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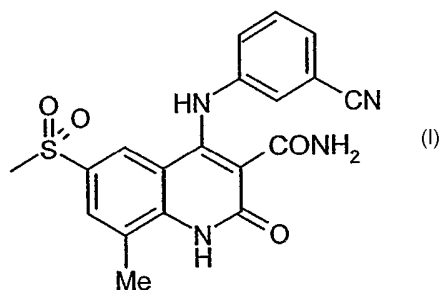
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(54) Title: 2-QUINOLONE COMPOUNDS AS INHIBITORS OF PHOSPHODIESTERASES

(57) Abstract: There is provided according to the invention novel compounds of formula (I) or pharmaceutically acceptable solvates thereof.

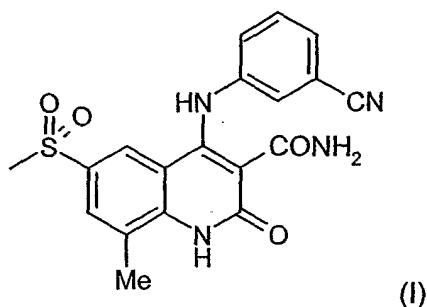


2-QUINOLONE COMPOUNDS AS INHIBITORS OF PHOSPHODIESTERASES

The present invention relates to 2-quinolone compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the 2-quinolone compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable solvate thereof:



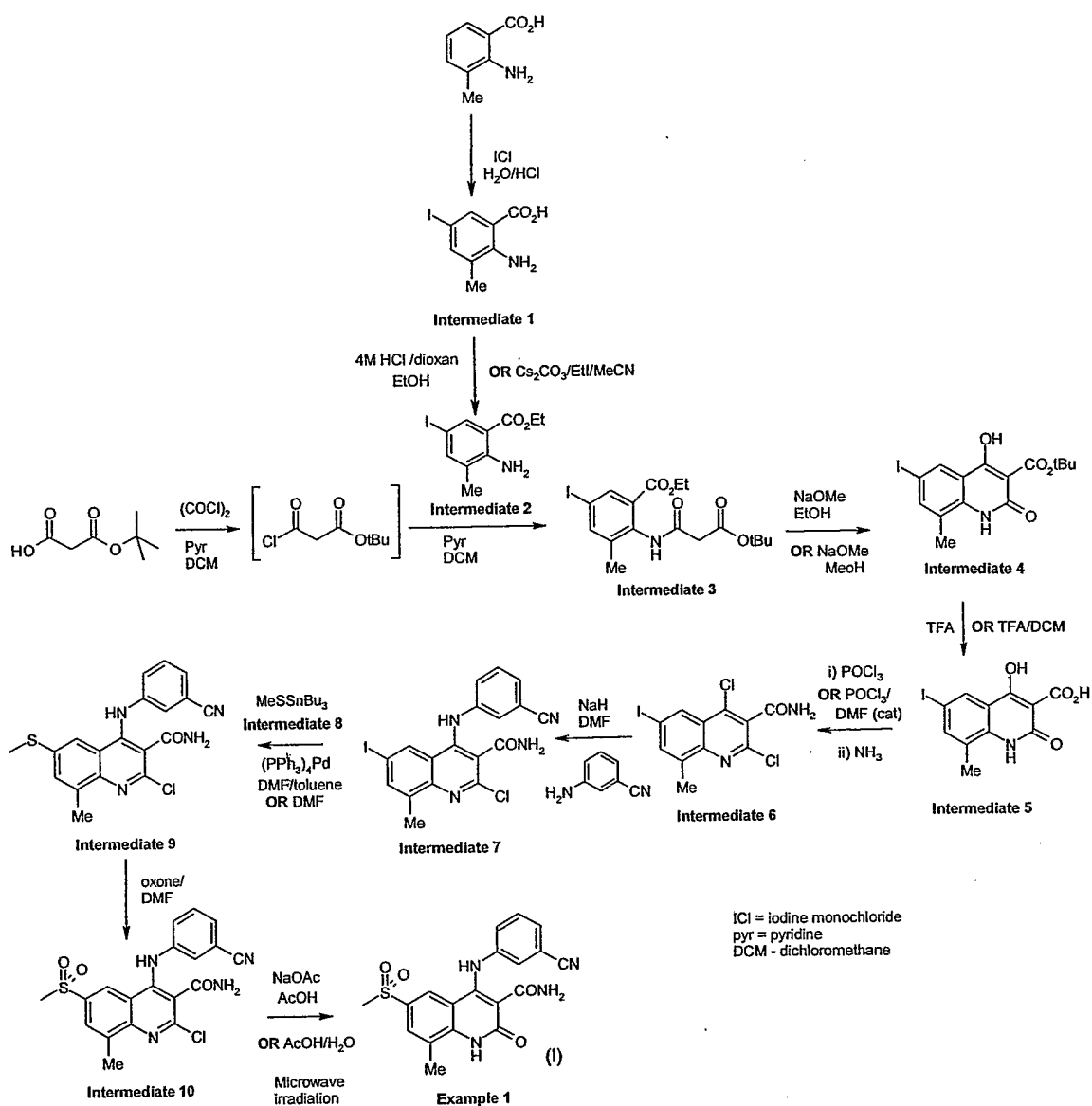
Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

