variety of signal transduction pathways. In relation to function and regulation of effector enzymes in phospholipids signaling pathways, class I PI3-kinases (e.g. PI3K δ) generate second messengers from the membrane phospholipid pools. Class I PI3Ks convert the membrane phospholipid PI(4,5)P₂ into PI(3,4,5)P₃, which functions as a second messenger. PI and PI(4)P are also substrates of PI3K and can be phosphorylated and converted into PI3P and PI(3,4)P₂, respectively. In addition, these phosphoinositides can be converted into other phosphoinositides by 5'-specific and 3'-specific phosphatases. Thus, PI3K enzymatic activity results either directly or indirectly in the generation of two 3'-phosphoinositide subtypes which function as second messengers in intracellular signal transduction pathways (Trends Biochem. Sci. 22(7) p. 267-72 (1997) by Vanhaesebroeck *et al.*; Chem. Rev. 101(8) p. 2365-80 (2001) by Leslie *et al.*; Annu. Rev. Cell Dev. Biol. 17 p. 615-75 (2001) by Katso *et al.*; and Cell. Mol. Life Sci. 59(5) p. 761-79 (2002) by Toker). To date, eight mammalian PI3Ks have been identified, divided into three main classes (I, II, and III) on the basis of sequence homology, structure, binding partners, mode of activation, and substrate preference. *In vitro*, class I PI3Ks can phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate (PI4P), and phosphatidylinositol-4,5-bisphosphate (PI(4,5)P₂) to produce phosphatidylinositol-3-phosphate (PI3P), phosphatidylinositol-3,4-bisphosphate (PI(3,4)P₂), and phosphatidylinositol-3,4,5-trisphosphate (PI(3,4,5)P₃), respectively. Class II PI3Ks can phosphorylate PI and PI4P. Class III PI3Ks can only phosphorylate PI (Vanhaesebroeck *et al.* (1997), above; Vanhaesebroeck *et al.* Exp. Cell Res. 253(1) p. 239-54 (1999); and Leslie *et al.* (2001), above).

Class I PI3K is a heterodimer consisting of a p110 catalytic subunit and a regulatory subunit, and the family is further divided into class Ia and class Ib enzymes on the basis of

regulatory partners and mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (p110 α , p110 β , and p110 δ) that dimerise with five distinct regulatory subunits (p85 α , p55 α , p50 α , p85 β , and p55 γ), with all catalytic subunits being able to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3K are generally activated in response to growth factor-stimulation of receptor tyrosine kinases, via interaction of the regulatory subunit SH2 domains with specific phosphotyrosine residues of the activated receptor or adaptor proteins such as IRS-1. Small GTPases (ras as an example) are also involved in the activation of PI3K in conjunction with receptor tyrosine kinase activation. Both p110 α and p110 β are constitutively expressed in all cell types, whereas p110 δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110 γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor (GPCR) systems and its expression appears to be limited to leukocytes.

15

Scheme A: Conversion of PI(4,5)P₂ to PI(3,4,5)P₃



As illustrated in Scheme A above, phosphoinositide 3-kinases (PI3Ks) phosphorylate the hydroxyl of the third carbon of the inositol ring. The phosphorylation of phosphoinositides to generate PtdIns(3,4,5)P₃, PtdIns(3,4)P₂ and PtdIns(3)P, produces second messengers for a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell size, cell survival, apoptosis, adhesion, cell motility, cell migration, chemotaxis, invasion, cytoskeletal rearrangement, cell shape changes, vesicle trafficking and metabolic pathway (Katso *et al.* (2001), above; and Mol. Med. Today 6(9) p. 347-57 (2000) by Stein *et al.*).

The activity of PI3-kinases responsible for generating these phosphorylated signalling products was originally identified as being associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylate phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou *et al.* Trends Cell Biol. 2 p. 358-60 (1992)). However, more recent biochemical studies have revealed that class I PI3-kinases (e.g. class IA isoform PI3Kδ) are dual-specific kinase enzymes,

meaning they display both lipid kinase (phosphorylation of phosphoinositides) as well as protein kinase activity, which have been shown to be capable of phosphorylation of other protein as substrates, including auto-phosphorylation as an intramolecular regulatory mechanism (EMBO J. 18(5) p. 1292-302 (1999) by Vanhaesebroeck *et al.*). Cellular processes in which PI3Ks play an essential role include suppression of apoptosis, reorganization of the actin skeleton, cardiac myocyte growth, glycogen synthase stimulation by insulin, TNF α -mediated neutrophil priming and superoxide generation, and leukocyte migration and adhesion to endothelial cells.

- 10 PI3-kinase activation, is believed to be involved in a wide range of cellular responses including cell growth, differentiation, and apoptosis (Parker, Current Biology 5(6) p. 577-79 (1995); and Yao *et al.* Science 267(5206) p. 2003-06 (1995)). PI3-kinase appears to be involved in a number of aspects of leukocyte activation. A p85-associated PI3-kinase has been shown to physically associate with the cytoplasmic domain of CD28, which is an important costimulatory molecule for the activation of T-cells in response to antigen (Pagès *et al.* Nature 369 p. 327-29 (1994); and Rudd, Immunity 4 p. 527-34 (1996)). Activation of T cells through CD28 lowers the threshold for activation by antigen and increases the magnitude and duration of the proliferative response. These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (Fraser *et al.* Science 251(4991) p. 313-16 (1991)).

- PI3K γ has been identified as a mediator of G beta-gamma-dependent regulation of JNK activity, and G beta-gamma are subunits of heterotrimeric G proteins (Lopez-Illasaca *et al.* J. Biol. Chem. 273(5) p. 2505-8 (1998)). Recently, (Laffargue *et al.* Immunity 16(3) p. 441-51 (2002)) it has been described that PI3K γ relays inflammatory signals through various G(i)-coupled receptors and is central to mast cell function, stimuli in the context of leukocytes, and immunology including cytokines, chemokines, adenosines, antibodies, integrins, aggregation factors, growth factors, viruses or hormones for example (J. Cell Sci. 114 (Pt 16) p. 2903-10 (2001) by Lawlor *et al.*; Laffargue *et al.* (2002), above; and Curr. Opinion Cell Biol. 14(2) p. 203-13 (2002) by Stephens *et al.*).

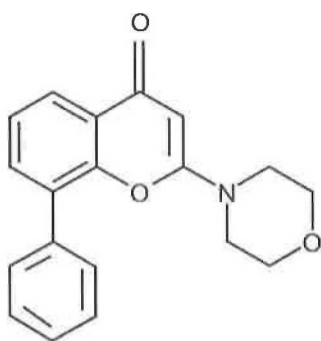
- Specific inhibitors against individual members of a family of enzymes provide invaluable tools for deciphering functions of each enzyme. Two compounds, LY294002 and wortmannin (hereinafter), have been widely used as PI3-kinase inhibitors. These compounds are non-specific PI3K inhibitors, as they do not distinguish among the four members of Class I PI3-kinases. For example, the IC₅₀ values of wortmannin against

each of the various Class I PI3-kinases are in the range of 1-10 nM. Similarly, the IC₅₀ values for LY294002 against each of these PI3-kinases is about 15-20 μ M (Fruman *et al.* Ann. Rev. Biochem. 67 p. 481-507 (1998)), also 5-10 μ M on CK2 protein kinase and some inhibitory activity on phospholipases. Wortmannin is a fungal metabolite which

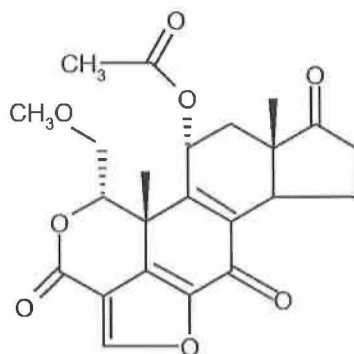
5 irreversibly inhibits PI3K activity by binding covalently to the catalytic domain of this enzyme. Inhibition of PI3K activity by wortmannin eliminates subsequent cellular response to the extracellular factor. For example, neutrophils respond to the chemokine fMet-Leu-Phe (fMLP) by stimulating PI3K and synthesizing PtdIns (3, 4, 5)P₃. This synthesis correlates with activation of the respiratory burst involved in neutrophil

10 destruction of invading microorganisms. Treatment of neutrophils with wortmannin prevents the fMLP-induced respiratory burst response (Thelen *et al.* Proc. Natl. Acad. Sci. USA 91 p. 4960-64 (1994)). Indeed, these experiments with wortmannin, as well as other experimental evidence, show that PI3K activity in cells of hematopoietic lineage, particularly neutrophils, monocytes, and other types of leukocytes, is involved in many of

15 the non-memory immune response associated with acute and chronic inflammation.



LY294002



WORTMANNIN

20

Based on studies using wortmannin, there is evidence that PI3-kinase function is also required for some aspects of leukocyte signaling through G-protein coupled receptors (Thelen *et al.* (1994), above). Moreover, it has been shown that wortmannin and

25 LY294002 block neutrophil migration and superoxide release.

It is now well understood that deregulation of oncogenes and tumour suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell growth and proliferation or increased cell survival. It is also now known that signaling

30 pathways mediated by the PI3K family have a central role in a number of cell processes

including proliferation and survival, and deregulation of these pathways is a causative factor a wide spectrum of human cancers and other diseases (Katso *et al.* Annual Rev. Cell Dev. Biol. (2001) 17 p. 615-675 and Foster *et al.* J. Cell Science (2003) 116(15) p. 3037-3040). PI3K effector proteins initiate signalling pathways and networks by
5 translocating to the plasma membrane through a conserved Pleckstrin Homology (PH) domain, which specifically interacts with PtdIns(3,4,5)P3 (Vanhaesebroeck *et al.* Annu. Rev. Biochem. (2001) 70 p. 535-602). The effector proteins signalling through PtdIns(3,4,5)P3 and PH domains include Serine/Threonine (Ser/Thr) kinases, Tyrosine
10 kinases, Rac or Arf GEFs (Guanine nucleotide exchange factors) and Arf GAPs (GTPase activating proteins).

In B and T cells PI3Ks have an important role through activation of the Tec family of protein tyrosine kinases which include Bruton's tyrosine kinase (BTK) in B cells and Interleukin-2-inducible T-cell kinase (ITK) in T cells. Upon PI3K activation, BTK or ITK
15 translocate to the plasma membrane where they are subsequently phosphorylated by Src kinases. One of the major targets of activated ITK is phospholipase C-gamma (PLC γ 1), which hydrolyses PtdIns(4,5)P2 into Ins(3,4,5)P3 and initiates an intracellular increase in calcium levels and diacylglycerol (DAG) which can activate Protein Kinases C in activated
20 T cells.

Unlike the Class IA p110 α and p110 β , p110 δ is expressed in a tissue restricted fashion. Its high expression level in lymphocytes and lymphoid tissues suggests a role in PI3K-mediated signalling in the immune system. The p110 δ kinase dead knock-in mice are also
25 viable and their phenotype is restricted to defects in immune signalling (Okkenhaug *et al.* Science (2002) 297 p. 1031-4). These transgenic mice have offered insight into the function of PI3K δ in B-cell and T-cell signalling. In particular, p110 δ is required for PtdIns(3,4,5)P3 formation downstream of CD28 and/or T cell Receptor (TCR) signalling. A key effect of PI3K signalling downstream of TCR is the activation of Akt, which
30 phosphorylates anti-apoptotic factors as well as various transcription factors for cytokine production. As a consequence, T cells with inactive p110 δ have defects in proliferation and Th1 and Th2 cytokine secretion. Activation of T cells through CD28 lowers the threshold for TCR activation by antigen and increases the magnitude and duration of the proliferative response. These effects are mediated by the PI3K δ -dependent increase in the transcription of a number of genes including IL2, an important T cell growth factor.

35 Therefore, PI3K inhibitors are anticipated to provide therapeutic benefit via its role in modulating T-cell mediated inflammatory responses associated to respiratory diseases

such as asthma, COPD and cystic fibrosis. In addition, there is indication that T-cell directed therapies may provide corticosteroid sparing properties (Alexander *et al.* Lancet (1992) 339 p. 324-8) suggesting that it may provide a useful therapy either as a standalone or in combination with inhaled or oral glucocorticosteroids in respiratory diseases. A PI3K inhibitor might also be used alongside other conventional therapies such as a long acting beta-agonists (LABA) in asthma.

In the vasculature, PI3K δ is expressed by endothelial cells and participates in neutrophil trafficking by modulating the proadhesive state of these cells in response to TNF α (Puri *et al.* Blood (2004) 103(9) p. 3448-56.). A role for PI3K δ in TNF α -induced signalling of endothelial cells is demonstrated by the pharmacological inhibition of Akt phosphorylation and PDK1 activity. In addition, PI3K δ is implicated in vascular permeability and airway tissue edema through the VEGF pathway (Lee *et al.* J. Allergy Clin. Immunol. (2006) 118(2) p. 403-9). These observations suggest additional benefits of PI3K δ inhibition in asthma by the combined reduction of leukocyte extravasation and vascular permeability associated with asthma. In addition, PI3K δ activity is required for mast cell function both *in vitro* and *in vivo* (Ali *et al.* Nature (2004) 431 p. 1007-11; and Ali *et al.* J. Immunol. (2008) 180(4) p. 2538-44) further suggesting that PI3K inhibition should be of therapeutical benefit for allergic indications such asthma, allergic rhinitis and atopic dermatitis.

