(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2008 (19.06.2008)

PCT

(10) International Publication Number
WO 2008/071665 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *A61P 25/00* (2006.01)
A61K 31/415 (2006.01)

(21) International Application Number:
PCT/EP2007/063620

(22) International Filing Date:
10 December 2007 (10.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/869,569 12 December 2006 (12.12.2006) US

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PATEL, Vipulkumar, Kantibhai** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **WALKER, Ann, Louise** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

(74) Agents: **SHORE, Andrew, David** et al.; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(54) **Title:** A NICOTINAMIDE DERIVATIVE USEFUL AS P38 KINASE INHIBITOR

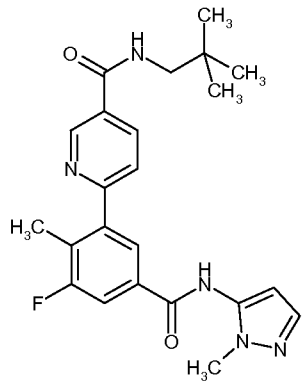
(57) **Abstract:** This invention relates to a nictonamide derivative and its use as a pharmaceutical, particularly as a p38 kinase inhibitor, for the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

WO 2008/071665 A1

A NICOTINAMIDE DERIVATIVE USEFUL AS P38 KINASE INHIBITOR

This invention relates to *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide and its use as a pharmaceutical, particularly as a p38 kinase inhibitor, for the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

WO 03/068747 describes nicotinamide derivatives that are inhibitors of p38 kinase. However, according to the present invention it has now been found that *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide, namely



has potent p38 kinase inhibitory activity together with a pharmacokinetic profile which may make it particularly suitable for development as a pharmaceutical.

According to the invention there is provided *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide, or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention there is provided *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide.

As used herein, the term “pharmaceutically acceptable” means a compound which is suitable for pharmaceutical use. Salts and solvates of compound of the invention which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the compound of the invention and its pharmaceutically acceptable salts and solvates.

The invention encompasses all pharmaceutically acceptable salts, solvates, or prodrugs, of the compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) the compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger’s Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and

Practice, which is incorporated herein by reference to the extent of teaching such derivatives.

The compound of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Salts of the compound of the present invention may, for example, comprise acid addition salts resulting from reaction of an acid with a basic nitrogen atom present in the compound of the invention. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compound of this invention. Suitable addition salts are formed from acids which form non-toxic salts and examples are benzenesulfonate, bisulfate, camsylate, edisylate, estolate, esylate, glutamate, hydrobromide, hydrochloride, hydroiodide, isethionate, maleate, mesylate, napsylate, nitrate, oxalate, phosphate, sulfate, tosylate and trifluoroacetate.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates”. As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. In one embodiment, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. In one embodiment, the solvent used is water. A complex with water is known as a “hydrate”. Solvates of the compound of the invention are within the scope of the invention.

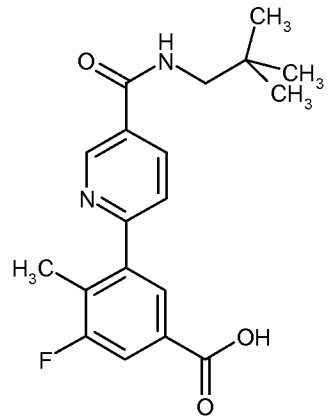
As used herein, the term “prodrug” means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series; Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; and in D. Fleisher, S. Ramon and H. Barbra “Improved oral drug delivery: solubility limitations overcome by the use of prodrugs”, Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

Prodrugs are any covalently bonded carriers that release *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

Furthermore, some of the crystalline forms of the compound according to the invention may exist as polymorphs, which are included in the present invention.

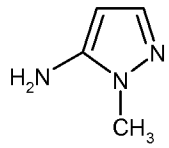
The compound of this invention may be made by a variety of methods, including standard chemistry. Illustrative general synthetic methods are set out below and then the specific compound of the invention is prepared in the working Examples.

N-(2,2-Dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide may be prepared by reacting a compound of formula (I)



(I)

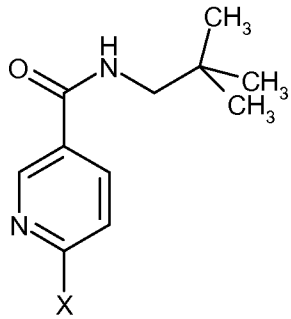
with an amine of formula (II)



(II)

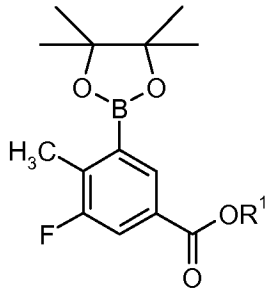
under suitable amide forming conditions, for example in the presence of a base such as DIPEA, HATU and a solvent such as DMF.

A compound of formula (I) may be prepared by reacting a compound of formula (III)

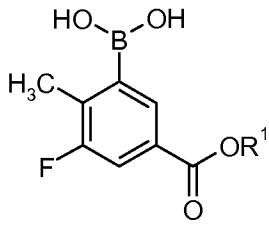


(III)

in which X is halogen, for example bromine or chlorine,
with a compound of formula (IVA) or (IVB)



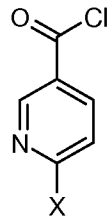
(IVA)



(IVB)

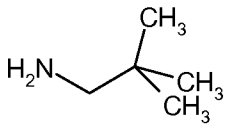
in which R^1 is a protecting group, for example C_{1-6}alkyl such as methyl,
in the presence of a catalyst, for example tetrakis(triphenylphosphine)palladium, and removing the protecting group R^1.

A compound of formula (III) may readily be prepared by reacting a compound of formula (V)



(V)

in which X is as hereinbefore defined,
with an amine compound of formula (VI)

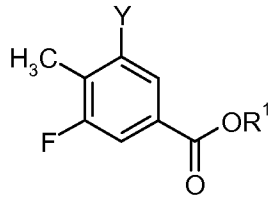


(VI)

under amide forming conditions.

Suitable amide forming conditions are well known in the art and include treating a solution of the compound of formula (V) in for example acetone or dichloromethane, with an amine of formula (VI) in the presence of potassium or sodium carbonate.