It is understood that the compound of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The compound of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative synthetic methods are set out below and then the specific compound of the invention is prepared according to the working Examples.

Process a

The compound of formula (I) may be prepared as outlined in the scheme below.



5

Process b

The compound of formula (I) may also be prepared by a process of deprotection of protected derivatives of compounds of formula (I). Examples of suitable protecting groups and the means for their removal can be found in T. W. Greene and P. G. M. Wuts 'Protective Groups in Organic Synthesis' (3rd Ed., J. Wiley and Sons, 1999).

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable solvate thereof for use as an active therapeutic substance in a mammal such as a human. The compound or solvate may be useful in the treatment and/or prophylaxis

of any of the conditions described herein and/or useful as a phosphodiesterase inhibitor, e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

5 Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

10 Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable solvate thereof.

15 Phosphodiesterase 4 inhibitors are believed to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis (seasonal or perennial), vasomotor rhinitis, nasal
20 polyps, allergic conjunctivitis, vernal conjunctivitis, occupational conjunctivitis, infective conjunctivitis, eosinophilic syndromes, eosinophilic granuloma, psoriasis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory
25 distress syndrome, multiple sclerosis, or memory impairment (including Alzheimer's disease) pain or depression.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD) including chronic bronchitis and
30 emphysema, asthma, rheumatoid arthritis, or allergic rhinitis, atopic dermatitis or psoriasis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD including chronic bronchitis and emphysema, or asthma or allergic rhinitis in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, **59(2)**, 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein) and COPD (e.g. see S.L.
35 Wolda, *Emerging Drugs*, 2000, **5(3)**, 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, **5**, 432-438; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (S.L. Wolda, *Emerging Drugs*, 2000, **5(3)**, 309-319).

40 PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14),
5 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and refs cited therein). See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and refs cited therein for atopic dermatitis use.

PDE4 inhibitors have been suggested as having analgesic properties and thus being
10 effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a
15 neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant
20 properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; and H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595).

For use in medicine, the compounds of the present invention are usually administered as
25 a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable solvate thereof and one or more pharmaceutically acceptable carriers and/or excipients.

30 The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be
35 administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled, nasal, transdermal or rectal administration, or as topical treatments (e.g. lotions, solutions, creams, ointments or gels). Accordingly, the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous or intramuscular), topical, inhaled or nasal administration. More preferably,
40 the pharmaceutical composition is suitable for topical, inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung, e.g. by aerosol or dry powder composition.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a solution, a syrup, a suspension or emulsion, a tablet, a capsule or a lozenge.