The role of PI3K δ in B cell proliferation, antibody secretion, B-cell antigen and IL-4 receptor signalling, B-cell antigen presenting function is also well established Okkenhaug *et al.* (2002), above; Al-Alwan *et al.* J. Immunol. (2007) 178(4) p. 2328-35; and Bilancio *et al.* Blood (2006) 107(2) p. 642-50) and indicates a role in autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus. Therefore PI3K inhibitors may also be of benefit for these indications.

Pharmacological inhibition of PI3K δ inhibits fMLP-dependent neutrophil chemotaxis on an ICAM coated agarose matrix integrin-dependent biased system (Sadhu *et al.*, J. Immunol. (2003) 170(5) p. 2647-54.). Inhibition of PI3K δ regulates neutrophil activation, adhesion and migration without affecting neutrophil mediated phagocytosis and bactericidal activity over *Staphylococcus aureus* (Sadhu *et al.* Biochem. Biophys. Res. Commun. (2003) 308(4) p. 764-9). Overall, the data suggest that PI3K δ inhibition should not globally inhibit neutrophil functions required for innate immune defence. PI3K δ 's role in neutrophils offers further scope for treating inflammatory diseases involving tissue remodeling such as COPD or rheumatoid arthritis.

In addition, there is also good evidence that class Ia PI3K enzymes also contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, *Nature Reviews Cancer* (2002) 2(7) p. 489-501). For example, inhibition of PI3K δ may have a therapeutic role for the treatment of malignant haematological disorders such as acute myeloid leukaemia (Billottet *et al.* *Oncogene* (2006) 25(50) p. 6648-59). Moreover, activating mutations within p110 α (PIK3CA gene) have been associated with various other tumors such as those of the colon and of the breast and lung (Samuels *et al.* *Science* (2004) 304(5670) p. 554).

It has also been shown that PI3K is involved in the establishment of central sensitization in painful inflammatory conditions (Pezet *et al.* *The J. of Neuroscience* (2008) 28 (16) p. 4261-4270).

A wide variety of retroviruses and DNA based viruses activate the PI3K pathway as a way of preventing host cell death during viral infection and ultimately exploiting the host cell synthesis machinery for its replication (Virology 344(1) p. 131-8 (2006) by Vogt *et al.*; and *Nat. Rev. Microbiol.* 6(4) p. 265-75 (2008) by Buchkovich *et al.*). Therefore PI3K inhibitors may have anti-viral properties in addition to more established oncolytic and anti-inflammatory indications. These antiviral effects raise interesting prospects in viral induced inflammatory exacerbations. For example, the common cold human rhinovirus (HRV) is responsible for more than 50% of respiratory tract infections but complications of these infections can be significant in certain populations. This is particularly the case in respiratory diseases such as asthma or chronic obstruction pulmonary disease (COPD). Rhinoviral infection of epithelial cells leads to a PI3K dependent cytokine and chemokine secretion (*J. Biol. Chem.* (2005) 280(44) p. 36952 by Newcomb *et al.*). This inflammatory response correlates with worsening of respiratory symptoms during infection. Therefore PI3K inhibitors may dampen an exaggerated immune response to an otherwise benign virus. The majority of HRV strains infect bronchial epithelial cells by initially binding to the ICAM-1 receptor. The HRV-ICAM-1 complex is then further internalised by endocytosis and it has been shown that this event requires PI3K activity (*J. Immunol.* (2008) 180(2) p. 870-880 by Lau *et al.*). Therefore, PI3K inhibitors may also block viral infections by inhibiting viral entry into host cells.

PI3K inhibitors may be useful in reducing other types of respiratory infections including the fungal infection aspergillosis (*Mucosal Immunol.* (2010) 3(2) p. 193-205 by Bonifazi *et al.*). In addition, PI3K δ deficient mice are more resistant towards infections by the protozoan

parasite *Leishmania major* (J. Immunol. (2009) 183(3) p. 1921-1933 by Liu *et al.*). Taken with effects on viral infections, these reports suggest that PI3K inhibitors may be useful for the treatment of a wide variety of infections.

- 5 PI3K inhibition has also been shown to promote regulatory T cell differentiation (Proc. Natl. Acad. Sci. U S A (2008) 105(22) p. 7797-7802 by Sauer *et al.*) suggesting that PI3K inhibitors may serve therapeutic purposes in auto-immune or allergic indications by inducing immuno-tolerance towards self antigen or allergen. Recently the PI3K δ isoform has also been linked to smoke induced glucocorticoid insensitivity (Am. J. Respir. Crit. Care Med. (2009) 179(7) p. 542-548 by Marwick *et al.*). This observation suggests that COPD patients, which otherwise respond poorly to corticosteroids, may benefit from the combination of a PI3K inhibitor with a corticosteroid.

- 15 PI3K has also been involved in other respiratory conditions such as idiopathic pulmonary fibrosis (IPF). IPF is a fibrotic disease with progressive decline of lung function and increased mortality due to respiratory failure. In IPF, circulating fibrocytes are directed to the lung via the chemokine receptor CXCR4. PI3K is required for both signalling and expression of CXCR4 (Int. J. Biochem. and Cell Biol. (2009) 41 p.1708-1718 by Mehrad *et al.*). Therefore, by reducing CXCR4 expression and blocking its effector function, a PI3K inhibitor should inhibit the recruitment of fibrocytes to the lung and consequently slow down the fibrotic process underlying IPF, a disease with high unmet need.

- Compounds which are PI3-kinase inhibitors may therefore be useful in the treatment of disorders associated with inappropriate kinase activity, in particular inappropriate PI3-kinase activity, for example in the treatment and prevention of disorders mediated by PI3-kinase mechanisms. Such disorders include respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF); viral infections including viral respiratory tract infections and viral exacerbation of respiratory diseases such as asthma and COPD; non-viral respiratory infections including aspergillosis and leishmaniasis; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory

pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and Central pain.

Attempts have been made to prepare compounds which inhibit PI3-kinase activity and a number of such compounds have been disclosed in the art.

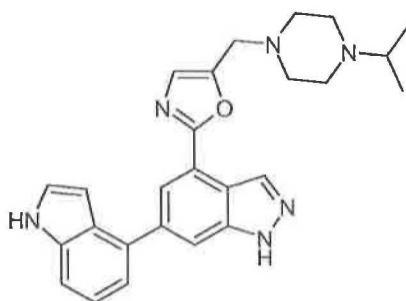
International patent application PCT/EP2010/055666 (publication number WO2010/125082) describes compounds having the general formula (I):



(I)

and salts thereof.

The examples of international patent application PCT/EP2010/055666 (publication number WO2010/125082) describe the preparation of 6-(1*H*-indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1*H*-indazole which may be represented by the formula (II):



(II)

hereinafter referred to as "Compound A" and the hydrochloride salts thereof.

The present inventors have now found a polymorph of Compound A and salts of Compound A and polymorphs thereof.

In one embodiment, the salts of Compound A may have properties which make them particularly suitable for administration as a drug, for example by inhalation. In a further embodiment, the hemi succinate salt of Compound A may have stability, for example in formulations containing excipients such as lactose, and solubility properties which make it particularly suitable for administration by inhalation.

SUMMARY OF THE INVENTION

The invention is directed to a polymorph of Compound A and salts of Compound A and polymorphs thereof (hereinafter "polymorphs and salts of the invention").

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows an X-ray powder diffraction (XRPD) pattern for a polymorph of Compound A.

Figure 2 shows an XRPD pattern for a polymorph of the tosylate salt of Compound A.

Figure 3 shows an XRPD pattern for a polymorph of the hemi fumarate salt of Compound A.

Figure 4 shows an XRPD pattern for a polymorph of the hemi succinate salt of Compound A.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention is directed to a polymorph of Compound A.

In one embodiment, the invention provides a polymorph of Compound A characterised in that it provides an XRPD pattern comprising peaks ($^{\circ}2\theta$) at about 9.0, about 9.6, about 10.4 and/or about 12.5.

In another embodiment, the invention provides a polymorph of Compound A characterised in that it provides an XRPD pattern comprising peaks substantially as set out in Table 1.

In a further embodiment, the invention provides a polymorph of Compound A characterised in that it provides an XRPD pattern substantially in accordance with Figure 1.

In a further aspect, the invention is directed to salts of Compound A and polymorphs thereof.

In one embodiment, the invention provides a salt of Compound A selected from tosylate,
5 hemi fumarate and hemi succinate.

In another embodiment, the invention provides a salt of Compound A selected from hemi fumarate and hemi succinate.

10 In another embodiment, the invention provides the hemi fumarate salt of Compound A.

In a further embodiment, the invention provides the hemi succinate salt of Compound A.

The tosylate salt of Compound A is the mono tosylate salt formed between 6-(1*H*-indol-4-yl)-4-(5-
15 {4-(1-methylethyl)-1-piperazinyl)methyl}-1,3-oxazol-2-yl)-1*H*-indazole and *p*-toluenesulfonic acid in a stoichiometric ratio of about 1:1. The hemi fumarate salt of Compound A is the salt formed between 6-(1*H*-indol-4-yl)-4-(5-
{4-(1-methylethyl)-1-piperazinyl)methyl}-1,3-oxazol-2-yl)-1*H*-indazole and fumaric acid in a stoichiometric ratio of about 2:1. The hemi succinate salt of Compound A is the salt formed between 6-(1*H*-
20 indol-4-yl)-4-(5-
{4-(1-methylethyl)-1-piperazinyl)methyl}-1,3-oxazol-2-yl)-1*H*-indazole and succinic acid in a stoichiometric ratio of about 2:1.

Also included within the scope of the invention are any solvates, for example hydrates, complexes and polymorphic forms of the salts of the invention.

25 The salts of the invention may exist in crystalline or noncrystalline form, or as a mixture thereof. For salts of the invention that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid,
30 ethanolamine, and EtOAc, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates". Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. As the skilled person will appreciate, the amount of water may depend upon the conditions,
35 for example humidity. For example, as humidity decreases the amount of water may decrease and as humidity increases the amount of water may increase. Such variations

in the amount of water are included within the scope of the invention. In one embodiment, the invention provides a hydrate of the hemi succinate salt of Compound A. In another embodiment, the hydrate of the hemi succinate salt of Compound A may be the monohydrate wherein the stoichiometric ratio of Compound A:succinic acid:water is about 2:1:1. In another embodiment, the invention provides a hydrate of the hemi fumarate salt of Compound A. In a further embodiment, the hydrate of the hemi fumarate salt of Compound A may be the dihydrate wherein the stoichiometric ratio of Compound A:fumaric acid:water is about 2:1:2.

10 In one embodiment, the invention provides a polymorph of the tosylate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks ($^{\circ}2\theta$) at about 6.3, about 9.3, about 11.3 and/or about 12.7.

In another embodiment, the invention provides a polymorph of the tosylate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks substantially as set out in Table 2.

In a further embodiment, the invention provides a polymorph of the tosylate salt of Compound A characterised in that it provides an XRPD pattern substantially in accordance with Figure 2.

In one embodiment, the invention provides a polymorph of the hemi fumarate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks ($^{\circ}2\theta$) at about 6.9, about 13.8 and/or about 14.4.

25 In another embodiment, the invention provides a polymorph of the hemi fumarate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks substantially as set out in Table 3.

30 In a further embodiment, the invention provides a polymorph of the hemi fumarate salt of Compound A characterised in that it provides an XRPD pattern substantially in accordance with Figure 3.

In one embodiment, the invention provides a polymorph of the hemi succinate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks ($^{\circ}2\theta$) at about 7.2, about 13.2 and/or about 14.0.

In another embodiment, the invention provides a polymorph of the hemi succinate salt of Compound A characterised in that it provides an XRPD pattern comprising peaks substantially as set out in Table 4.

- 5 In a further embodiment, the invention provides a polymorph of the hemi succinate salt of Compound A characterised in that it provides an XRPD pattern substantially in accordance with Figure 4.

10 When it is indicated herein that there is a peak in an XRPD pattern at a given value, it is typically meant that the peak is within ± 0.2 of the value quoted, for example within ± 0.1 of the value quoted.

The invention encompasses the polymorph of Compound A and the salts of Compound A and polymorphs thereof isolated in pure form or when admixed with other materials, for
15 example other polymorphs, or salts or solvates (inclusive of their polymorphs) of Compound A, or any other material.

Thus, in one aspect there is provided a polymorph of Compound A or salt of Compound A or polymorph thereof in isolated or pure form. "Isolated" or "pure" form refers to a sample
20 in which the polymorph of Compound A or salt of Compound A or polymorph thereof is present in an amount of >75%, particularly >90%, more particularly >95% and even more particularly >99% relative to other materials which may be present in the sample.

Terms and Definitions

25 As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless
30 otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

DCM	Dichloromethane
35 DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMSO	Dimethylsulfoxide

	EtOAc	Ethyl acetate
	g	Grams
	h	hour(s)
	HPLC	High performance liquid chromatography
5	IMS	Industrial methylated spirits
	IPA	Isopropyl alcohol
	LCMS	Liquid chromatography mass spectroscopy
	L	Litre
	M	Molar
10	MDAP	Mass directed automated preparative HPLC
	Me	Methyl
	MeCN	Acetonitrile
	MeOH	Methanol
	mg	Milligrams
15	mins	Minutes
	ml	Millilitres
	mmol	Millimoles
	Rt	Retention time
	RT	Room temperature
20	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	UPLC	Ultra high performance liquid chromatography
	UV	Ultraviolet
	XRPD	X-ray powder diffraction

25

All references to brine are to a saturated aqueous solution of NaCl.