A compound of formula (IVA) may be prepared by reacting a compound of formula (VII)

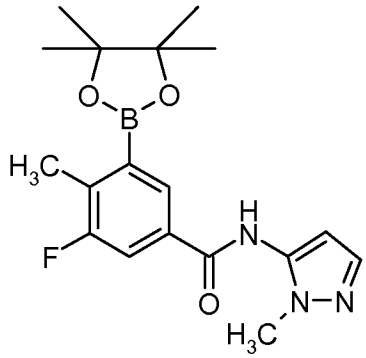


(VII)

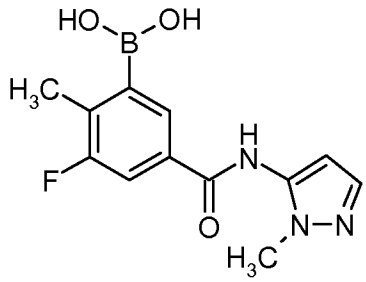
in which R^1 is as hereinbefore defined and Y is halogen, for example bromine or iodine, with bis(pinnacolato)diboron, $Pd(dppf)Cl_2$ and potassium acetate in a solvent such as DMF.

A compound of formula (IVB) may be prepared by, for example, reacting a compound of formula (VII) as hereinbefore defined with n-butyllithium and triisopropylborate in a solvent such as THF.

Alternatively, *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide may be prepared by reacting a compound of formula (III) as hereinbefore defined with a compound of formula (VIIIA) or (VIIIB)



(VIIIA)

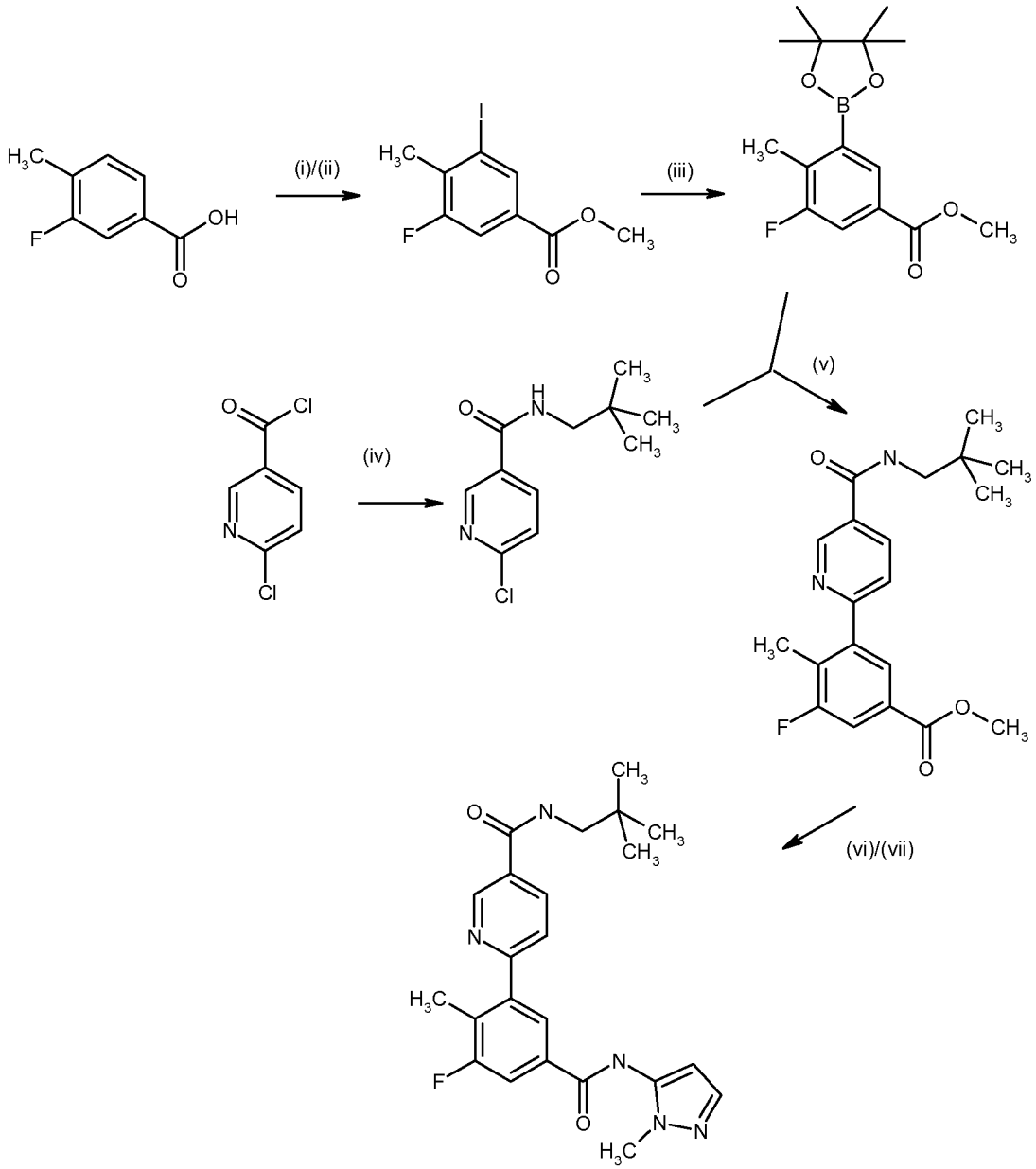


(VIIIB)

in the presence of a catalyst, for example tetrakis(triphenylphosphine)palladium.

The compounds of formula (VIIIA) and (VIIIB) may be prepared in an analogous manner to the compounds of formula (IVA) and (IVB).

For example, one method for preparing *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide comprises the reactions set out in Scheme 1 below.



Scheme 1

i. Trifluoromethanesulphonic acid, iodosuccinimide.

ii. Thionyl chloride, triethylamine, methanol.

iii. Bis(pinnacolato)diboron, $Pd(dppf)Cl_2$, KOAc, DMF.