5

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable solvate in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, aqueous ethanol or aqueous glycerine, or an oil, or a non-aqueous solvent, such as a surfactant, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

10

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

15

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion, or suspension or solution can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous solution, aqueous gum or an oil and the dispersion, or suspension or solution then filled into a soft or hard gelatin capsule.

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The compound of formula (I) and/or the pharmaceutical composition may be administered by a controlled or sustained release formulation as described in WO 00/50011.

30

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable solvate in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

35

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or solvate of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle

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size of the size-reduced (e.g. micronised) compound or solvate is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

5 Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary
10 dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic
15 propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion
20 characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

25 For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or solvate thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such
30 as L-leucine or another amino acid, cellobiose octaacetate and/or metals salts of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or solvate thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle
35 size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-
40 300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in

diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUSTM device, marketed by GlaxoSmithKline. The DISKUSTM inhalation device is for example described in GB 2242134 A, and in such a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

For application topically to the skin, the compound of formula (I) or a pharmaceutically acceptable solvate thereof could 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 could 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.

A pharmaceutical composition may be presented in unit dose form containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable solvate thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains

from 0.001 to 50 mg, more preferably 0.005 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable solvate thereof, calculated as the free base.

The pharmaceutically acceptable compounds or solvates of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.005 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable solvate thereof, calculated as the free base.

The compounds, solvates and/or pharmaceutical compositions according to the invention may also be used in combination with one or more other therapeutically active agents, for example, 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 (e.g. antibiotics or antivirals).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable solvate thereof with one or more other therapeutically active agents, for example, 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 (e.g. antibiotics or antivirals).

Examples of β_2 -adrenoreceptor agonists include 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. Long-acting β_2 -adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Examples of anti-histamines include methapyrilene, or loratadine, cetirizine, desloratadine or fexofenadine.

Examples of anti-inflammatory steroids include fluticasone propionate and budesonide.

Examples of anticholinergic compounds which may be used in combination with a compound of formula (I) or a pharmaceutically acceptable solvate thereof are described in WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1. For example, anticholinergic agents include muscarinic M3 antagonists, such as ipratropium bromide, oxitropium bromide or tiotropium bromide.

Other suitable combinations include, for example, combinations comprising a compound of formula (I) or a pharmaceutically acceptable solvate thereof together with other anti-inflammatory agents (e.g. anti-inflammatory corticosteroids, NSAIDs, leukotriene

antagonists (e.g. montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists, chemokine antagonists such as CCR3 antagonists, and adenosine 2a agonists, 5-lipoxygenase inhibitors and antiinfective agents such as an antibiotic or an antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

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

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions.

Biological Test Methods

PDE3, PDE4B, PDE4D, PDE5 and PDE6 Primary assay methods

The activity of the compounds can be measured as described below. Preferred compounds of the invention are selective PDE4 inhibitors, *i.e.* they inhibit PDE4 (e.g. PDE4B and/or PDE4D) to a greater extent than they inhibit other PDE's such as PDE3 and/or PDE5.

PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also in M.M. McLaughlin et al., "A low Km, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, e.g. after induction by addition of 150 μ M CuSO₄, and 100,000 x *g* supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phosphodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

- 5 PDE3 may be purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

- 10 PDE6 may be purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

15

Inhibition of PDE activity: Fluorescence Polarisation (FP) assay

- 20 The ability of compounds to inhibit PDE catalytic activity was determined by IMAP Fluorescence Polarisation (FP) assay (Molecular Devices Ltd code: R8062) in 384-well format. Test compounds (small volume, e.g. 0.5 μ l, of solution in DMSO) were preincubated at ambient temperature in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM MgCl₂, 0.1% (w/v) bovine serum albumin, 0.05% NaN₃ for 10-30 minutes. The enzyme level was set so that reaction was linear throughout the incubation.