Polymorph and Salt Preparation

30 The invention is also directed to processes for preparing the polymorphs and salts of the invention.

In one aspect, the invention provides a process for preparing a polymorph of Compound A which comprises purifying Compound A by chromatography and crystallising the polymorph from the purified fractions.

35

In a further aspect, the invention provides a process for preparing a salt of Compound A or a polymorph thereof which comprises contacting Compound A with a suitable acid such

as p-toluenesulfonic acid, fumaric acid or succinic acid, in the presence of a suitable solvent such as industrial methylated spirits (IMS), acetonitrile or DMSO.

Compound A may be prepared according to known procedures, such as those disclosed
5 in international patent application PCT/EP2010/055666 (publication number WO2010/125082) and the Examples section below. The disclosure of international patent application PCT/EP2010/055666 (publication number WO2010/125082) is incorporated herein by reference.

10 **Methods of Use**

The polymorphs and salts of the invention may be useful in the treatment of disorders wherein the underlying pathology is (at least in part) attributable to inappropriate PI3-kinase activity, such as asthma and chronic obstructive pulmonary disease (COPD). "Inappropriate PI3-kinase activity" refers to any PI3-kinase activity that deviates from the
15 normal PI3-kinase activity expected in a particular patient. Inappropriate PI3-kinase may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of PI3-kinase activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation. Accordingly, in another aspect the invention is
20 directed to methods of treating such disorders.

Such disorders include respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF); viral infections including viral respiratory tract infections and viral exacerbation of respiratory diseases
25 such as asthma and COPD; non-viral respiratory infections including aspergillosis and leishmaniasis; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; neurodegenerative diseases;
30 pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and Central pain. In one embodiment, such disorders include
35 respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD); allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders

including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and Central pain

The methods of treatment of the invention comprise administering a safe and effective amount of a polymorph or salt of the invention to a patient in need thereof. Individual embodiments of the invention include methods of treating any one of the above-mentioned disorders by administering a safe and effective amount of a polymorph or salt of the invention to a patient in need thereof.

As used herein, "treat" in reference to a disorder means: (1) to ameliorate or prevent the disorder or one or more of the biological manifestations of the disorder, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the disorder or (b) one or more of the biological manifestations of the disorder, (3) to alleviate one or more of the symptoms or effects associated with the disorder, or (4) to slow the progression of the disorder or one or more of the biological manifestations of the disorder.

As indicated above, "treatment" of a disorder includes prevention of the disorder. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a disorder or biological manifestation thereof, or to delay the onset of such disorder or biological manifestation thereof.

As used herein, "safe and effective amount" in reference to a polymorph or salt of the invention or other pharmaceutically-active agent means an amount sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the disorder being treated; the severity of the disorder being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be

treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

- 5 As used herein, "patient" refers to a human (including adults and children) or other animal. In one embodiment, "patient" refers to a human.

The polymorphs and salts of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration.

10 Systemic administration includes oral administration, parenteral administration, transdermal administration and rectal administration. Parenteral administration refers to routes of administration other than enteral or transdermal, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Topical administration includes application to the skin

15 as well as intraocular, otic, intravaginal, inhaled and intranasal administration. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. In one embodiment, the polymorphs and salts of the invention may be administered orally. In another embodiment, the polymorphs and salts of the invention may be administered by inhalation. In a further embodiment, the

20 polymorphs and salts of the invention may be administered intranasally.

The polymorphs and salts of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or

25 four times per day. In one embodiment, a dose is administered once per day. In a further embodiment, a dose is administered twice per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a polymorph or salt of the invention depend on the pharmacokinetic properties of that polymorph or salt, such as absorption, distribution, and

30 half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a polymorph or salt of the invention depend on the disorder being treated, the severity of the disorder being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect,

35 and like factors within the knowledge and expertise of the skilled artisan. It will be further

understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

5 Typical daily dosages may vary depending upon the particular route of administration chosen. Typical daily dosages for oral administration range from 0.001mg to 50mg per kg of total body weight, for example from 1mg to 10mg per kg of total body weight. For example, daily dosages for oral administration may be from 0.5mg to 2g per patient, such as 10mg to 1g per patient.

10

In one aspect, the invention thus provides a method of treating a disorder mediated by inappropriate PI3-kinase activity comprising administering a safe and effective amount of a polymorph or salt of the invention to a patient in need thereof.

15 In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is selected from the group consisting of respiratory diseases (including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)); viral infections (including viral respiratory tract infections and viral exacerbation of respiratory diseases such as asthma and COPD); non-viral respiratory infections (including aspergillosis and
20 leishmaniasis); allergic diseases (including allergic rhinitis and atopic dermatitis); autoimmune diseases (including rheumatoid arthritis and multiple sclerosis); inflammatory disorders (including inflammatory bowel disease); cardiovascular diseases (including thrombosis and atherosclerosis); hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm
25 motility; transplantation rejection; graft rejection; lung injuries; and pain (including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and Central pain).

30 In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is a respiratory disease. In another embodiment, the disorder mediated by inappropriate PI3-kinase activity is asthma. In another embodiment, the disorder mediated by inappropriate PI3-kinase activity is chronic obstructive pulmonary disease (COPD). In a further embodiment, the disorder mediated by inappropriate PI3-kinase activity is idiopathic
35 pulmonary fibrosis (IPF).

In one embodiment, the disorder mediated by inappropriate PI3-kinase activity is pain.

In one embodiment, the present invention provides a method of treating a respiratory disease comprising administering a safe and effective amount of a polymorph or salt of the invention to a patient in need thereof.

5

In another embodiment, the present invention provides a method of treating asthma comprising administering a safe and effective amount of a polymorph or salt of the invention to a patient in need thereof.

10 In one aspect, the invention provides a polymorph or salt of the invention for use in medical therapy.

In another aspect, the invention provides a polymorph or salt of the invention for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity.

15

In a further aspect, the invention provides the use of a polymorph or salt of the invention in the manufacture of a medicament for use in the treatment of a disorder mediated by inappropriate PI3-kinase activity.

20 **Compositions**

The polymorphs and salts of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient.

25 Accordingly, in one aspect the invention is directed to pharmaceutical compositions comprising a polymorph or salt of the invention and one or more pharmaceutically acceptable excipients.

In another aspect the invention is directed to pharmaceutical compositions comprising 0.05 to 1000mg of a polymorph or salt of the invention and 0.1 to 2g of one or more
30 pharmaceutically acceptable excipients.

In a further aspect the invention is directed to a pharmaceutical composition for the treatment or prophylaxis of a disorder mediated by inappropriate PI3-kinase activity comprising a polymorph or salt of the invention

35

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a polymorph or salt of the invention can be

extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a polymorph or salt of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically may contain, for example, from 0.5mg to 1g, or from 1mg to 700mg, or from 5mg to 100mg of a polymorph or salt of the invention.

The pharmaceutical compositions of the invention typically contain one polymorph or salt of the invention.

10

As used herein, "pharmaceutically acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the polymorph or salt of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must of course be pharmaceutically-acceptable eg of sufficiently high purity.

20 The polymorph or salt of the invention and the pharmaceutically acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols, solutions, and dry powders; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

30

Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain

35

pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the polymorph or salt of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other excipients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically acceptable excipients and may be useful in selecting suitable pharmaceutically acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

Accordingly, in another aspect the invention is directed to process for the preparation of a pharmaceutical composition comprising a polymorph or salt of the invention and one or more pharmaceutically acceptable excipients which comprises mixing the ingredients. A pharmaceutical composition comprising a polymorph or salt of the invention may be prepared by, for example, admixture at ambient temperature and atmospheric pressure.

In one embodiment, the polymorph or salt of the invention will be formulated for oral administration. In another embodiment, the polymorph or salt of the invention will be formulated for inhaled administration. In a further embodiment, the polymorph or salt of the invention will be formulated for intranasal administration.

5

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a polymorph or salt of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch),
10 cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further
15 comprise a disintegrant. Suitable disintegrants include croscopovidone, sodium starch glycolate, croscarmellose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

20 Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

25 The polymorphs and salts of the invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidophenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the polymorphs and salts of the invention may be
30 coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

35 In another aspect, the invention is directed to a liquid oral dosage form. Oral liquids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given

quantity contains a predetermined amount of a polymorph or salt of the invention. Syrups can be prepared by dissolving a polymorph or salt of the invention in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the polymorph or salt of the invention in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

10 In another aspect, the invention is directed to a dosage form adapted for administration to a patient by inhalation, for example as a dry powder, an aerosol, a suspension, or a solution composition. In one embodiment, the invention is directed to a dosage form adapted for administration to a patient by inhalation as a dry powder. In a further embodiment, the invention is directed to a dosage form adapted for administration to a patient by inhalation via a nebulizer.

Dry powder compositions for delivery to the lung by inhalation typically comprise a polymorph or salt of the invention as a finely divided powder together with one or more pharmaceutically-acceptable excipients as finely divided powders. Pharmaceutically-acceptable excipients particularly suited for use in dry powders are known to those skilled in the art and include lactose, starch, mannitol, and mono-, di-, and polysaccharides. The finely divided powder may be prepared by, for example, micronisation and milling. Generally, the size-reduced (eg micronised) compound can be defined by a D_{50} value of about 1 to about 10 microns (for example as measured using laser diffraction).

25

The dry powder may be administered to the patient via a reservoir dry powder inhaler (RDPI) having a reservoir suitable for storing multiple (un-metered doses) of medicament in dry powder form. RDPIs typically include a means for metering each medicament dose from the reservoir to a delivery position. For example, the metering means may comprise a metering cup, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

Alternatively, the dry powder may be presented in capsules (e.g. gelatin or plastic), cartridges, or blister packs for use in a multi-dose dry powder inhaler (MDPI). MDPIs are inhalers wherein the medicament is comprised within a multi-dose pack containing (or

otherwise carrying) multiple defined doses (or parts thereof) of medicament. When the dry powder is presented as a blister pack, it comprises multiple blisters for containment of the medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of the medicament therefrom. For example, the blisters may be arranged in a generally circular fashion on a disc-form blister pack, or the blisters may be elongate in form, for example comprising a strip or a tape. Each capsule, cartridge, or blister may, for example, contain between 20µg-10mg of the polymorph or salt of the invention.

Aerosols may be formed by suspending or dissolving a polymorph or salt of the invention in a liquified propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (HFA-134a), 1,1-difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA-227a), perfluoropropane, perfluorobutane, perfluoropentane, butane, isobutane, and pentane. Aerosols comprising a polymorph or salt of the invention will typically be administered to a patient via a metered dose inhaler (MDI). Such devices are known to those skilled in the art.

The aerosol may contain additional pharmaceutically-acceptable excipients typically used with MDIs such as surfactants, lubricants, cosolvents and other excipients to improve the physical stability of the formulation, to improve valve performance, to improve solubility, or to improve taste.

There is thus provided as a further aspect of the invention a pharmaceutical aerosol formulation comprising a polymorph or salt of the invention and a fluorocarbon or hydrogen-containing chlorofluorocarbon as propellant, optionally in combination with a surfactant and/or a cosolvent.

According to another aspect of the invention, there is provided a pharmaceutical aerosol formulation wherein the propellant is selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixtures thereof.

The formulations of the invention may be buffered by the addition of suitable buffering agents.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatine, may be formulated containing a powder mix for inhalation of a polymorph or salt of the invention and a suitable powder base such as lactose or starch. Each capsule or cartridge may generally contain from 20 μ g to 10mg of the polymorph or salt of the invention. Alternatively, the polymorph or salt of the invention may be presented without excipients such as lactose.

The proportion of the active polymorph or salt in the local compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 10% by weight. Generally, for most types of preparations, the proportion used will be within the range of from 0.005 to 1%, for example from 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used will normally be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains from 20 μ g to 10mg, preferably from 20 μ g to 2000 μ g, more preferably from about 20 μ g to 500 μ g of a polymorph or salt of the invention. Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range from 100 μ g to 10mg, preferably from 200 μ g to 2000 μ g. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double that delivered with aerosol formulations.

In the case of suspension aerosol formulations, the particle size of the particulate (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and in particular in the range of from 1 to 10 microns, such as from 1 to 5 microns, more preferably from 2 to 3 microns.

The formulations of the invention may be prepared by dispersal or dissolution of the medicament and a polymorph or salt of the invention in the selected propellant in an appropriate container, for example, with the aid of sonication or a high-shear mixer. The process is desirably carried out under controlled humidity conditions.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to

those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per
5 actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The stability of the suspension aerosol formulations according to the invention may be measured by conventional techniques, for example, by measuring flocculation size
10 distribution using a back light scattering instrument or by measuring particle size distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the
15 "respirable fraction" of the aerosol formulations to be calculated. One method used to calculate the "respirable fraction" is by reference to "fine particle fraction" which is the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above.

20

The term "metered dose inhaler" or MDI means a unit comprising a can, a secured cap covering the can and a formulation metering valve situated in the cap. MDI system includes a suitable channelling device. Suitable channelling devices comprise for example, a valve actuator and a cylindrical or cone-like passage through which
25 medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient such as a mouthpiece actuator.