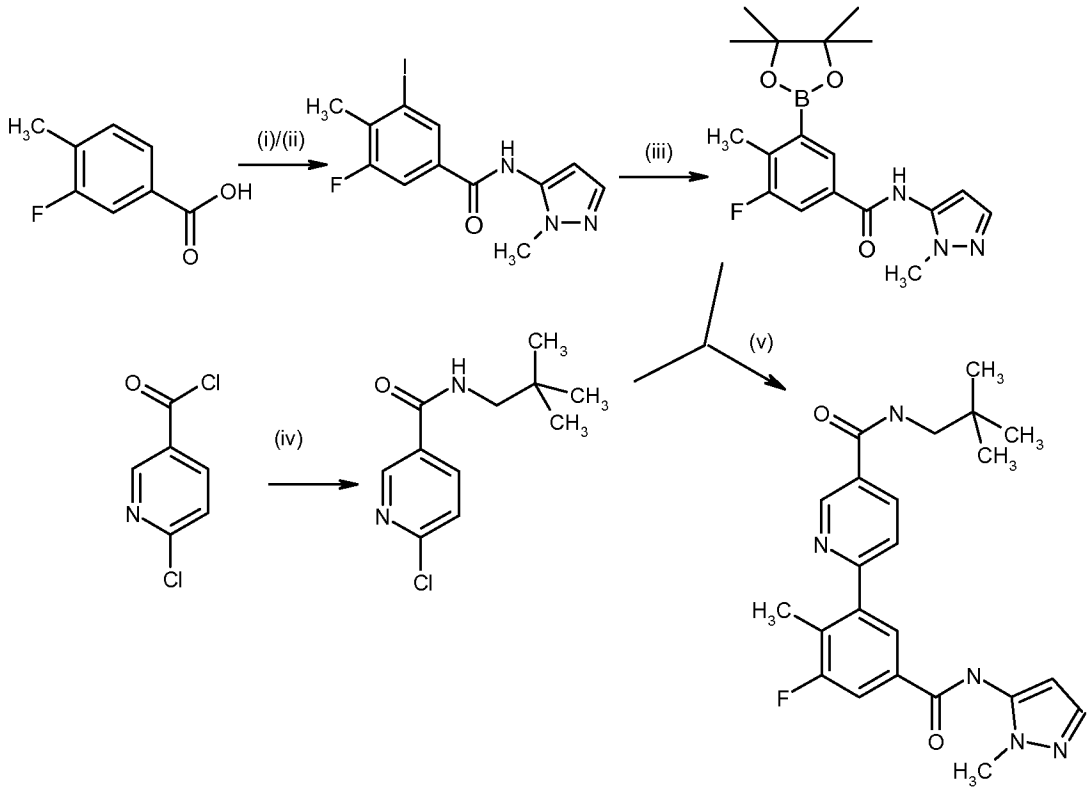
iv. $(CH_3)_3CCH_2NH_2$, Na_2CO_3, DCM.

v. $NaHCO_3$, tetrakis(triphenylphosphine)palladium, propan-2-ol.

vi. 2M NaOH.

vii. DIPEA, HATU, 1-methyl-1*H*-pyrazol-5-amine, DMF.

For example, a further method for preparing *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide comprises the reactions set out in Scheme 2 below.



Scheme 2

i. Trifluoromethanesulphonic acid, iodosuccinimide.

ii DIPEA, HATU, 1-methyl-1*H*-pyrazol-5-amine, DMF or thionyl chloride, K_2CO_3, DCM.

iii. Bis(pinnacolato)diboron, Pd(dppf)Cl_2, KOAc, DMF.

iv. $(CH_3)_3CCH_2NH_2$, Na_2CO_3, DCM.

v. $NaHCO_3$, tetrakis(triphenylphosphine)palladium, propan-2-ol.

Those skilled in the art will appreciate that in the preparation of the compound of the invention or a derivative thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl

(Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate.

Whilst it is possible for the compound of the present invention to be administered as the raw chemical, the compound and its pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions eg when the agent is in admixture with a suitable pharmaceutical excipient, diluent and/or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers. The excipient, diluent or carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deletrious to the receipient thereof.

According to a further aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof, in association one or more pharmaceutically acceptable excipients, diluents and/or carriers for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by an inhibitor of p38 kinase.

The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, diluent and/or carrier (including combinations thereof).

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient, diluent and/or carrier.

The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable excipient, diluent or carrier. Acceptable carriers or diluents for therapetic use are well known in the pharmaceutical art, and are described, for example, in Remington’s Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical excipient, diluent or carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice.

The pharmaceutical compositions may comprise as – or in addition to – the excipient, diluent or carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s) and solubilising agent(s).

Preservatives, stabilisers, dyes and even flavouring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

For some embodiments, the agent of the present invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e. g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO 91/11172, WO 94/02518 and WO 98/55148.

The compound of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see WO 02/00196 (SmithKline Beecham).

There may be different composition/formulation requirements dependent on the different delivery systems. By way of example, the pharmaceutical composition of the present invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestable solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by both routes.

Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit though the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration the compositions may

be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

The routes for administration (delivery) include, but are not limited to, one or more of: oral (e. g. as a tablet, capsule, or as an ingestable solution), topical, mucosal (e. g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e. g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural and sublingual. It is to be understood that if the composition comprises more than one active component, then those components may be administered by different routes.

The compound of the invention and its pharmaceutically acceptable salts and solvates may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation, or for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compound of the invention and its pharmaceutically acceptable derivatives. In one embodiment, the agents of the present invention are delivered systemically such as orally, buccally or sublingually. In a further embodiment, the method of administration, and corresponding formulation, is oral administration.

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), ovules, pills, powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. The tablets may also contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (for example corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Examples of excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound 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 compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers,

preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation 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.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compound of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compound of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compound of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, for example 0.5 to 90% of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

If the compound of the present invention is administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques. For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or

emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation optionally with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (for example to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

The compositions of the present invention may be administered by direct injection.

The compound of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compound of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For application topically to the skin, the agent of the present invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, it can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For administration by inhalation the compound according to the invention is conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as tetrafluoroethane or heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to

deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Alternatively, the compound of the present invention can be administered in the form of a suppository or pessary, or it may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder.

The compound of the present invention may also be administered by the pulmonary or rectal routes. It may also be administered by the ocular route. For ophthalmic use, the compound can be formulated as a micronised suspension in isotonic, pH adjusted, sterile saline, or as a solution in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, it may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in humans is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. For example, in most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0. 1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the activity of the specific compound to be employed, the metabolic stablity and length of action of that compound, age, weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, severity of the particular condition and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial. For oral and parenteral administration to humans, the daily dosage level of the agent may be in single or divided doses.