25

- For the PDE3, PDE4B and PDE4D assays Fluorescein adenosine 3',5'-cyclic phosphate (Molecular Devices Ltd code: R7091) was added to give ~ 40nM final concentration. For the PDE5 and PDE6 assays Fluorescein guanosine 3',5'-cyclic phosphate (Molecular Devices Ltd code: R7090) was added to give ~ 40nM final concentration. Plates were mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (Molecular Devices Ltd code: R7207) was added (60 μ l of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates were allowed to stand at ambient temperature for 1hour. The FP ratio of parallel to perpendicular light was measured using an AnalystTM plate reader (from Molecular Devices Ltd). For inhibition curves, 11 concentrations (0.5nM - 30 μ M) of each compound were assayed; more potent compounds were assayed over lower concentration ranges (assay concentrations were generally between 30 μ M and 50fM). Curves were analysed using ActivityBase and XLfit (ID Business Solutions Limited). Results were expressed as pIC₅₀ values.

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Example 1 of the invention inhibits the catalytic activity at the PDE4B (human recombinant) enzyme with pIC₅₀ of 9.0 (This data is thought to be accurate to within ± 0.5

of the value stated). This potency is at least 100 fold greater than that at the PDE3, PDE5 and PDE6 enzymes.

5 *Emesis:* Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5, 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention causes only limited or manageable emetic side-effects. Compounds having such a profile may have an improved side-effect profile when compared with existing therapies. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud et al., "Emesis induced by inhibitors of PDE IV in the ferret" *Neuropharmacology*, 1999, 38, 289-297, erratum 15 *Neuropharmacology*, 2001, 40, 465-465.

20 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

25 In this section, "intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

HPLC	high performance liquid chromatography
NMR	nuclear magnetic resonance
30 LC/MS	liquid chromatography/mass spectroscopy
SPE	solid phase extraction column. Unless otherwise specified the solid phase will be silica gel. Aminopropyl SPE refers to a silica SPE column with aminopropyl residues immobilised on the solid phase (eg. IST Isolute™ columns).
35 SCX	solid phase extraction (SPE) column with benzene sulfonic acid residues immobilised on the solid phase (eg. IST Isolute™ columns).

General Experimental Details

LC/MS (Liquid Chromatography/Mass Spectroscopy)

40 Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nm

Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS

Flow Rate : 3ml/min

Injection Volume : 5µl

Solvent A : 95% acetonitrile + 0.05% formic acid

5 Solvent B : 0.1% formic acid + 10mM ammonium acetate

Gradient: Mixtures of Solvent A and Solvent B are used according to the following gradient profiles (expressed as % Solvent A in the mixture): 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

10 Mass Directed Automated Preparative HPLC Column, Conditions and Eluent

The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5µm)

UV detection wavelength : 200-320nm

Flow rate: 20ml/min

15 Injection Volume: 0.5ml

Solvent A: 0.1% formic acid

Solvent B: 95% acetonitrile + 0.05% formic acid

Gradient systems: mixtures of Solvent A and Solvent B are used according to a choice of 5 generic gradient profiles (expressed as % Solvent B in the mixture), ranging from a start of 0 to 50% Solvent B, with all finishing at 100% Solvent B to ensure total elution.

20

'Hydrophobic Frit'

This refers to a Whatman PTFE filter medium (frit), pore size 5.0µm, housed in a polypropylene tube.

25 Evaporation of product fractions after purification

Reference to column chromatography, SPE and preparative HPLC purification includes evaporation of the product containing fractions to dryness by an appropriate method.

Aqueous ammonia solutions

30 '880 Ammonia' or '0.880 ammonia' refers to concentrated aqueous ammonia (specific gravity 0.880).

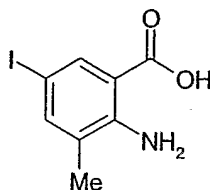
All temperatures are given in degrees Celsius.