MDI canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or
30 preferably a metal can, for example, aluminium or an alloy thereof which may optionally be anodised, lacquer-coated and/or plastic-coated (for example incorporated herein by reference WO96/32099 wherein part or all of the internal surfaces are coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers), which container is closed with a metering valve. The cap may be secured onto
35 the can via ultrasonic welding, screw fitting or crimping. MDIs taught herein may be prepared by methods of the art (e.g. see Byron, above and WO96/32099). Preferably the

canister is fitted with a cap assembly, wherein a drug-metering valve is situated in the cap, and said cap is crimped in place.

5 In one embodiment of the invention the metallic internal surface of the can is coated with a fluoropolymer, more preferably blended with a non-fluoropolymer. In another embodiment of the invention the metallic internal surface of the can is coated with a polymer blend of polytetrafluoroethylene (PTFE) and polyethersulfone (PES). In a further embodiment of the invention the whole of the metallic internal surface of the can is coated with a polymer blend of polytetrafluoroethylene (PTFE) and polyethersulfone (PES).

10

The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, bromobutyl, EPDM, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bepak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. SpraymiserTM).

20 In various embodiments, the MDIs may also be used in conjunction with other structures such as, without limitation, overwrap packages for storing and containing the MDIs, including those described in U.S. Patent Nos. 6,119,853; 6,179,118; 6,315,112; 6,352,152; 6,390,291; and 6,679,374, as well as dose counter units such as, but not limited to, those described in U.S. Patent Nos. 6,360,739 and 6,431,168.

25

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method for preparing suspension aerosol formulations a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquefied propellant together with the optional excipients is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister. In one example bulk manufacturing method for preparing solution aerosol formulations a metering valve is crimped onto an aluminium can to form an empty canister. The liquefied

30

35

propellant together with the optional excipients and the dissolved medicament is pressure filled through the charge vessel into a manufacturing vessel.

5 In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold to ensure the formulation does not vaporise, and then a metering valve crimped onto the canister.

Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release
10 testing.

Suspensions and solutions comprising a polymorph or salt of the invention may also be administered to a patient via a nebulizer. The solvent or suspension agent utilized for nebulization may be any pharmaceutically-acceptable liquid such as water, aqueous
15 saline, alcohols or glycols, e.g., ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol, etc. or mixtures thereof. Saline solutions utilize salts which display little or no pharmacological activity after administration. Both organic salts, such as alkali metal or ammonium halogen salts, e.g., sodium chloride, potassium chloride or organic salts, such as potassium, sodium and ammonium salts or organic acids, e.g., ascorbic
20 acid, citric acid, acetic acid, tartaric acid, etc. may be used for this purpose.

Other pharmaceutically-acceptable excipients may be added to the suspension or solution. The polymorph or salt of the invention may be stabilized by the addition of an inorganic acid, e.g., hydrochloric acid, nitric acid, sulphuric acid and/or phosphoric acid;
25 an organic acid, e.g., ascorbic acid, citric acid, acetic acid, and tartaric acid, etc., a complexing agent such as EDTA or citric acid and salts thereof; or an antioxidant such as vitamin E or ascorbic acid. These may be used alone or together to stabilize the polymorph or salt of the invention. Preservatives may be added such as benzalkonium chloride or benzoic acid and salts thereof. Surfactant may be added
30 particularly to improve the physical stability of suspensions. These include lecithin, disodium dioctylsulphosuccinate, oleic acid and sorbitan esters.

In a further aspect, the invention is directed to a dosage form adapted for intranasal administration.

Formulations for administration to the nose may include pressurised aerosol formulations and aqueous formulations administered to the nose by pressurised pump. Formulations which are non-pressurised and adapted to be administered topically to the nasal cavity are of particular interest. Suitable formulations contain water as the diluent or carrier for this purpose. Aqueous formulations for administration to the lung or nose may be provided with conventional excipients such as buffering agents, tonicity modifying agents and the like. Aqueous formulations may also be administered to the nose by nebulisation.

10 The polymorph and salts of the invention may be formulated as a fluid formulation for delivery from a fluid dispenser, for example a fluid dispenser having a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO05/044354, the entire content of which is hereby incorporated herein by reference. The dispenser has a housing which houses a fluid discharge device having a compression pump mounted on a container for containing a fluid formulation. The housing has at least one finger-operable side lever which is movable inwardly with respect to the housing to cam the container upwardly in the housing to cause the pump to compress and pump a metered dose of the formulation out of a pump stem through a nasal nozzle of the housing. In one embodiment, the fluid dispenser is of the general type illustrated in Figures 30-40 of WO05/044354.

Pharmaceutical compositions adapted for intranasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the polymorph or salt of the invention.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the patient for a prolonged period of time. For example, the active ingredient may be

delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol. Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions may be applied as a topical ointment or cream. When formulated in an ointment, the polymorph or salt of the invention may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the a polymorph or salt of the invention may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers,

bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored
5 in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

10 The polymorphs and salts and pharmaceutical compositions according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an $M_1/M_2/M_3$ receptor antagonist), β_2 -adrenoreceptor agonists, antiinfective agents, such as antibiotics or antivirals, or antihistamines. The invention thus provides, in a further aspect,
15 a combination comprising a polymorph or salt of the invention together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent, such as a corticosteroid or an NSAID, an anticholinergic agent, a β_2 -adrenoreceptor agonist, an antiinfective agent, such as an antibiotic or an antiviral, or an antihistamine. One embodiment of the invention encompasses combinations comprising a polymorph or
20 salt of the invention together with a β_2 -adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor, and/or an antihistamine.

In one embodiment, the invention encompasses a method of treating a disorder mediated by inappropriate PI3-kinase activity comprising administering a safe and effective amount
25 of a combination comprising a polymorph or salt of the invention together with one or more therapeutically active agents.

In a further aspect, the invention provides a combination comprising a polymorph or salt of the invention which is selective for PI3K δ together with a compound or pharmaceutically
30 acceptable salt thereof which is selective for another PI3-kinase, for example PI3K γ .

One embodiment of the invention encompasses combinations comprising one or two other therapeutic agents.

35 It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as

solvates, for example hydrates to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

- 5 In one embodiment, the invention encompasses a combination comprising a polymorph or salt of the invention together with a β_2 -adrenoreceptor agonist.

Examples of β_2 -adrenoreceptor agonists include salmeterol (which may be a racemate or a single enantiomer such as the *R*-enantiomer), salbutamol (which may be a racemate or
10 a single enantiomer such as the *R*-enantiomer), formoterol (which may be a racemate or a single diastereomer such as the *R,R*-diastereomer), salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol
15 or the fumarate salt of formoterol. In one embodiment, long-acting β_2 -adrenoreceptor agonists, for example, compounds which provide effective bronchodilation for about 12 hrs or longer, are preferred.

Other β_2 -adrenoreceptor agonists include those described in WO 02/066422, WO
20 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO 2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, WO 2004/039766, WO01/42193 and WO03/042160.

Examples of β_2 -adrenoreceptor agonists include:

- 25 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino]hexyl}oxy}butyl)benzenesulfonamide;
3-(3-{[7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl]phenyl)ethyl]-amino}heptyl)oxy}propyl)benzenesulfonamide;
4-({(1*R*)-2-[(6-{2-[(2, 6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
30 4-({(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;
N-[2-hydroxy-5-[(1*R*)-1-hydroxy-2-[[2-4-[(2*R*)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide;

N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolin-5-yl)ethylamine; and
 5-[(*R*)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one.

5

The β_2 -adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic,
 10 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

Suitable anti-inflammatory agents include corticosteroids. Suitable corticosteroids which may be used in combination with the polymorphs or salts of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity.

15 Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, 6 α ,9 α -difluoro-17 α -[(2-furanylcabonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester (fluticasone furoate), 6 α ,9 α -difluoro-11 β -
 20 hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid *S*-(2-oxo-tetrahydro-furan-3*S*-yl) ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3- tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid *S*-cyanomethyl ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-
 25 fluoromethyl ester, beclomethasone esters (for example the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (for example mometasone furoate), triamcinolone acetonide, rofleponide, ciclesonide (16 α ,17-[[(*R*)-cyclohexylmethylene]bis(oxy)]-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone
 30 propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, 6 α ,9 α -difluoro-17 α -[(2-furanylcabonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3- tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid
 35 *S*-cyanomethyl ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid *S*-

fluoromethyl ester. In one embodiment the corticosteroid is 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

- 5 Examples of corticosteroids may include those described in WO2002/088167, WO2002/100879, WO2002/12265, WO2002/12266, WO2005/005451, WO2005/005452, WO2006/072599 and WO2006/072600.

- 10 Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy include those covered in the following patents: WO03/082827, WO98/54159, WO04/005229, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651 and WO03/08277. Further
15 non-steroidal compounds are covered in: WO2006/000401, WO2006/000398 and WO2006/015870.

Examples of anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

20

- Examples of NSAID's include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (for example montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin
25 antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (for example chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-lipoxygenase inhibitors. An iNOS (inducible nitric oxide synthase inhibitor) is preferably for oral administration. Examples of iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, WO95/34534 and
30 WO99/62875. Examples of CCR3 inhibitors include those disclosed in WO02/26722.

- In one embodiment, the invention provides the use of the polymorphs and salts of the invention in combination with a phosphodiesterase 4 (PDE4) inhibitor, especially in the case of a formulation adapted for inhalation. The PDE4-specific inhibitor useful in this
35 aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not

compounds which inhibit other members of the PDE family, such as PDE3 and PDE5, as well as PDE4.

Compounds include *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Also, *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

Other compounds include AWD-12-281 from Elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Further compounds are disclosed in the published international patent application WO04/024728 (Glaxo Group Ltd), WO04/056823 (Glaxo Group Ltd) and WO04/103998 (Glaxo Group Ltd) (e.g. Example 399 or 544 disclosed therein). Further compounds are also disclosed in WO2005/058892, WO2005/090348, WO2005/090353, and WO2005/090354, all in the name of Glaxo Group Limited.

Examples of anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M₁ or M₃ receptors, dual antagonists of the M₁/M₃ or M₂/M₃ receptors or pan-antagonists of the

M₁/M₂/M₃ receptors. Exemplary compounds for administration via inhalation include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (for example, as the bromide, CAS 30286-75-0) and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of
5 interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/04118. Exemplary compounds for oral administration include pirenzepine (CAS 28797-61-7), darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-
10 5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

15 Additional compounds are disclosed in WO 2005/037280, WO 2005/046586 and WO 2005/104745, incorporated herein by reference. The present combinations include, but are not limited to:

(3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane iodide;
(3-*endo*)-3-(2-cyano-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane
20 bromide;
4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.2]octane bromide; and
(1*R*,5*S*)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-{2-[(phenylmethyl)oxy]ethyl}-8-
azoniabicyclo[3.2.1]octane bromide.

25 Other anticholinergic agents include compounds which are disclosed in US patent application 60/487981 including, for example:

(3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
(3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
30 (3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane 4-
methylbenzenesulfonate;
(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide; and/or
(3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-8-azoniabicyclo[3.2.1]octane
35 bromide.

Further anticholinergic agents include compounds which are disclosed in US patent application 60/511009 including, for example:

(endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

- 5 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;
(endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;
3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
10 (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;
N-benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
(endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;
15 1-benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
1-ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;
N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
20 (endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;
N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-
benzenesulfonamide;
[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
25 N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-
methanesulfonamide; and/or
(endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-
bicyclo[3.2.1]octane bromide.

- 30 Further compounds include:
(endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-
bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
35 (endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;

(endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or

(endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

5

In one embodiment the invention provides a combination comprising a polymorph or salt of the invention together with an H1 antagonist. Examples of H1 antagonists include, without limitation, amexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrillamine, promethazine, terfenadine, tripeleminamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine. In a further embodiment the invention provides a combination comprising a polymorph or salt of the invention together with an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include, for example, those compounds disclosed in WO2004/035556 and in WO2006/045416. Other histamine receptor antagonists which may be used in combination with the polymorphs and salts of the present invention include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski *et al.*, *J. Med. Chem.* 46:3957-3960 (2003).

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with a non-steroidal GR agonist.

35

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with an antihistamine.

- 5 The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with a PDE4 inhibitor and a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a polymorph or salt of the invention together with an anticholinergic and a PDE-4 inhibitor.

10

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

15

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual components will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents

20 will readily be appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with another therapeutically active agent.

25

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with a PDE4 inhibitor.

- 30 The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with a β_2 -adrenoreceptor agonist.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with a corticosteroid.

35

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with a non-steroidal GR agonist.

- 5 The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with an anticholinergic.

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with an antihistamine.

10

The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with a PDE4 inhibitor and a β_2 -adrenoreceptor agonist.

- 15 The invention thus provides, in a further aspect, a pharmaceutical composition comprising a combination of a polymorph or salt of the invention together with an anticholinergic and a PDE4 inhibitor.

The invention will now be illustrated by way of the following non-limiting examples.

20

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to
25 prepare and use the polymorphs, salts, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

- 30 When the name of a commercial supplier is given after the name of a compound or a reagent, for instance "compound X (Aldrich)" or "compound X/Aldrich", this means that compound X is obtainable from a commercial supplier, such as the commercial supplier named. If not referenced herein the compound or reagent can be purchased from a standard supplier such as Sigma Aldrich, Lancaster, Fluorochem, TCI etc.

35

The names of the compounds have been obtained using a compound naming programme which matches structure to name (e.g. ACD/Name Batch v 9.0).

General Experimental Details**Liquid Chromatography Mass Spectroscopy (LCMS) Methods**

- 5 LCMS analysis has been carried out using one of the methods listed below.