In another aspect, the present invention provides *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof, for use in therapy.

The compound of the present invention is an inhibitor of the serine/threonine kinase p38 and is therefore also an inhibitor of cytokine production which is mediated by

p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compound of the invention may be selective for one or more of the isoforms of p38, for example p38α, p38β, p38γ and/or p38δ. In one embodiment, the compound of the invention selectively inhibits the p38α and p38β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1H-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof. The compound may be administered as a single or polymorphic crystalline form or forms, or an amorphous form.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of the compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, or an amorphous form.

The present invention treats these conditions by providing a therapeutically effective amount of the compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments. It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

The compound of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compound may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys and humans. In one embodiment, the mammal is a human.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, depression, anxiety, sleep disorders, schizophrenia, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer, prostatic cancer or multiple mylenoma, which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, chronic pulmonary inflammation, chronic obstructive pulmonary disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from depression (including bipolar disorders and mood disorders), anxiety (including panic attacks, phobias and obsessive compulsive disorder), sleep disorders (including hypersomnia, narcolepsy and circadian rhythm disorders) or schizophrenia (including the sub-types paranoid type, disorganised type, catatonic type, undifferentiated type and residual type) which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt hereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from chronic obstructive pulmonary disease which comprises administering to said subject a therapeutically effective amount of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides the use of *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

N-(2,2-Dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide and its derivatives may be employed

alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. The invention thus provides, in a further aspect, a combination comprising the compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

The compound of the invention or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art. The amounts of the compound of the invention or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of the compound of the invention required for treatment will vary with the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian.

In rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Suitable examples of pharmaceutically active agents which may be employed in combination with the compound of the invention and its salts and solvates for rheumatoid arthritis therapy include: immunosuppresants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNFα agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychoroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

In COPD therapy, combination with other therapeutically active agents such as a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid), an anticholinergic agent or an antiinfective agent is envisaged. Suitable examples of pharmaceutically active agents which may be employed in combination with the compound of the invention and its salts and solvates for COPD therapy include: β_2-adrenoreceptor agonists such as salmeterol (*e.g.* as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol; anti-inflammatory steroids such as fluticasone propionate and budesonide; anticholinergic

agents such as ipratropium bromide, oxitropium bromide or tiotropium bromide; non-steroidal anti-inflammatory (NSAID) drugs such as a leukotriene antagonist (e.g. montelukast), an iNOS inhibitor, a tryptase inhibitor, an elastase inhibitor, a beta-2 integrin antagonist, an adenosine a2a agonist, a chemokine antagonist such as a CCR3 antagonist and a 5-lipoxygenase inhibitor; or an antiinfective agent such as an antibiotic or an antiviral.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

LCMS was conducted on a column (3.3cm x 4.6mm ID, 3um ABZ+PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm. Solvent A: 10mM Aqueous ammonium acetate + 0.1% formic acid. Solvent B: 95% Acetonitrile + 0.05% formic acid. Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min.

Intermediate 1: 3-Fluoro-5-iodo-4-methylbenzoic acid – preparation 1

3-Fluoro-4-methylbenzoic acid (182g) was added to trifluoromethanesulphonic acid (1.12l) and the solution cooled to -20°C under nitrogen. Iodosuccinimide (266g) was added in portions over 75min, maintaining a reaction temperature of -18 to -19°C, and the reaction was then stirred at -20°C for 4hours. Iodosuccinimide (54.8g) was added portionwise and the reaction stirred at -20°C overnight. Iodosuccinimide (19g) added before stirring at -20°C for a further 24hours. The reaction was warmed to -5°C and the suspension poured into a stirred mixture of ice (3kg) and sodium thiosulphate solution (10%). The mixture was filtered and the solid partially dried on the sinter. The solid was partitioned between ethyl acetate (5l) and sodium thiosulphate solution (10%, 1.5l), the organic washed with sodium thiosulphate solution (10%) and dried (sodium sulphate), before concentrating *in vacuo* to ca. 600ml. The resulting slurry was allowed to stand for 4hours, filtered, the residue washed with ethyl acetate and dried, to give 3-fluoro-5-iodo-4-methylbenzoic acid (215g). LCMS: $[M-H]^-$ 279, retention time 3.75min.

Intermediate 1: 3-Fluoro-5-iodo-4-methylbenzoic acid – preparation 2

3-Fluoro-4-methylbenzoic acid (150.3g) was added to trifluoromethanesulphonic acid (1.05l) and the solution cooled to -22°C under nitrogen. Iodosuccinimide (200.8g) was added in portions over 60min, maintaining a reaction temperature of -19 to -22°C, and the reaction was then stirred at -20°C for 2.5hours. Iodosuccinimide (51.0) was added portionwise over 30min and the reaction stirred at -20°C overnight. Iodosuccinimide (19g) added before stirring at -20°C for a further 17hours. A further portion of iodosuccinimide

(28.2g) and stirring continued at -20°C for a further 24hours. The reaction was poured into a stirred mixture of ice (3kg) and 10% sodium thiosulphate solution (1.5L). The mixture was filtered, washed with water and the solid dried on the sinter. The solid was partitioned between ethyl acetate (5l) and sodium thiosulphate solution (10%, 1.5l). The organic layer was washed with sodium thiosulphate solution (10%, 1.5l) and the aqueous phases back extracted with ethyl acetate. The organic phases were combined and drwashed with brine and dried (magnesium sulphate), before concentrating *in vacuo* to approximately 750ml. The resulting mixture was allowed to stand for 24hours, filtered, the residue washed with ethyl acetate and dried, to give 3-fluoro-5-iodo-4-methylbenzoic acid (126.5g). LCMS: $[M-H]^-$ 279, retention time 3.6min.