35 Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

Intermediate 1. 2-Amino-5-iodo-3-methylbenzoic acid

40



A solution of iodine monochloride (2.6g, available from Aldrich) in 2M aqueous hydrochloric acid (10ml) was cooled in an ice bath and added slowly to a solution of 2-amino-3-methylbenzoic acid (2.3g, available from Aldrich) in 1M aqueous hydrochloric acid (50ml). The mixture was stirred at room temperature for 1h. The resulting precipitate was filtered off, washed with water and dried *in vacuo* to give the title compound as a beige solid (4.1g).

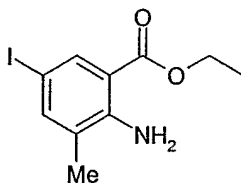
LC/MS R_t 3.29 min, m/z 278 [MH^+]

Intermediate 1 (alternative procedure) 2-Amino-5-iodo-3-methylbenzoic acid

A stirred solution /suspension of 2-amino-3-methylbenzoic acid (available from Aldrich, 125g) in 1N hydrochloric acid (2.5l) was maintained at room temperature. An ice-cooled solution of iodine monochloride (available from Aldrich, 148g) in 2N hydrochloric acid (500ml) was added at a constant rate *via* a cannula over ca. 1h. As the iodine monochloride solution added, the reaction initially took on a darker colour followed by precipitation of a pale brown solid. No exotherm was observed. Following completion of the addition the mixture was stirred for a further 1.5h, followed by the addition of a further ice-cooled solution of iodine monochloride (13.4g) in 2N hydrochloric acid (50ml) over 10 min. Stirring was continued for 1h after which time the mixture (containing ca. 7% unreacted starting material) was filtered under reduced pressure, and the filtered solid was washed with water, and dried *in vacuo* at 50° to obtain a pale brown solid (217g). Recrystallisation from acetonitrile (ca. 7.5l) gave the title compound as a pale beige crystalline solid (167g).

LC/MS R_t 3.24 min, m/z 278 [MH^+]

Intermediate 2. Ethyl 2-amino-5-iodo-3-methylbenzoate



Intermediate 1 (1.8g) was dissolved in anhydrous ethanol (25ml) and 4M hydrogen chloride in 1,4-dioxane (5ml) was added. The mixture was heated under reflux at 80°C for 3 days. After cooling, the solvent was evaporated and the residue was purified using an aminopropyl SPE column (70g), eluting with methanol. The fractions were combined and

evaporated to give the title compound as an orange oil (0.48g, approx. 40:60 mixture of the title compound and ethyl 2-amino-3-methylbenzoate by nmr spectroscopy).

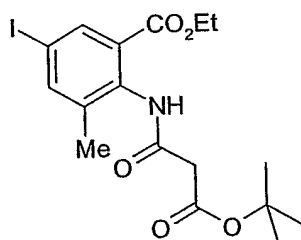
LC/MS R_t 3.64 min, m/z 306 $[MH^+]$

5 **Intermediate 2 (alternative procedure). Ethyl 2-amino-5-iodo-3-methylbenzoate**

A stirred suspension of Intermediate 1 (from alternative procedure) (166g) in acetonitrile (3l) was treated with caesium carbonate (293g) causing the suspension to turn more gelatinous. After stirring for 10mins iodoethane (50.4ml) was added over 5mins (no exotherm observed). The mixture was heated at 75° for 4h, then cooled to room temperature and filtered. The filtrate was evaporated *in vacuo* and the residue was partitioned between dichloromethane (800ml) and saturated sodium bicarbonate (500ml). The layers were separated and the aqueous phase was further extracted with dichloromethane (2x200ml). The combined organic extracts were washed with water (700ml), dried (Na_2SO_4) and evaporated *in vacuo* to obtain the product as a cream-coloured solid (174g).