Method A:

LCMS instrumentation consists of the following:

Column: Acquity UPLC BEH C₁₈ 1.7µm 2.1mm x 50mm. Column oven set to 40 degrees
10 centigrade

Solvent A: Water 0.1% Formic Acid + 10mM Ammonium Acetate

Solvent B: MeCN: Water 95:5 + 0.05% Formic Acid

Injection volume: 0.5µl

Injection technique: Partial loop overfill

- 15 UV detection: 220 to 330 nm

UV sampling rate: 40 points per second

MS scan range: 100 to 1000 amu

MS scanning rate: 0.2 second scan with a 0.1 second inter scan delay

MS scan function: Electrospray with pos neg switching

- 20 Cycle time: 2minutes and 30 seconds

Gradient :

Time	Flow ml/min	%A	%B
0	1	97	3
0.1	1	97	3
1.4	1	0	100
1.9	1	0	100
2	1	97	3

Method B:

- 25 The HPLC analysis was conducted on a Sunfire C18 column (30mm x 4.6mm i.d. 3.5µm packing diameter) at 30 degrees centigrade.

Solvent A = 0.1% v/v solution of Formic Acid in Water.

Solvent B = 0.1% v/v solution of Formic Acid in Acetonitrile.

The gradient employed was:

Time (min)	Flow Rate (ml/min)	% A	% B
------------	--------------------	-----	-----

0	3	97	3
0.1	3	97	3
4.2	3	0	100
4.8	3	0	100
4.9	3	97	3
5.0	3	97	3

The UV detection was an averaged signal from wavelength of 210nm to 350nm and mass spectra were recorded on a mass spectrometer using alternate-scan positive and negative mode electrospray ionization.

5

Method C:

The HPLC analysis was conducted on a Phenomenex Luma C18(2) (50mm x 2mm i.d. 3µm packing diameter, or validated equivalent) at 40 degrees centigrade.

Solvent A = 0.05% v/v solution of TFA in Water.

10 Solvent B = 0.05% v/v solution of TFA in Acetonitrile.

The gradient employed was:

Time (min)	Flow Rate (ml/min)	% A	% B
0	1	100	0
8	1	5	95
8.01	1	100	0

The UV detection wavelength was analyte dependent and mass spectra were recorded on a mass spectrometer using positive ion electrospray.

15

Method D:

The HPLC analysis was conducted on a Phenomenex Luma C18(2) (50mm x 2mm i.d. 3µm packing diameter, or validated equivalent) at 60 degrees centigrade.

Solvent A = 0.05% v/v solution of TFA in Water.

20 Solvent B = 0.05% v/v solution of TFA in Acetonitrile.

The gradient employed was:

Time (min)	Flow Rate (ml/min)	% A	% B
0	1.5	100	0
2.5	1.5	5	95
2.7	1.5	5	95

2.9	1.5	100	0
-----	-----	-----	---

The UV detection wavelength was analyte dependent and mass spectra were recorded on a mass spectrometer using positive ion electrospray.

5 **Mass Directed Automated Preparative HPLC Methods**

The methods for the mass-directed automated preparative HPLC used for the purification of compounds are described below:

Method A - High pH

10 **Column Details:** Waters_XBRIDGE Prep C18 column 5um OBD (30 x 150 mm)

The solvents employed were:

A=10 mM Ammonium Bicarbonate in water adjusted to pH 10 with aq. Ammonia solution

15

B= Acetonitrile + 0.1 % aq. Ammonia

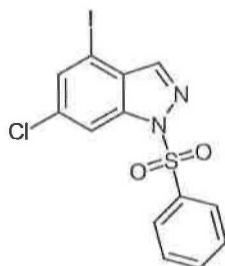
Collection was triggered by uv, ms or a combination of the two. The UV detection was an averaged signal from wavelength of 210nm to 350nm. Mass spectra were recorded on a
20 mass spectrometer using an alternate-scan positive and negative mode electrospray ionization.

PREPARATION OF COMPOUND A

25 **Intermediates and Examples**

Intermediate 1

6-Chloro-4-iodo-1-(phenylsulfonyl)-1H-indazole



30 **Method A**

6-Chloro-4-iodo-1*H*-indazole (30 g, 108 mmol, available from Sinova) was dissolved in *N,N*-dimethylformamide (300 ml) and cooled in an ice water bath under nitrogen. Sodium hydride (5.17 g, 129 mmol) was added portionwise, maintaining the temperature below 10°C. After full addition the reaction mixture was stirred for 20 mins then benzenesulfonyl chloride (16.5 ml, 129 mmol) was added dropwise over 15 mins. The reaction was left to warm to RT overnight then poured onto ice water (2 L). The precipitated product was collected by filtration, washed with water (ca. 400 ml) and dried in a vacuum oven overnight to give the title compound (43.3 g).

LCMS (Method A): Rt 1.38 mins, MH⁺ 419.

Method B

To a stirred solution of 6-chloro-4-iodo-1*H*-indazole (633.6 g) in THF (5.7L) was added sodium hydroxide (227.4 g) followed by tetra-*n*-butylammonium bisulphate (38.0 g) at 20±3°C, under a nitrogen atmosphere. The mixture was stirred at 20±3°C for 1 h 3 min, then benzenesulphonyl chloride (319 ml) was added at such a rate as to maintain the internal temperature at <25°C. Residual benzenesulphonyl chloride was rinsed into the vessel with THF (630 mL), then the mixture stirred for 1 h 10 min. The mixture was cooled to <5°C and water (12.7 L) added at such a rate as to maintain internal temperature below 5±3°C, then the mixture stirred at 0-5°C for 1 h 20 min. The solids were collected by vacuum filtration, washed with water (2x 1.9 L), sucked dry then further dried under vacuum with a nitrogen bleed at 40°C±3°C overnight to give the title compound (780.8 g).

LCMS (Method C): Rt 6.28 min, MH⁺ 419.

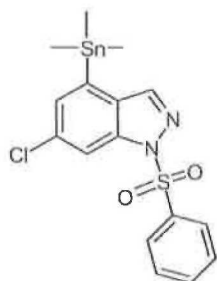
Method C

All weights, volumes and equivalents are relative to 6-chloro-4-iodo-1*H*-indazole.

6-Chloro-4-iodo-1*H*-indazole (1.0 eq., 1 wt, 50 g), sodium hydroxide (2.25 eq., 0.324 wt, 16.16 g) and tetrabutylammonium hydrogensulphate (0.05 eq., 0.061 wt, 3.05 g) are stirred in THF (9.5 vols, 475 ml) at 20±3 °C under a nitrogen atmosphere for 1 hr. The mixture is cooled to 15±3 °C and benzenesulfonyl chloride (1.10 eq., 0.51 vols, 25.5 ml) is added dropwise over 20 mins maintaining the reaction temperature at <25 °C and is washed in with THF (0.5 vols, 25 ml). The resulting mixture is then stirred under a nitrogen atmosphere at 20±3 °C for at least 1hr before checking for completion by HPLC. The reaction mixture is then added to 0.25 M hydrochloric acid solution (18 vols, 900 ml) cooled to 0±3°C over 15 minutes maintaining the temperature of the aqueous suspension at <20°C. This is washed in with 0.25M hydrochloric acid solution (2 vols, 100 ml). The

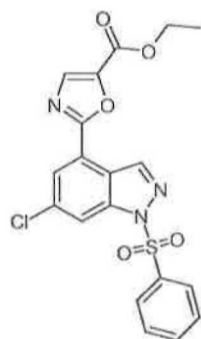
resulting orange suspension is then stirred at 2 ± 3 °C for at least 1 hr. The solid is filtered, washed with water (2 x 3 vols, 2 x 150 ml) and sucked dry for 20 mins, then dried under high vacuum at 40 °C (± 3 °C) to constant probe temperature to afford 6-chloro-4-iodo-1-(phenylsulfonyl)-1H-indazole as an orange solid.

5

Intermediate 2**6-Chloro-1-(phenylsulfonyl)-4-(trimethylstannanyl)-1H-indazole**

6-Chloro-4-iodo-1-(phenylsulfonyl)-1H-indazole (30 g, 71.7 mmol),
10 tetrakis(triphenylphosphine)palladium(0) (8.1 g, 7.01 mmol), xylene (200 ml), triethylamine (19.98 ml, 143 mmol) and hexamethylditin (21.8 ml, 105 mmol) were heated at 150°C for 2 h. The reaction mixture was filtered hot through Celite, washing with further xylene and the solvent was evaporated *in vacuo*. The residue was triturated with cyclohexane and the precipitate collected by filtration and dried in a vacuum oven to give the title compound
15 (14.4 g).

LCMS (Method A): Rt 1.51 mins, MH^+ 457.

Intermediate 3a**Ethyl 2-[6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazole-5-carboxylate**

20

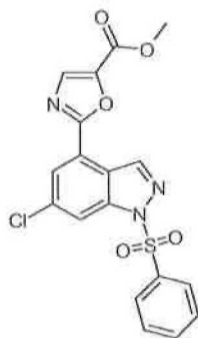
In 4 batches, tetrakis(triphenylphosphine)palladium(0) (3.37 g, 2.92 mmol), ethyl 2-chloro-1,3-oxazole-5-carboxylate (6.65 g, 37.9 mmol, available from Apollo Scientific) and copper(I) iodide (1.11 g, 5.83 mmol) were added to a solution of 6-chloro-1-(phenylsulfonyl)-4-(trimethylstannanyl)-1H-indazole (13.28 g, 29.2 mmol) in *N,N*-

dimethylformamide (52 ml). In 3 of the batches, tetrakis(triphenylphosphine)palladium(0) (1.03 g, 0.89 mmol), ethyl 2-chloro-1,3-oxazole-5-carboxylate (2.03 g, 11.59 mmol) and copper(I) iodide (0.34 g, 1.78 mmol) were added to a solution of 6-chloro-1-(phenylsulfonyl)-4-(trimethylstannanyl)-1*H*-indazole (4.06 g, 8.91 mmol) in *N,N*-dimethylformamide (16 ml). In the fourth batch, tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.24 mmol), ethyl 2-chloro-1,3-oxazole-5-carboxylate (0.55 g, 3.14 mmol) and copper(I) iodide (0.09 g, 0.48 mmol) were added to a solution of 6-chloro-1-(phenylsulfonyl)-4-(trimethylstannanyl)-1*H*-indazole (1.10 g, 2.42 mmol) in *N,N*-dimethylformamide (4 ml). Each batch was heated and stirred at 100°C under microwave irradiation for 30 min. The mixtures were allowed to cool to RT and the combined precipitated product suspended in diethyl ether and collected by filtration, washing with further diethyl ether then drying in a vacuum oven for 72 h. Approximately 5.2 g of the resultant solid was dissolved in dichloromethane and passed through Celite, eluting with further dichloromethane. The solvent was evaporated *in vacuo* to give the title compound as a pale orange solid (4.95 g).

LCMS (Method A): Rt 1.38 mins, MH^+ 432.

Intermediate 3b

Methyl 2-[6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl]-1,3-oxazole-5-carboxylate



20

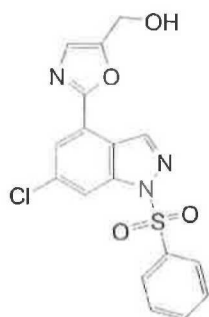
To a stirred solution of 6-chloro-4-iodo-1-(phenylsulphonyl)-1*H*-indazole (549.8 g) in toluene (1.43 L) was added triethylamine (380 ml) at 20±3°C under an atmosphere of nitrogen. Hexamethylditin (385 ml) in toluene (825 ml) was added, followed by toluene (275 ml) then tetrakis(triphenylphosphine) palladium (0) (154.7 g). The reaction mixture was heated to 120°C and stirred at this temperature for 3 h. The mixture was allowed to cool to 20±3°C, filtered, then washed with toluene (4.95 L). The filtrate was transferred to a clean vessel through a 5µm Dominick hunter in-line filter, rinsing with further toluene (550 ml). The batch was then washed with 50% aqueous KF solution (5.5 L), the aqueous slurry filtered and the filtrate recombined with the organic phase. The aqueous was separated and the organics washed successively with 50% aqueous KF (5.5 L),

30

followed by water (5.5 L). The organic layer was diluted with DMPU (2.75 L) then concentrated by vacuum distillation to ca. 5.4vols. To the resultant solution was added copper (I) iodide (25.5 g) followed by methyl 2-chloro-1,3-oxazole-5-carboxylate (279 g, available from Apollo Scientific) at $20\pm 3^{\circ}\text{C}$. The solution was degassed *via* vacuum and nitrogen purges (x3). Tetrakis(triphenylphosphine) palladium (0) (78 g) was added, the mixture degassed (x3) and then heated to $85\text{--}90^{\circ}\text{C}$ for 10 h. The mixture was diluted with DMSO (13.75 L) and cooled to $20\pm 3^{\circ}\text{C}$, then water (2.75 L) added in ca. 1vol portions over ca. 15 mins until crystallisation was initiated. The resultant suspension was aged at $20^{\circ}\text{C}\pm 3^{\circ}\text{C}$ for 1.5 h. The solids were collected by vacuum filtration, washed with water (2x 2.75 L), sucked dry and then further dried *in vacuo* with a nitrogen bleed at $45^{\circ}\text{C}\pm 5^{\circ}\text{C}$ overnight to give the title compound (341.1 g).
LCMS (Method C): Rt 6.08 mins, MH^{+} 418

Intermediate 4

{2-[6-Chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazol-5-yl}methanol



Method A

A solution of ethyl 2-[6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazole-5-carboxylate (5.11 g, 11.8 mmol) in dichloromethane (80 ml) was cooled to -25°C in an oven dried round bottomed flask. Diisobutylaluminium hydride (25 ml, 37.5 mmol, 1.5M solution in toluene) was added dropwise and the reaction stirred at -20°C for 3 h. A 10% aqueous solution of potassium sodium tartrate (80 ml) was added and the reaction mixture stirred for 5 min. The precipitated solid was filtered off and partitioned between ethyl acetate (500 ml) and water (500 ml). The layers were separated and the aqueous washed with further ethyl acetate (3x 150 ml). The combined organics were dried and evaporated *in vacuo* to give the title compound as a yellow solid (1.1 g).
LCMS (Method A): Rt 1.09 mins, MH^{+} 390.