Intermediate 2: Methyl 3-fluoro-5-iodo-4-methylbenzoate

A mixture of 3-fluoro-5-iodo-4-methylbenzoic acid (28g) and thionyl chloride (40ml) was heated at reflux under nitrogen for 3 hours, before the reaction was allowed to cool and the excess thionyl chloride evaporated *in vacuo,* azeotroping with DCM (3x50ml). The remaining oil was dissolved in DCM (50ml) and added dropwise with stirring to a solution of dry methanol (30ml) and triethylamine (20ml) in DCM (150ml) with ice/water cooling. The reaction was stirred under nitrogen at room temperature overnight, diluted with DCM (100ml), then washed with water (200ml), hydrochloric acid (2M, 2x 200ml), water (200ml) and brine (100ml). The organic phase was dried (magnesium sulphate) and reduced to dryness under vacuum. The residual oil was purified by chromatography on a silica gel column eluting with DCM / hexane (10-20% DCM) to give, after evaporation of the solvent *in vacuo,* methyl 3-fluoro-5-iodo-4-methylbenzoate.
NMR: $CDCl_3$ δH 8.27,(1H, s), 7.65,(1H, dd), 3.92,(3H, s), 2.41,(3H, d).

Intermediate 3: Methyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

Potassium acetate (50.5g) was added to a solution of methyl 3-fluoro-5-iodo-4-methylbenzoate (30.3g) in DMF (300ml). Bis(pinnacolato)diboron (39.4g) was added to the mixture and the mixture degassed. $Pd(dppf)Cl_2$ (0.85g) was added to the mixture and the reaction heated at 80-85°C for 18 hours, allowed to cool and the DMF evaporated *in vacuo*. The residue was partitioned between ethyl acetate (400ml) and water (250ml) and the aqueous extracted with ethyl acetate (300ml). The combined organic phases were washed with hydrochloric acid (2M, 3x150ml), aqueous lithium chloride (10%, 2x200ml) and brine (200ml) before drying over magnesium sulphate. The ethyl acetate was evaporated under vacuum and the residue triturated with DCM (100ml), the white precipitate was filtered off and washed with DCM. The solid was recrystallised from acetonitrile to give methyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (5.42g). The DCM fraction was reduced to dryness *in vacuo* and triturated with DCM (70ml), to give after filtration and drying a further 3.32g of methyl 3-fluoro-4-

methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate. The DCM fraction was further purified by flash chromatography on silica, eluting with 10% ethyl acetate in cyclohexane. The purest fractions were combined to further give quantities of methyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (4.2g). Other product fractions were combined and evapotated and the resulting solid recrystallised from acetonitrile (200ml) to give a further 14.7g of methyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate. (combined yield 27.6g).
LCMS $[MNH_4]^+$ 312, retention time 3.84min.

Intermediate 4: 6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide – preparation 1

A solution of neopentylamine (125ml) in DCM (400ml) was treated with sodium carbonate (175g) and the stirred miture cooled to 5°C. A suspension of 6-chloronicotinyl chloride (175g) in DCM (400ml) was added in portions maintaining a temperature below 25°C. The mixture was stirred for 1hour and then allowed to warm to room temperature and stirred for a further 2hours. The reaction was partitioned between water and DCM. The aqueous was extracted with DCM and the combined organic phases washed with brine, dried (sodium sulphate) and reduced to dryness under vacuum to give 6-chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (216.9g).
LCMS; MH+ 227/229, retention time 2.67min.

Intermediate 4: 6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide – preparation 2

A solution of neopentylamine (35ml) in DCM (50ml) was added over 20 minutes to a stirred mixture of sodium carbonate (50g) and 6-chloronicotinyl chloride (50.4g) in DCM (200ml) at 0°C. A hydrochloride salt of the amine was formed in the addition funnel amd this solid was supended in further aliquot of DCM and added to the reaction mixture and the mixture allowed to warm to room temperature. A further portion of neopentylamine (5mL) was added and stirring continued for a further 2 hours. Water was added to the reaction mixture, the organic phase separated and twice extracted with 2N sodium hydroxide. The aqueous phases were back extracted with dichloromethane and then the organic extracts combined and revaporated to give 6-chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (58.5g). LCMS; MH+ 227/229, retention time 2.72min.

Intermediate 5: Methyl 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoate

6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (3.0g), methyl 3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3.89g), tetrakis(triphenylphosphine)palladium (305mg) and sodium hydrogen carbonate (1M,

41ml) were mixed in propan-2-ol (55ml) and the degassed reaction mixture heated at 85°C under nitrogen for 17hours. The reaction mixture was stirred at room temperature for 24hours, before addition of sodiumhydrogen carbonate (1M, 15ml). The reaction mixture was concentrated *in vacuo*, the residue partitioned between ethyl acetate and sodiumhydrogen carbonate (1M). The aqueous phase was neutralised with hydrochloric acid (2M) and the white precipitate of 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoic acid filtered off and dried (1.12g). The organic phase was absorbed onto silica and purified by chromatography on silica eluting with an ethyl acetate / cyclohexane gradient. The product fractions were combined and reduced to dryness under vacuum to give methyl 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoate (2.12g) as a cream solid.
LCMS: MH^+ 359, retention time 3.28min.

Intermediate 6: 3-(5-{[(2,2-Dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoic acid

Aqueous sodium hydroxide (2M, 10ml) was added to a solution of methyl 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoate (2.12g) in methanol (15ml) and the reaction stirred at room temperature overnight. The solvents were evaporated *in vacuo*, the residue partitioned between sodium hydroxide solution (2M) and DCM. The aqueous layer was neutralised with hydrochloric acid (2M) and the precipitate filtered off and dried to give 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoic acid as a white solid (1.857g).
LCMS: MH^+ 3-45, retention time 3.15min.

Intermediate 7: 3-Fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide – preparation 1

DIPEA (9.3ml) and HATU (8.17g) were added to a solution of 3-fluoro-5-iodo-4-methylbenzoic acid (5.08g) in DMF (95ml) and the mixture stirred for 10min at room temperature. 2-methyl-3-aminopyrazole (2.23g) was added to the reaction and stirring continued overnight. The solvent was evaporated from the reaction mixture *in vacuo*, the residue applied to an SPE cartridge (Si, 50g) and eluted with an ethyl acetate / cyclohexane gradient (0-100% ethyl acetate), then methanol and acetone. The pure product fractions were combined, reduced to dryness *in vacuo* The less pure fractions were combined, evaporated and dissolved in methanol. Pure 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide remained as undissolved white solid; the solution was filtered through two SPE cartridges (aminopropyl 10g) and cartdriges washed with methanol. The filtrate and washings were evaporated and combined the 'pure' prduct fractions and this mixture recrystallised from methanol to give further amounts of 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide The methanolic and acetone fraction from the silica SPE purification above were filtered through an SPE (aminopropyl, 20g and 10g), reduced to dryness *in vacuo* and the residue triturated with methanol to

give 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide. The second and third batches of the required compound were combined to give 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide as an off-white solid (5.16g).