LC/MS R_t 3.63 min, m/z 306 $[MH^+]$

20 **Intermediate 3. Ethyl 2-({3-[(1,1-dimethylethyl)oxy]-3-oxopropanoyl}amino)-5-iodo-3-methylbenzoate**



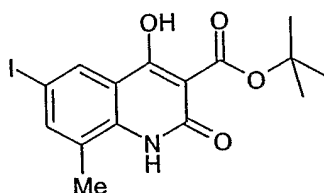
Mono-tert-butyl malonate (0.33ml, available from Aldrich) was dissolved in dichloromethane (10ml) and pyridine (0.17ml) was added. The mixture was cooled to 0°C under nitrogen and oxalyl chloride (0.24ml) was added. After stirring at room temperature for 1h, the solvent was removed *in vacuo* and the residue was azeotroped twice with toluene. The resulting residue was dissolved in anhydrous dichloromethane (5ml) and added slowly to a solution of Intermediate 2 (0.48g) and pyridine (0.17ml) in anhydrous dichloromethane (10ml). The mixture was stirred at room temperature over the weekend. LC-MS analysis of the crude reaction mixture showed the reaction had not gone to completion. A further portion of mono-tert-butyl malonate (0.33ml) was converted to the acid chloride using pyridine (0.17ml) and oxalyl chloride (0.24ml) as described previously, and the acid chloride was added to the reaction mixture. After stirring at room temperature for 2h, the mixture was washed with water (50ml) and the organic layer evaporated to give a green oil. Purification by chromatography on silica gel (IST Isolute™ column, 20g), eluting with an ethyl acetate/cyclohexane gradient, gave the title compound as a colourless oil which eluted with 20% ethyl acetate/cyclohexane and 1:1 ethyl

acetate/cyclohexane (0.49g, approx. 2:3 mixture of the title compound and ethyl 2-({3-[(1,1-dimethylethyl)oxy]-3-oxopropanoyl}amino)-3-methylbenzoate).
LC/MS R_t 3.45 min, m/z 448 $[MH^+]$

5 **Intermediate 3 (alternative procedure).** Ethyl 2-({3-[(1,1-dimethylethyl)oxy]-3-oxopropanoyl}amino)-5-iodo-3-methylbenzoate

A stirred solution of mono-tert-butyl malonate (available from Aldrich, 111g) in dry dichloromethane (1l) under nitrogen was treated with pyridine (55.6ml) then cooled to 0° (ice/salt bath). Oxalyl chloride (54.5ml) was added dropwise over 30min maintaining the
10 reaction temperature below 5°. Stirring was continued for 18h leaving the cooling bath in place so the mixture warmed slowly to room temperature. The dark brown reaction mixture was re-cooled to 0° then treated with a solution of Intermediate 2 (from alternative procedure) (141g) in dry dichloromethane (1l) containing pyridine (55.6ml) over 30mins, maintaining the reaction temperature below 5°. The cooling bath was removed and stirring
15 was continued for 2h. The reaction mixture was washed with water (2l), dried (Na_2SO_4) and evaporated *in vacuo*. The residual dark brown oil (237g) was purified using Biotage chromatography (2.5kg cartridge, eluent 0-2% ethyl acetate in dichloromethane) to obtain the title compound as a slightly off-white solid (193g) (contains ca. 10% by nmr of an impurity, possibly di-tert butyl malonate).
20 LC/MS R_t 3.43min, m/z 448 $[MH^+]$

Intermediate 4. 1,1-Dimethylethyl 4-hydroxy-6-iodo-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate



25

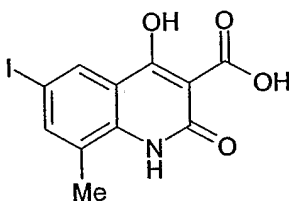
Intermediate 3 (0.48g) was dissolved in ethanol (20ml) and sodium methoxide (0.07g) was added. The mixture was stirred at room temperature for 1h. The solvent was evaporated and the residue partitioned between ethyl acetate (20ml) and water (20ml).
30 The aqueous layer was acidified to pH 3-4 using 2M aqueous hydrochloric acid, and the resulting precipitate filtered off to give the title compound as a white solid (0.32g, approx. 2:3 mixture of the title compound and 1,1-dimethylethyl 4-hydroxy-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate).
LC/MS R_t 3.76 min, m/z 400 $[MH^+]$