The remaining filtrate was largely concentrated *in vacuo* and the residue partitioned between ethyl acetate (500 ml) and water (500 ml). The layers were separated and the

aqueous extracted with further ethyl acetate (3x 150 ml). The combined organics were washed with water (2x 150 ml), dried over anhydrous sodium sulfate and evaporated to give the title compound as a yellow solid (1.9 g).

LCMS (Method A): Rt 1.09 mins, MH⁺ 390.

5

Method B

To a solution of ethyl 2-[6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazole-5-carboxylate (1.15 g) in THF (17.25 ml), stirred under nitrogen in an ice bath was added a solution of diisobutylaluminium hydride (5.08 ml, 5.64 mmol) in toluene. The reaction mixture was stirred at 0°C for 2 h. Sodium sulphate decahydrate (2.5 g) was added, the mixture stirred at RT for 1 h, then filtered, washed with THF (2x 5 vols) and concentrated under reduced pressure to give the title compound (0.98 g).

10

LCMS (Method D): Rt 2.20 mins, MH⁺ 390.

Method C

To a solution of ethyl 2-[6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazole-5-carboxylate (604.5 g) in THF (8.7 L), stirred under nitrogen at 0±3°C was added a solution of approximately 1.3M diisobutylaluminium hydride (1.8 kg) in toluene. The reaction mixture was stirred at 0±3°C for 30 mins and then diluted with THF (3 L). Sodium sulphate decahydrate (1.3 kg) was added, maintaining the temperature below 5°C. The mixture was stirred at 0±3°C for 10 mins and was then warmed to 20±3°C and held at this temperature for 1 h. The suspension was filtered, washed with THF (4 x 3 L) and concentrated under reduced pressure to give the title compound (529.6 g).

20

LCMS (Method C): Rt 5.18 min, MH⁺ 390.

25

Method D

All weights, volumes and equivalents are relative to 6-chloro-4-iodo-1-(phenylsulfonyl)-1H-indazole.

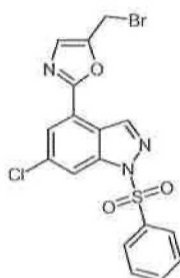
Zinc chloride (3.6 eq, 1.17 wt, 52.7 g) in tetrahydrofuran (5 vols, 225 ml) is cooled to 0 to 5 °C. A solution of the ethyl oxazole-5-carboxylate (1.1 eq, 0.37 wt, 18.1 g, corrected for 92 wt% assay) in tetrahydrofuran (5 vols, 225 ml) is added to the vessel. The suspension is cooled to -10 °C (+/-5 °C) under a nitrogen atmosphere and a 1M solution of bis-(trimethylsilyl)-lithiumamide in tetrahydrofuran (1.80 eq, 4.30 vols, 193 ml) is added over 15 minutes maintaining the temperature at -10 °C (+/-5 °C). The resulting solution is stirred under a nitrogen atmosphere at -10 °C (+/-5 °C) for 1 hour. To the solution is added 6-chloro-4-iodo-1-(phenylsulfonyl)-1H-indazole (1.0 eq, 1.0 wt, 45.0 g) and tetrakis

30

35

triphenylphosphine palladium (0.03 eq, 0.083 wt, 3.73 g) (the mixture is degassed with vacuum/nitrogen 3 times) and then heated to 60°C (+/-3°C) for at least 6 hours. The reaction is then checked by HPLC for completion. The reaction solution is cooled to 0 °C (+/-3 °C) and a solution of 25% w/w diisobutylaluminium hydride in toluene (4.0 eq, 6.4
5 vols, 288 ml) is added maintaining the temperature at <5°C. The resulting reaction solution is then stirred at 0°C (+/-3°C) for at least 1 hour. The reaction is then checked by HPLC (generic) for completion. The reaction mixture is added portion wise to a solution of citric acid (4.0 eq, 2.0 wt, 90 g) in water (10 vols, 450 ml) at 0 °C (+/-5 °C) over ~1h. The resulting solution is stirred at 20 °C for 15 minutes, extracted with ethyl acetate (10 vols,
10 450 ml), the organic layer is washed with water (2 x 3 vols, 2 x 135 ml) and filtered through a porosity 4 sinter. The organic layer is then evaporated under reduced pressure (45 °C, 100 mbar) to 2 to 3 volumes, dimethyl sulphoxide (10 vols, 450 ml) is added and the solution evaporated under reduced pressure (45 °C, 50 mbar) to remove all traces of other solvents. To the solution at 45 °C is added water (5 vols, 225 ml) dropwise over 30
15 minutes, the resulting reaction mixture is cooled to 20 °C over 3hr and stirred at 20 °C for at least 15 hrs. The product is filtered, washed with a solution of dimethylsulphoxide:water (1:2) (2 vols, 90 ml), then washed with water (3 vols, 135 ml), then dried under high vacuum at 60 °C (±3 °C) to constant probe temperature to afford (2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)oxazol-5-yl)methanol as a beige solid.

20

Intermediate 5**4-[5-(Bromomethyl)-1,3-oxazol-2-yl]-6-chloro-1-(phenylsulfonyl)-1H-indazole****Method A**

25 {2-[6-Chloro-1-(phenylsulfonyl)-1H-indazol-4-yl]-1,3-oxazol-5-yl}methanol (1.626 g, 4.17 mmol) was dissolved in anhydrous dichloromethane (20 ml) and carbon tetrabromide (2.77 g, 8.34 mmol) added. The reaction mixture was cooled to 0°C and a solution of triphenylphosphine (2.188 g, 8.34 mmol) in dichloromethane (20 ml) added dropwise. After allowing to warm to RT and stirring for a further 3 h, the solvent was partially
30 removed *in vacuo* and the solution purified directly by silica gel chromatography, eluting

with 0-100% ethyl acetate in dichloromethane. The appropriate fractions were combined to give the title compound as a cream solid (1.16 g).

LCMS (Method B): Rt 3.70 mins, MH⁺ 454.

5 Method B

Triphenylphosphine dibromide (20.60 g, 48.8 mmol) was added to a suspension of {2-[6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl]-1,3-oxazol-5-yl}methanol (9.06 g, 23.2 mmol) in dichloromethane (181 ml) at 0°C. The reaction mixture was stirred at 0°C until completion. Water (91 ml) and saturated sodium bicarbonate solution (91 ml) were added
10 and the mixture stirred, then separated. The aqueous layer was extracted with further dichloromethane (45 ml) and the organics combined and washed with water (91 ml). The layers were separated and the organic concentrated to dryness then redissolved in methanol (136 ml). After stirring for 30 mins the resultant white suspension was filtered and the solid dried under vacuum to give the title compound as an off-white solid (9.58 g).
15 LCMS (Method D): Rt 2.57min, MH⁺ 452/454.

Method C

Triphenylphosphine dibromide (1.2 kg) was added to a suspension of {2-[6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl]-1,3-oxazol-5-yl}methanol (544.7 g) in dichloromethane
20 (3.8 L) stirred under nitrogen at 10±3°C. The reaction mixture was stirred at 10±3°C for 20 min. Water (2.7 L) and saturated sodium bicarbonate solution (5.4 L) were added and the mixture stirred, then separated. The aqueous layer was extracted with further dichloromethane (2.7 L) and the organics combined and washed with water (2.7 L). The layers were separated and the organic concentrated to dryness then redissolved in
25 methanol (6.5 L). After stirring for 5 hours the resultant white suspension was filtered, washed with methanol (2 x 1.1 L) and the solid dried under vacuum at 40±5°C to give the title compound as an off-white solid (514.0 g).
LCMS (Method C): Rt 6.40 min, MH⁺ 453/455.

30 Method D

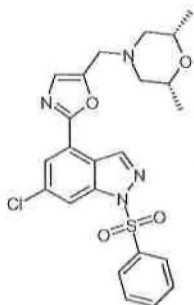
All weights, volumes and equivalents are relative to (2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazol-5-yl)methanol.

(2-(6-Chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazol-5-yl)methanol (1.0 eq., 1 wt, 34.0
35 g) and triphenylphosphine dibromide (1.3 eq., 1.32 wt, 45.0 g) are stirred in dichloromethane (15 vols, 510 ml) at 20 (±3°C) under a nitrogen atmosphere for 1hr. The reaction is then checked by HPLC for completion. Once complete methanol (0.8 vols, 27.2

ml) is added to the reaction, with vigorous stirring 8%w/w sodium hydrogen carbonate solution (10 vols, 340 ml) is added drop wise over 15 minutes (check aqueous pH >7). The mixture is heated to 30°C ($\pm 3^\circ\text{C}$) and stirred together for 10 minutes, then separated, the aqueous is back extracted with dichloromethane (5 vols, 170 ml) and the combined
5 dichloromethane layers are washed with water (5 vols, 170 ml). The dichloromethane solution is then evaporated under reduced pressure to a volume of approximately 4 vols. To the solution is added methanol (15 vols, 510 ml) and the solution evaporated under reduced pressure at 260 mbar, 20 °C to remove the remaining dichloromethane down to ~15 vols. The suspension is then stirred at 20 °C for at least 6 hrs. The solid is filtered,
10 washed with methanol (2x 1 vols, 2 x 34 ml), sucked dry for 20 minutes, then dried under high vacuum at 30 °C ($\pm 3^\circ\text{C}$) to constant probe temperature to afford 5-(bromomethyl)-2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)oxazole as a beige solid.

Intermediate 6a

15 **6-Chloro-4-(5-([(2R,6S)-2,6-dimethyl-4-morpholinyl]methyl)-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1H-indazole**



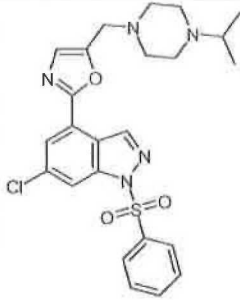
4-[5-(Bromomethyl)-1,3-oxazol-2-yl]-6-chloro-1-(phenylsulfonyl)-1H-indazole (0.580 g, 1.28 mmol) was dissolved in dichloromethane (5 ml) and (2R, 6S)-2,6-dimethylmorpholine (0.317 ml, 2.56 mmol) added. The reaction mixture was stirred at RT for 3 h then the solvent removed under a stream of nitrogen. The resultant yellow solid was dissolved in
20 dichloromethane (5 ml) and washed with water (2x 2.5 ml). The layers were separated (hydrophobic frit) and the organic evaporated *in vacuo* to give the title compound as a pale yellow solid (0.60 g).

25 LCMS (Method A): Rt 0.86 mins, MH^+ 487.

^1H NMR (400MHz, Chloroform- d) δ (ppm) 8.93 (d, J = 1.0 Hz, 1 H), 8.33 (dd, J = 1.0, 1.5 Hz, 1 H), 8.04 - 8.00 (m, 2 H), 7.98 (d, J = 1.5 Hz, 1 H), 7.62 (tt, J = 1.5, 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.15 (s, 1 H), 3.67 (s, 2 H), 3.75 - 3.66 (m, 2 H), 2.79 - 2.72 (m, 2 H), 1.86 (dd, J = 10.5, 11.0 Hz, 2 H), 1.16 (d, J = 6.5 Hz, 6 H).

30

Similarly prepared using the appropriate amine was:

Intermediate Number	Name	Structure	Amine	LC/MS R _t min	LC/MS MH ⁺
6b	6-chloro-4-(5- {{[4-(1-methylethyl)- 1-piperazinyl]methyl}-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1 <i>H</i> -indazole		1-(1-methylethyl)piperazine	0.77	500

Intermediate 6bMethod B

- 5 Isopropylpiperazine (165 ml) was added to a suspension of 4-[5-(Bromomethyl)-1,3-oxazol-2-yl]-6-chloro-1-(phenylsulfonyl)-1*H*-indazole (250.1 g) in dichloromethane (2.5 L) stirred under nitrogen at 22±3°C. The reaction mixture was stirred at 22±3°C for 1.25 hours and then water (2.5 L) was added, the mixture was stirred, then separated. The aqueous layer was extracted with further dichloromethane (0.5 L) and the organics
- 10 combined and washed with water (2.5 L). The layers were separated and the organic concentrated to dryness, under vacuum, to give the title compound as a yellow solid (274.6 g).

LCMS (Method B): R_t 3.33 min, MH⁺ 500.

15 Method C

All weights, volumes and equivalents are relative to 5-(bromomethyl)-2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazole (corrected for assay).