NMR: D_6-DMSO δH 10.41,(1H, s), 8.28,(1H, s), 7.78,(1H, d), 7.39,(1H, s), 6.23,(1H, s), 3.69,(3H, s), 3.33,(3H, s).

Intermediate 7: 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide – preparation 2

A mixture of 3-fluoro-5-iodo-4-methylbenzoic acid (28.9g) and thionyl chloride (30ml) was heated under nitrogen at 100ºC for 2.5 hours. The reaction mixture was a pale yellow solution with a small quantity of floating solid. Thionyl chloride was evaporated in vacuo and the residual oil azeotroped with toluene. The oil was dissolved in DCM (60ml), filtered and added over approximately 5 minutes to a mixture of 2-methyl-3-aminopyrazole (10g), potassium carbonate (20.4g) in DCM (100ml). The reaction mixture was stirred at room temperature overnight. The solvent had evaporated so the residue was resuspended in DCM (150ml) and diisopropylethylamine (18ml) added. The reaction mixture was stirred for 45 minutes to give a yellow solution. It was then partitioned between ethyl acetate and water. An aqueous suspension was formed and this was extracted four times with ethyl acetate; the combined organic fractions washed with water, 2N hydrochloric acid, water and twice with brine. The organic solution was dried with anhydrous magnesium sulphate, concentrated to dryness in vacuo and the resulting solid triturated with diethyl ether and dried at 40ºC under vacuum to give 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide (28.33g). LCMS MH^+ 360, retention time 3.13 min.

Intermediate 8: 3-Fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide – preparation 1

3-Fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide (4.32g), bis(pinnacolato)diboron (4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane 9.42g), Pd(dppf)Cl_2 (210mg) and potassium acetate (3.84g) were mixed in dry DMF (17ml), the mixture degassed and then heated at 85°C under nitrogen for 18hours. DMF was removed in vacuo and the residue dissolved in ethyl acetate and the solution absorbed onto silica. The solid was applied to SPE cartridge(Si, 50g), eluting with an ethyl acetate / cyclohexane gradient (0-100% ethyl acetate). The pure product fractions were reduced to dryness *in vacuo* and the residue triturated with water to give 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide as a beige solid (320mg).

NMR: D_6-DMSO δH 10.39,(1H, b), 8.07,(1H, s), 7.86,(1H, d), 7.39,(1H, d), 6.22,(1H, s), 3.68,(3H, s), 3.33,(3H, s), 1.34,(12, s)

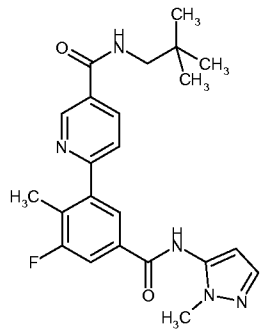
Intermediate 8: 3-Fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide – preparation 2

3-Fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide (720mg), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.57g), $Pd(dppf)Cl_2$ (35mg) and potassium acetate (640mg) were mixed in dry DMF (17ml), the mixture degassed and then heated at 85°C under nitrogen for 24hours. The reaction was absorbed onto silica and applied to an SPE (Si, 20g), eluting with an ethyl acetate / cyclohexane gradient (0-100% ethyl acetate). The product fractions were reduced to dryness *in vacuo* and the residue triturated with 40/60 petrol to give 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide as a beige solid (320mg).
NMR: D_6-DMSO δH 10.39,(1H, b), 8.07,(1H, s), 7.86,(1H, d), 7.39,(1H, d), 6.22,(1H, s), 3.68,(3H, s), 3.33,(3H, s), 1.34,(12, s)

Intermediate 8: 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide – preparation 3

A mixture of 3-fluoro-5-iodo-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)benzamide (27.65g), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (60.29g) and potassium acetate (24.58g) in anhydrous DMF (500ml) was deoxygenated using a cycle of evacuation and refilling with nitrogen three times. $Pd(dppf)Cl_2$ (1.34g) was added to the reaction mixture which was agin deoxygenated and the mixture heated under nitrogen at 85ºC for 24 hours and then left at room temerature for 44 hours. The solvent was removed under vacuum, the residue partially redissolved in ethyl acetate and absorbed onto silca (200ml). The resulting solid was applied to a silica gel flash column and eluted with 20%-70% ethyl acetate in cyclohexane. Pure product containing fractions were combined, evaporated and the resulting waxy solid washed with water to give a pale yellow solid that was dried at 40ºC under vacuum overnight to give 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (15.56g) containing traces of DMF and pinacol related impurities. LCMS MH^+ 360, retention time 3.34 min

Example 1: *N*-(2,2-Dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide

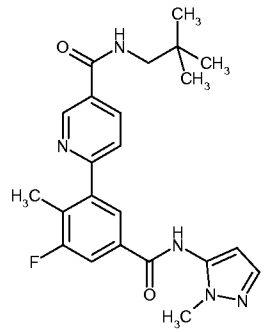


DIPEA (0.303ml) was added to a solution of 3-(5-{[(2,2-dimethylpropyl)amino]carbonyl}-2-pyridinyl)-5-fluoro-4-methylbenzoic acid (200mg), 1-methyl-1*H*-pyrazol-5-amine (62mg) and HATU (243mg) in DMF (5ml) and the reaction stirred for 24hours at room temperature. The DMF was evaporated *in vacuo* and the residual oil dissolved in methanol, filtered through an aminopropyl SPE cartridge (5g). The filtrate was applied to a SCX-2 SPE (2g) and cartridge washed with methanol followed by aqueous ammonia (d=0.880)/methanol mixture. Product was contained in both the washing and the basic fraction so the combined mixture was absorbed onto silica and purified by chromatography (silica SI SPE 5g)) eluting with an ethyl acetate / cyclohexane gradient. The product fractions were combined and reduced to dryness under vacuum. The oily residue was washed with water, dried and triturated with methanol / ether to give *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide as a white solid (46mg).

LCMS: MH^+ 424, retention time 2.97min.

NMR: D_6-DMSO δH 10.44,(1H, b), 9.13,(1H, d), 8.64,(1H, t)8.35,(1H, dd), 7.94,(1H, s), 7.86,(1H, d), 7.78,(1H, d), 7.40,(1H, d), 6.24,(1H, d), 3.70,(3H, s), 3.16,(2H, d), 2.32,(3H, s), 0.93,(9H, s).

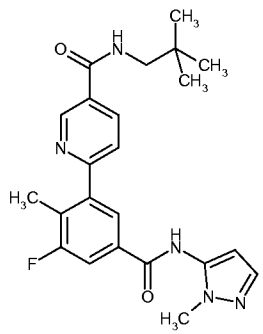
Example 2: *N*-(2,2-Dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide



6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (100mg), 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (150mg), sodium hydrogen carbonate (1M, 0.9ml) and tetrakis(triphenylphosphine)palladium (7mg) were mixed in propan-2-ol (1.8ml). The mixture was degassed and then heated at 80°C under nitrogen for 18hours. The solvents

were evaporated from the cooled reaction mixture *in vacuo* and the residue partially dissolved in ethyl acetate. The solution was applied sequentially to two spe columns (SCX-2), the column washed with ethyl acetate and then the product eluted with ethyl acetate / methanol / 0.880 ammonia. The product fraction was reduced to dryness in vacuo, dissolved in ethyl acetate and filtered through a 1g Si SPE. The eluent was concentrated in vacuo and the residue triturated with methanol / ether to give *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide (128mg).
LCMS: MH^+ 424, retention time 2.97min.
NMR: D_6-DMSO δH 10.44 (1H, b), 9.13 (1H, d), 8.64 (1H, t), 8.35 (1H, dd), 7.94 (1H, s), 7.86 (1H, d), 7.78 (1H, d), 7.40 (1H, d), 6.24 (1H, d), 3.70 (3H, s), 3.16 (2H, d), 2.32 (3H, s), 0.93 (9H, s).

Example 3: *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide



To a mixture of 3-fluoro-4-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (15.0g) 6-chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (9.97g) and tetrakis(triphenylphosphine)palladium (500mg) in propan-2-ol (180ml) was added 1M aqueous sodium hydrogen carbonate solution (90ml). The mixture was degassed before heating at 85ºC overnight. The mixture was allowed to cool and the solvents evaporated and the resulting sticky brown solid partitioned between ethyl acetate and water. The organic phase was washed with water, brine and then dried over anhydrous magnesium sulphate. Whilst filtering the magnesium sulphate the product began to precipitate. The bed was washed with ethyl acetate and the combined filtrate and washing reduced to approximately 200ml. The magnesium sulphate bed was dissolved in water and filtered. This bed was washed with water and then this residue combined with the concentrated organic filtrate. This mixture was stirred at room temperature for 30 minutes and filtered. Further amounts of the title compound were recovered from this filtrate as explained below. The residue was washed with little ethyl acetate and dried at 40ºC under vacuum to give a cream solid (14.7g). This solid was recrystallised from methanol (approximately 200ml) to give the title compound (13.42g) as a white crystals after filtration, washing with chilled methanol and drying at 40ºC under vacuum. Further amounts of the title compound were recovered from the mother liquors

as explained below. The filtrate, from above, was evaporated to give a brown oil which was dissolved in a mixture of methanol and ethyl acetate. This solution was applied to a 20g SCX-2 SPE cartridge. The cartridge was eluted with further quantities of methanol and ethyl acetate mixture followed by a mixture of aqueous ammonia (d=0.880), methanol and ethyl acetate. The basic fraction was evaporated and the resulting glassy solid dissolved in ethyl acetate. This ethyl acetate solution was filtered through a 2g silica SPE cartridge eluting with ethyl acetate. The filtrate and washings were evaporated to give a brown solid. This brown solid was combined with the evaporated mother liquors from the large scale recrystallisation and this mixture recrystallised from methanol (30mL) to give a second batch of the title compound as an off-white solid after filtration and washing with methanol.(1.85g).

NMR (major batch): δH 10.44 (1H, b), 9.13 (1H, d), 8.64 (1H, t) 8.35 (1H, d), 7.94 (1H, s), 7.86 (1H, d), 7.78 (1H, d), 7.40 (1H, d), 6.24 (1H, s), 3.70 (3H, s), 3.16 (2H, d), 2.32 (3H, s), 0.93 (9H, s). LCMS MH^+ 424, retention time 2.89 min (major batch)

NMR (minor batch): δH 10.44 (1H, b), 9.13 (1H, d), 8.64 (1H, t) 8.35 (1H, dd), 7.94 (1H, s), 7.86 (1H, d), 7.78 (1H, d), 7.40 (1H, d), 6.24 (1H, d), 3.70 (3H, s), 3.16 (2H, d), 2.32 (3H, s), 0.93 (9H, s).

Abbreviations

DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
KOAc	Potassium acetate
$Pd(dppf)Cl_2$	[1,1'-bis(Diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1)
SPE	Bond-elut (solid phase extraction column)
THF	Tetrahydrofuran

Biological Examples

The activity of the compound of the invention as a p38 inhibitor may be determined by the following *in vitro* assays:

Assay 1: Fluorescence anisotropy kinase binding assay

The kinase enzyme, fluorescent ligand and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10 x K_i) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

The concentration of kinase enzyme should preferably be 2 x K_f. The concentration of fluorescent ligand required will depend on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration.

Recombinant human p38α was expressed as a GST-tagged protein. To activate this protein, 3.5 µM unactivated p38α was incubated in 50 mM Tris-HCl pH 7.5, 0.1 mM EGTA, 0.1% 2-mercaptoethanol, 0.1mM sodium vanadate, 10mM MgAc, 0.1mM ATP with 200nM MBP-MKK6 DD at 30 degrees for 30 mins. Following activation p38α was re-purified and the activity assessed using a standard filter-binding assay.