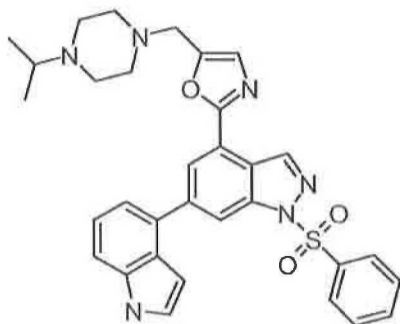
- DMSO (7 vols, 70 ml) and isopropylpiperazine (1.5 eq, 0.387 wt, 0.431 vol, 4.31 ml, 3.87 g) are charged to a clean vessel. 5-(Bromomethyl)-2-(6-chloro-1-(phenylsulfonyl)-1*H*-indazol-4-yl)oxazole (1.0 eq, 10 g (9.13 g corrected for assay), 1 wt) is added in 5 portions at 20 °C over 1 hr and the mixture stirred for 1 hr. The mixture is heated to 50 °C and aged for 1 hr, then checked for consumption of starting material by HPLC. Triethylamine (1.2 eq, 0.244 wt, 0.336 vol, 2.44 g, 3.36 ml) is added over 10 mins and the mixture aged
- 25 for 30 mins, then cooled to 20 °C over 1 hr and further aged for 2 hrs. The thick slurry is filtered and washed with DMSO (2 x 1.5 vols, 2 x 15 ml) followed by acetone:water 1:2 (3

x 2 vols, 3 x 20 ml). The resultant solid is blown dry on the filter and dried at 60 °C *in vacuo* to constant weight/temperature to afford 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole as an off-white solid.

Recrystallisation - All weights, volumes and equivalents are relative to 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole. DMSO (7.7 wt, 231 g) is charged to a clean vessel followed by 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (1wt, 30 g). The batch is heated to 75 °C until complete dissolution is observed and the mixture is filtered and line-washed with DMSO (1.1 wt, 33 g, pre-heated to 75 °C). The mixture is cooled to 20 °C over 2 hrs, aged for a further 2 hrs, and filtered. The cake is washed with DMSO (2.2 wt, 66 g) followed by 3:1 water:acetone (3 x 2 vols, 3 x 60 ml). The product is blown dry on the filter and dried at 60 °C *in vacuo* to constant weight/temperature to afford 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole as an off-white solid.

Intermediate 7

6-(1H-Indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1H-indazole



20 Method A

A solution of sodium bicarbonate (228.0 g) in water (2.7 L) was added to a suspension of 6-Chloro-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1H-indazole (271.2 g) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (263.2 g, available from Apollo Scientific Limited) in isopropanol (2.7 L) stirred under nitrogen at ambient temperature. After degassing, via evacuation and flushing with nitrogen, 2'-(dimethylamino)-2-biphenyl-palladium(II) chloride dinorbornylphosphine complex (29.83 g) was added. The mixture was degassed again and was then heated to 90±3°C and held at this temperature for 2 hours. The mixture was cooled to 20±5°C over 25 minutes and aged at this temperature overnight. The resultant suspension was

filtered, washed with water (1.35 L) and then slurried with toluene (4 x 1.35 L). The solid was dried under vacuum at 50°C to give the title compound as grey solid (302.7 g).

LCMS (Method B): Rt 3.20 min, MH⁺ 581.

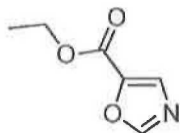
5 Method B

All weights, volumes and equivalents are relative to 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole.

A mixture of 2-(6-chloro-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (1.0 eq., 1 wt, 10.0 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (1.1 eq., 0.535 wt, 5.35 g) and K₃PO₄ (1.2 eq., 0.509 wt, 5.09 g) are charged sequentially to a stirred vessel containing IPA (5 vols, 50 ml) and water (5 vols, 50 ml). KHF₂ (2.2 eq., 0.344 wt, 3.44 g) is then added and the mixture heated to 75-80 °C under a flow of N₂ for at least 1 hr to degas. Meanwhile, IPA (5 vols, 50 ml) is charged to a separate vessel and heated to reflux for 1 hr under a stream of N₂ to degas. The IPA is cooled to 20 °C and Pd(OAc)₂ (0.02 eq., 0.0090 wt, 90.0 mg) and tricyclohexylphosphine (0.04 eq., 0.0224 wt, 224 mg) are added sequentially and aged for 1 hr until a yellow solution is observed. The yellow solution is then added over 10 mins to the first vessel maintaining the temperature at 75-80 °C and stirred for at least 4 hours. The mixture is cooled to 20 °C and aged for at least 1 hr. The slurry is then filtered and washed with 1:1 IPA:water (2 vols, 20 ml) followed by water (2 x 2 vols, 2 x 20 ml) and dried *in vacuo* at 60±3 °C to constant temperature to afford 2-(6-(1H-indol-4-yl)-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole as a yellow solid.

25 **Intermediate 8**

Ethyl oxazole-5-carboxylate



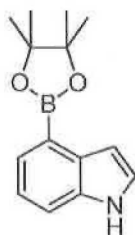
All weights, volumes and equivalents are relative to toluenesulfonylmethyl isocyanide.

Toluenesulfonylmethyl isocyanide (TosMIC) (12.31 g, 1 wt, 1 eq) is dissolved in DCM (61.6 ml, 5 vols) at 0 °C under N₂. In a separate vessel, ethyl glyoxalate (50 wt% solution in toluene, 20.6 g, 20.0 ml, 1.67 wt) is diluted with DCM (61.6 ml, 5 vols) under N₂ and DBU (12.48 g, 12.35 ml, 1.3 eq, 1.01 wt) is added resulting in a purple solution. The second solution is added to the TosMIC solution over 1 hr, maintaining temperature at 0 °C, then checked by HPLC for completion after a further 20 mins. The reaction is

quenched by slow addition of 2M HCl (10 vols, 123 ml) and the DCM layer separated. The aqueous layer is re-extracted with DCM (5 vols, 61.6 ml), and the combined organics dried over Na₂SO₄, then evaporated on Buchi, 25 °C, 100 mbar to remove DCM and toluene. Distilled at 12 mbar, jacket temperature 105 °C, vapour temperature 60-80 °C to afford ethyl oxazole-5-carboxylate as a colourless oil.

Intermediate 9

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



All weights, volumes and equivalents are relative to 4-bromoindole.

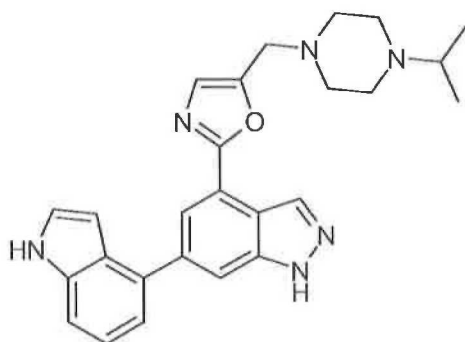
Bis(pinacolato)diboron (1.555 wt, 1.20 eq, 31.1 g), potassium acetate (1.00 wt, 2.0 eq, 20.0 g) and 4-bromoindole (1.00 wt, 0.64 vols, 1.00 eq, 20.0 g), are charged sequentially under N₂ to a clean, dry vessel containing toluene (5 vols, 100 ml) and washed in with toluene (2 vols, 40 ml). The mixture is degassed by vacuum/N₂ purge x3 and heated to 100 °C. In a separate clean, dry vessel, trisbenzylideneacetonedipalladium (0.0234 wt, 0.005 eq, 0.467 g) and tricyclohexylphosphine (0.0286 wt, 0.02 eq, 0.572 g) are combined under N₂ and toluene (1 vol, 20 ml) is added. The mixture is degassed by vacuum/N₂ purge x3 and stirred for 30 mins. The catalyst solution is added to the reaction vessel and the mixture heated at 95-100 °C for at least 3 hrs, until all the 4-bromoindole is consumed as indicated by HPLC analysis. The mixture is cooled to 60 °C and filtered to remove inorganics. The cake is washed with toluene (2 x 2 vols, 2 x 40 ml). The dark solution is then distilled down to 4 vols (80 ml) under vacuum (50-60 °C, 100 mbar) and aged at 60 °C for 1 hr. The resultant slurry is cooled to 20 °C over 2 hrs and heptane (12 vols, 240 ml) added over 1 hr. The mixture is aged for at least 1 hr and filtered. The cake is washed with toluene:heptane (1:4, 2 vols, 40 ml) followed by heptane (2 vols, 40 ml) and dried *in vacuo* at 50-60 °C to constant probe temperature to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole as a beige solid.

Recrystallisation - All weights, volumes and equivalents are relative to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole. Isopropanol (6 vols, 4.72 wts, 54.3 Kg) is

charged to a clean vessel followed by 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (1 wt, 11.5 Kg) and the mixture stirred and heated to reflux (82 °C) for 40 mins. The batch is cooled to 70 ± 3 °C and water (6 vols, 6 wts, 69 Kg) is added *via* peristaltic pump water over 1 hour maintaining temperature at 70 ± 3 °C. The contents are aged at 70 ± 3 °C for 60 mins and cooled to 20 °C over 2 hours. The slurry is aged at 20 °C for at least 6 hrs and filtered. The cake is washed with 1:1 IPA:water (2 vols, 23 L) and 1:3 IPA:water (2 vols, 23 L) and dried *in vacuo* at 60 °C to constant temperature to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole as a white solid.

10 Example 1

6-(1H-Indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1H-indazole



Method A

15 6-Chloro-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1H-indazole (97 mg, 0.194 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (61.3 mg, 0.252 mmol, available from Frontier Scientific Europe), chloro[2'-(dimethylamino)-2-biphenyl]palladium-(1*R*,4*S*)-bicyclo[2.2.1]hept-2-yl[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]phosphane (10.87 mg, 0.019 mmol) and potassium phosphate tribasic (124 mg, 0.582 mmol) were dissolved in 1,4-dioxane (1 ml) and water (0.1 ml) and heated in a Biotage Initiator microwave at 100°C for 30 min. Additional 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (61.3 mg, 0.252 mmol) and chloro[2'-(dimethylamino)-2-biphenyl]palladium-(1*R*,4*S*)-bicyclo[2.2.1]hept-2-yl[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]phosphane (5 mg) were added and the reaction heated at 110°C
25 for 30 min, then 140°C for 30 min. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography, eluting with 0-25% methanol in dichloromethane. The appropriate fractions were combined and concentrated to give a brown solid which was dissolved in MeOH:DMSO (1ml, 1:1, v/v) and purified by MDAP (method A). The appropriate fractions were concentrated *in vacuo* to give the title compound as a white
30 solid (30 mg).

LCMS (Method A): Rt 0.57 mins, MH⁺ 441.

Method B

6-Chloro-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-
5 1H-indazole (75.17 g, 150 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (73.1 g, 301 mmol), sodium bicarbonate (37.9 g, 451 mmol), and chloro[2'-(dimethylamino)-2-biphenyl]palladium-(1*R*,4*S*)-bicyclo[2.2.1]hept-2-yl[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]phosphane (8.43 g, 15.03 mmol) were suspended in nitrogen
10 purged 1,4-dioxane (1200 mL) and water (300 mL). The reaction vessel was placed under alternating vacuum and nitrogen five times with overhead stirring, then finally placed under a nitrogen atmosphere and heated to 120°C for 2.5 h.

The reaction mixture was cooled to 45°C and then treated with 2M aqueous sodium hydroxide (376 mL, 752 mmol). After stirring at 45°C overnight (~ 13h), the mixture was
15 cooled to RT and DCM (600 ml) and water (400 ml) were added. The layers were separated and the aqueous re-extracted with DCM:1,4-dioxane (1:1). Brine was added and the mixture filtered through Celite, washing with DCM:1,4-dioxane (1:1). The layers were separated and 2M HCl (1000 ml) added to the organic. The mixture was again filtered through Celite washing with 500 ml 2M HCl keeping the washings separate. The
20 filtrate layers were then separated and the organic layer was washed with the acid washings from the Celite. Layers were separated and the acidic aqueous combined. This was then back-washed with 2x500 ml of DCM; each wash requiring a Celite filtration. The acidic aqueous was then given a final filtration through Celite washing the Celite pad with 150 ml of 2M HCl.

25 The acidic aqueous was transferred to a beaker (5000 ml) and with vigorous stirring 2M NaOH was added to basify the mixture to pH 10-11. The mixture was then extracted using 1,4-dioxane:DCM (1:1) (5 x 500 ml). The combined organics were washed with brine, dried over magnesium sulphate, filtered and evaporated to yield a brown foam that was
30 dried *in vacuo* at 50°C overnight.

This material was split into three batches and each was purified by reverse phase column chromatography (3x 1.9 kg C18 column), loading in DMF/TFA (1:1, 30 ml) then eluting with 3-40% MeCN in Water + 0.25% TFA (Note: Columns 2 & 3 used a different gradient
35 starting with 10% MeCN).

Appropriate fractions were combined, the acetotnitrile removed *in vacuo* and the acidic aqueous basified to pH10 by addition of saturated aqueous sodium carbonate solution to the stirred solution. The resultant solid was collected by filtration, washed with water then dried *in vacuo* at 65°C overnight to give the title compound (28.82 g) as a pale brown foam.

LCMS (Method A): Rt 0.68 mins, MH⁺ 441.