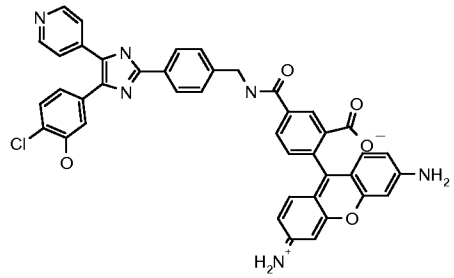
A typical protocol is:

All components are dissolved in buffer of composition 62.5 mM HEPES, pH 7.5, 1.25 mM CHAPS, 1 mM DTT, 12.5 mM $MgCl_2$ with final concentrations of 12nM p38α and 5nM fluorescent ligand. 30µl of this reaction mixture is added to wells containing 1µl of various concentrations of test compound (0.28 nM - 16.6 µM final) or DMSO vehicle (3% final) in NUNC 384 well black microtitre plate and equilibrated for 30-60 mins at room temperature. Fluorescence anisotropy is read in Molecular Devices Acquest (excitation 485nm/emission 535nm).

Definitions: K_i = dissociation constant for inhibitor binding

K_f = dissociation constant for fluorescent ligand binding

The fluorescent ligand is the following compound:



which is derived from 5-[2-(4-aminomethylphenyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-2-chlorophenol and rhodamine green.

Assay 2: Time-resolved fluorescence resonance energy transfer kinase assay

Recombinant human p38α was expressed as a His-tagged protein. To activate this protein, 3 µM unactivated p38α was incubated in 200mM Hepes pH7.4, 625mM NaCl, 1mM DTT with 27 nM active MKK6 (Upstate), 1mM ATP and 10mM $MgCl_2$. The activity of

the MKK6-activated p38α was assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay.

Biotinylated-GST-ATF2 (residues 19-96, 400nM final), ATP (125μM final) and $MgCl_2$ (5mM final) in assay buffer (12.5 mM HEPES pH 7.4, 1 mM DTT) were added to wells containing 1μl of various concentrations of compound or DMSO vehicle (3% final) in NUNC 384 well black plate. The reaction was initiated by the addition of MKK6-activated p38α (100pM final) to give a total volume of 30 μl. The reaction was incubated for 120 minutes at room temperature, then terminated by the addition of 15 μl of 100 mM EDTA pH 7.4. Detection reagent (15 μl) in buffer (100 mM HEPES pH 7.4, 150 mM NaCl, 0.1% w/v BSA, 1mM DTT) containing antiphosphothreonine-ATF2-71 polyclonal antibody (Cell Signalling Technology, Beverly Massachusetts, USA) labelled with W-1024 europium chelate (Wallac OY, Turku, Finland), and APC-labelled streptavidin (Prozyme, San Leandro, California, USA) was added and the reaction was further incubated for 60 minutes at room temperature. The degree of phosphorylation of GST-ATF2 was measured using a Packard Discovery plate reader (Perkin-Elmer Life Sciences, Pangbourne, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

Results

The compound described in the Examples was tested as described above and had an IC_{50} value of <150 nM.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

CLAIMS

1. *N*-(2,2-Dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is *N*-(2,2-dimethylpropyl)-6-(3-fluoro-2-methyl-5-{[(1-methyl-1*H*-pyrazol-5-yl)amino]carbonyl}phenyl)-3-pyridinecarboxamide.

3. A pharmaceutical composition comprising a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

4. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof.

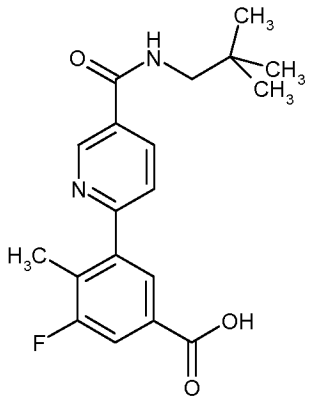
5. A compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, for use in therapy.

6. Use of a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

7. A compound as claimed in claim 1 for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

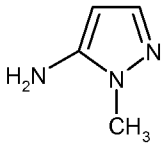
8. A process for preparing a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, which comprises

(a) reacting a compound of formula (I)



(I)

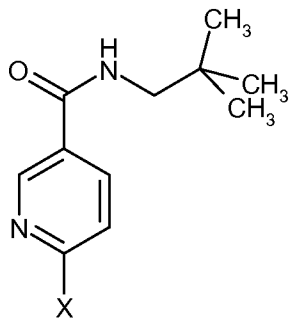
with an amine of formula (II)



(II)

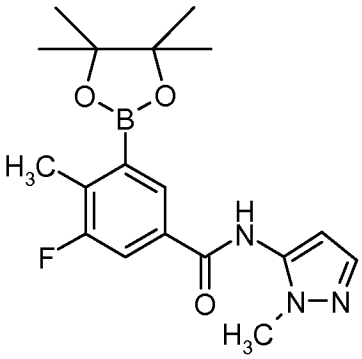
under suitable amide forming conditions; or

(b) reacting a compound of formula (III)

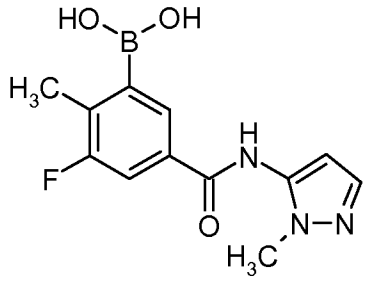


(III)

in which X is halogen,
with a compound of formula (VIIIA) or (VIIIB)



(VIIIA)



(VIIIB)

in the presence of a catalyst.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/063620

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/415 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/068747 A (SMITHKLINE BEECHAM CORP [US]; ASTON NICOLA MARY [GB]; BAMBOROUGH PAUL) 21 August 2003 (2003-08-21) cited in the application claim 1; example 36 -----	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2008	25/03/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, Bart

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/063620

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/063620

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03068747 A	21-08-2003	AT 375980 T	15-11-2007
		AU 2003207298 A1	04-09-2003
		BR 0307351 A	14-12-2004
		CA 2474192 A1	21-08-2003
		CN 1633416 A	29-06-2005
		DK 1474395 T3	11-02-2008
		EP 1474395 A1	10-11-2004
		IS 7337 A	28-06-2004
		JP 2005519932 T	07-07-2005
		MX PA04007838 A	15-10-2004
		NZ 533865 A	24-02-2006
		RU 2309951 C2	10-11-2007
		US 2006264479 A1	23-11-2006
		US 2005176964 A1	11-08-2005