¹H NMR (400MHz, DMSO-d₆) δ = 13.41 (br. s., 1 H), 11.35 (br. s., 1 H), 8.59 (br. s., 1 H), 8.07 (d, J = 1.5 Hz, 1 H), 7.90 (br. s., 1 H), 7.51 - 7.44 (m, 2 H), 7.32 (s, 1 H), 7.27 - 7.21 (m, 2 H), 6.61 - 6.58 (m, 1 H), 3.73 (br. s., 2 H), 2.64 - 2.36 (m, 9 H), 0.97 - 0.90 (m, 6 H)

Method C

Potassium hydroxide (145.6 g) was added to a suspension of 6-(1H-indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1-(phenylsulfonyl)-1H-indazole (300.7 g) and cetyltrimethylammonium bromide (9.3 g) in tetrahydrofuran (6.0 L) and water (30 ml) stirring under nitrogen at ambient temperature. The mixture was heated at reflux for 17 hours and was then cooled to 20-25°C. Ethyl acetate (3.0 L) and water (3.0 L) were added, stirred for 10 minutes and then separated. The organic layer was extracted with hydrochloric acid (1M, 1 x 3.0 L, 2 x 1.5L) and the acidic extracts combined and basified to ~pH 8 by the addition of saturated sodium carbonate solution (2.1 L). After ageing for 30 minutes the resultant suspension was filtered, washed with water (300 ml) and the solid dried under vacuum at 65°C to give the title compound as a pale yellow solid (127.9 g).

LCMS (Method B): Rt 2.44 min, MH⁺ 441.

Method D

All weights, volumes and equivalents are relative to 2-(6-(1H-indol-4-yl)-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole.

Potassium hydroxide (0.483 wt, 5 eq, 242 g) is added to a suspension of 2-(6-(1H-indol-4-yl)-1-(phenylsulfonyl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (1 wt, 1 eq, 501 g), and CTAB (cetyltrimethylammonium bromide) (0.031 wt, 0.05 eq, 15.5 g) in 2-methyltetrahydrofuran (10 vols, 5.01 L) then heated at reflux (79°C) for at least 4 hrs until the reaction is complete. The mixture is cooled to 50 °C and washed at 50 °C with water (2 x 10 vols, 2 x 5 L). The solution is diluted with 2-methyl tetrahydrofuran (5 vols, 2.5 L) and filtered while at 50 °C to remove precipitated palladium residues. The organic solution is then distilled (100 mbar, 20°C) down to 2 vols (1 L), diluted with 2-methyl tetrahydrofuran (1 vol, 0.5 L) and 3-pentanone (3 vols, 1.5 L) and distilled (100 mbar, 30

°C) down to 2 vols (1 L). The solution is again diluted with 3-pentanone (3 vols, 1.5 L) and distilled (80 mbar, 25°C) down to 2 vol (1 L). The solution is again diluted with 3-pentanone (3 vols (1.5 L) and distilled (100 mbar, 30°C) down to 3 vols (1.5 L). The suspension is cooled to 20°C over 1 hr and aged at 20 °C for at least 2 hrs. The product is
5 filtered under vacuum, washed with 3-pentanone (1 vol, 0.5 L) and dried under vacuum at 60 °C to afford 2-(6-(1H-indol-4-yl)-1H-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole as a tan solid.

PREPARATION OF THE POLYMORPH OF COMPOUND A

10 6-(1H-Indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1H-indazole (25g) was dissolved in dimethylformamide (DMF, 240ml) and filtered (porosity 4 filter). DMF (10ml) was used as a line rinse to wash the glassware and filtered. The material was chromatographed in 14 x 17-18ml injections and a final injection of ca. 10ml.
15 Fractions containing 6-(1H-indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1H-indazole were evaporated under vacuum at temperatures up to 40°C. The resulting solid was filtered, washed with water (100ml) and dried at 60°C under vacuum overnight.

20 Chromatography conditions:

HPLC system Varian SD-1

Column: Phenomenex Luna C18(II), 50x243mm

Eluent A: 0.1M ammonium acetate adjusted to pH 8.0 with 0.88 ammonia

Eluent B: Acetonitrile

25 Detector: 350nm range 12

Injection: approx 17-18ml of solution in DMF (1g per 10ml DMF)

NMR concordant with expected spectrum:

NMR (400MHz, DMSO d₆): 13.42 (br s, 1H), 11.35 (br s, 1H), 8.60 (s, 1H), 8.08 (d J = 1.2Hz, 1H), 7.91 (s, 1H), 7.48 (m, 2H), 7.32 (s, 1H), 7.24 (m, 2H), 6.61 (s, 1H), 3.73 (s,
30 1H), 2.58 (m, 1H), 2.45 (br s, 4H), 0.94 (d J = 6.6Hz, 6H)

Broad singlet at 2.45ppm is likely to contain some of the remaining aliphatic protons; however the integration is unlikely to be accurate due to the overlap with the DMSO (d₅) peak. The remaining aliphatic protons are likely to be underneath the DMSO (d₅) peak.

35 PREPARATION OF THE SALTS OF COMPOUND A AND POLYMORPHS THEREOF

Tosylate

6-(1*H*-Indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1*H*-indazole (1.5013g) was suspended in acetonitrile (10ml) and stirred. Separately, p-toluenesulfonic acid monohydrate (679.5mg, 1.05eq) was dissolved in acetonitrile (5ml) and added. Immediately a gummy precipitate formed and was sonicated and triturated to mobilise the solid mass. The suspension was seeded with crystalline tosylate salt and allowed to stir overnight. The solids were isolated and dried under vacuum at 50°C.

NMR concordant with expected spectrum:

NMR (400MHz, DMSO d6): 13.45 (br s, 1H), 11.37 (br s, 1H), 8.92 (br s, 1H), 8.64 (s, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 7.48 (m, 4H), 7.43 (s, 1H), 7.24 (m, 2H), 7.12 (d J = 8.1Hz, 2H), 6.61 (s, 1H), 3.97 (s, 2H), 3.42 (m, 3H), 3.13 (m, 4H), 2.54 (m, 1H), 2.28 (s, 3H), 1.23 (d J = 6.4Hz, 6H)

Aliphatic protons not seen here are likely to be residing under the DMSO (d5) peak

The crystalline tosylate salt seed may be prepared by the following method:

6-(1*H*-Indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1*H*-indazole (0.1003g) was suspended in acetonitrile (1.5ml) and stirred. Separately, toluenesulfonic acid monohydrate (45.6mg, 1.05eq) was dissolved in acetonitrile (0.5ml) and added to the suspension of 6-(1*H*-indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1*H*-indazole. A gummy precipitate formed which was allowed to stir for 10mins. The sample was heated to approximately 50°C and sonicated with little visual effect. The solids were manually agitated with a spatula to mobilise them and stirred for 4 days at room temperature. The solids were filtered and sucked dry.

Hemi fumarate

6-(1*H*-Indol-4-yl)-4-(5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-1,3-oxazol-2-yl)-1*H*-indazole (1.5014g) and fumaric acid (217.2mg, 0.56eq) were suspended in IMS (15ml) and stirred at room temperature overnight. The slurry was filtered and sucked dry before being dried under vacuum at 50°C overnight.

NMR concordant with expected spectrum:

NMR (400MHz, DMSO d6): 13.47 (br s, 1H), 11.37 (br s, 1H), 8.60 (s, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.48 (m, 2H), 7.34 (s, 1H), 7.24 (m, 2H), 6.61 (s, 1H), 6.56 (s, 1H), 3.76 (s, 2H), 2.74 (m, 1H), 2.58 (br s, 7H), 1.00 (d J = 6.6Hz, 6H)

Broad singlet at 2.58ppm is likely to contain remaining aliphatic protons; however the integration is unlikely to be accurate due to the overlap with the DMSO (d5) peak.

Hemi succinate

Method A

Industrial methylated spirits (IMS, 1ml) was added to 6-(1*H*-indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1*H*-indazole (0.1006g) and stirred. Separately succinic acid (28.3mg, 1.05eq) was dissolved in IMS (1ml) and then added to the 6-(1*H*-indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1*H*-indazole suspension and stirred at room temperature over the weekend (ca. 72hrs). The solids were isolated by filtration and washed with IMS (ca. 1ml) before being dried under vacuum at 50°C.

NMR concordant with expected spectrum:

NMR (400MHz, DMSO *d*₆): 13.42 (br s, 1H), 11.36 (br s, 1H), 8.61 (s, 1H), 8.09 (d *J* = 1.2Hz, 1H), 7.92 (s, 1H), 7.48 (m, 2H), 7.34 (s, 1H), 7.25 (m, 2H), 6.62 (s, 1H), 3.76 (s, 2H), 2.67 (m, 1H), 2.40 (s, 2H), 0.98 (d *J* = 6.6Hz, 6H)

Aliphatic protons not seen here are likely to be residing under the DMSO (*d*₅) peak

Method B

All weights, volumes and equivalents are relative to 2-(6-(1*H*-indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole.

A mixture of 2-(6-(1*H*-indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole (1 wt, 440 g) and succinic acid (0.14 wt, 0.52 eq, 61.6 g) is stirred in DMSO (2.9 vol, 1.28 L) at 20-25°C. The resulting clear solution is transferred to a crystallising vessel via a 5µm Dornick hunter in-line filter, then the line is washed with further DMSO (0.1 vol, 44 ml). To the solution is added methanol (1 vol, 440 ml) over 10 mins via the previous filter, followed by a slurry of 2-(6-(1*H*-indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole hemi succinate (0.005 wt, 2.2 g) in methanol (0.05 vol, 22 ml). The suspension is aged at 20-25°C for 3 hrs, then methanol (3 vols, 1.32 L) is added via the previous filter over ca 1 hr and the slurry is further aged at this temperature for at least 16 hrs. The resulting solids are filtered, washed with pre-filtered methanol (2 x 10 vols, 2 x 4.4 L) before being sucked dry for 0.5 hr. The batch is dried *in vacuo* at 50-55 °C to constant probe temperature to afford 2-(6-(1*H*-indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropylpiperazin-1-yl)methyl)oxazole, hemisuccinic acid salt, as an off-white solid.

Water content

The water content of the hemi succinate salt was determined by a coulometric Karl Fischer titration method aligned with USP <921> Water Determination (Method 1c), BP Determination of Water (Method III), Ph. Eur. Water: Micro Determination (Method

2.5.32) and JP Water Determination (Karl Fischer Method). Based on an average of 2 measurements, a water content of 1.8% w/w was observed using the coulometric solid (oven) technique with Hydranal Coulomat AK reagent and an oven temperature set to 110°C.

5

X-RAY POWDER DIFFRACTION (XRPD) FOR THE POLYMORPH OF COMPOUND A AND THE POLYMORPHS OF THE SALTS OF COMPOUND A

The data were acquired on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60 using an X'Celerator detector. The acquisition conditions were: radiation: Cu K α , generator tension: 40 kV, generator current: 45 mA, start angle: 2.0° 2 θ , end angle: 40.0° 2 θ , step size: 0.0167° 2 θ , time per step: 31.75 seconds. The sample was prepared by mounting a few milligrams of sample on a silicon wafer (zero background) plate, resulting in a thin layer of powder.

15

Polymorph of Compound A

The XRPD data are shown in Figure 1.

Characteristic XRPD angles and d-spacings for the solid state form are summarised in Table 1. Peak positions were measured using Highscore software.

20

2θ / °	d-spacing / Å
8.0	11.0
9.0	9.9
9.6	9.2
10.4	8.5
12.5	7.1
13.3	6.7
14.4	6.1
16.5	5.4
19.3	4.6
19.7	4.5
20.3	4.4
21.6	4.1
22.7	3.9
24.4	3.6

Table 1

Polymorph of the tosylate salt of Compound A

The XRPD data are shown in Figure 2.

- 5 Characteristic XRPD angles and d-spacings for the solid state form are summarised in Table 2. Peak positions were measured using Highscore software.

2θ / °	d-spacing / Å
6.3	13.9
9.3	9.5
11.3	7.9
11.6	7.6
12.7	7.0
13.2	6.7
14.2	6.2
15.6	5.7
15.8	5.6
17.1	5.2
18.7	4.7
19.5	4.5
20.3	4.4
21.0	4.2
22.3	4.0
25.7	3.5

Table 2

10

Polymorph of the hemi fumarate salt of Compound A

The XRPD data are shown in Figure 3.

- 15 Characteristic XRPD angles and d-spacings for the solid state form are summarised in Table 3. Peak positions were measured using Highscore software.

2θ / °	d-spacing / Å
6.9	12.7
8.7	10.2
13.8	6.4
14.4	6.1

17.6	5.0
18.0	4.9
18.9	4.7
21.1	4.2
22.6	3.9
25.8	3.5

Table 3**5 Polymorph of the hemi succinate salt of Compound A**

The XRPD data are shown in Figure 4.

Characteristic XRPD angles and d-spacings for the solid state form are summarised in Table 4. Peak positions were measured using Highscore software.

10

2θ / °	d-spacing / Å
7.2	12.3
13.2	6.7
14.0	6.3
18.0	4.9
19.1	4.6
19.7	4.5
20.7	4.3
23.2	3.8
26.3	3.4

Table 4

What is claimed is

1. 6-(1H-Indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1H-indazole hemi succinate.
2. A polymorph of the hemi succinate salt of 6-(1H-indol-4-yl)-4-(5-([4-(1-methylethyl)-1-piperazinyl]methyl)-1,3-oxazol-2-yl)-1H-indazole characterized in that it provides an XRPD pattern comprising peaks ($^{\circ}2\theta$) at about 7.2, about 13.2 and/or about 14.0.
3. A polymorph according to claim 2 characterized in that it provides an XRPD pattern comprising peaks substantially as set out in Table 4.
4. A pharmaceutical composition comprising a salt as defined in claim 1 and one or more pharmaceutically acceptable excipients.