35

Intermediate 4 (alternative procedure). 1,1-Dimethylethyl 4-hydroxy-6-iodo-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate

A stirred solution of Intermediate 3 (from alternative procedure) (193g) in anhydrous methanol (1.5l), under nitrogen, was cooled to ca. 5°. Sodium methoxide (35g) was added in 4 approximately equal portions over ca. 30mins. (As the first addition resulted in no apparent exotherm, the cooling bath was removed for the subsequent additions). Three further additions of sodium methoxide (4.67g) were required to complete the reaction. The reaction mixture was concentrated *in vacuo* to ca. 1/3 volume, and the resulting cream-coloured thick suspension was poured into water (7-8l of water were required to achieve complete dissolution). The solution was washed with ether (1.5l) then the aqueous phase was adjusted to pH5 by the addition of 2N hydrochloric acid. The precipitate was collected by filtration under reduced pressure, washed with water and dried *in vacuo* at 50° to give the title compound as a white solid (165g).
LC/MS R_t 3.76 min, m/z 400 [MH⁺]

Intermediate 5. 4-Hydroxy-6-iodo-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid
acid



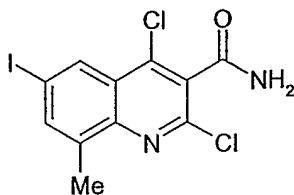
Intermediate 4 (0.044g) was dissolved in trifluoroacetic acid (1ml) and the mixture was left standing at room temperature for 4h. The mixture was diluted with methanol and the resulting precipitate filtered off to give the title compound as a white solid (0.027g, approx. 2:3 mixture of the title compound and 4-hydroxy-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid).
LC/MS R_t 4.05 min, m/z 346 [MH⁺]

Intermediate 5 (alternative procedure). 4-Hydroxy-6-iodo-8-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid

A stirred suspension of Intermediate 4 (from alternative procedure) (164g) in dichloromethane (750ml) was treated with trifluoroacetic acid (500ml). After stirring for 1h the mixture was concentrated *in vacuo*. The residue was treated with methanol (750ml), filtered, washed with methanol and dried *in vacuo* to give the title compound as a white solid (141g).

¹H NMR (400MHz, D₆DMSO) δ 2.44, (s, 3H); 7.97 (d, 1H); 8.13 (d, 1H).

Intermediate 6. 2,4-Dichloro-6-iodo-8-methyl-3-quinolinecarboxamide



Intermediate 5 (0.24g) was suspended in phosphorous oxychloride (10ml) and the mixture was heated at 100°C for 1h. The resulting solution was heated at 50°C for a further 1h. After cooling, the solvent was evaporated *in vacuo* and the residue azeotroped twice with toluene. The resulting residue was treated with 0.880 ammonia (10ml) and the mixture was stirred at room temperature for 1h. The precipitate was filtered off to give the title compound as a white solid (0.15g, approx. 1:1 mixture of the title compound and 2,4-dichloro-8-methyl-3-quinolinecarboxamide).

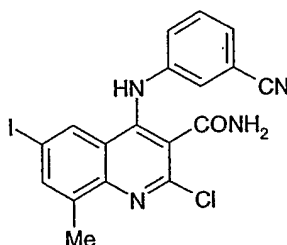
LC/MS R_t 3.34 min, m/z 381/383 [MH^+]

Intermediate 6 (alternative procedure). 2,4-Dichloro-6-iodo-8-methyl-3-quinolinecarboxamide

A stirred suspension of Intermediate 5 (from alternative procedure) in phosphorous oxychloride (600ml) was treated with *N,N*-dimethylformamide (0.5ml). The mixture was heated at 115° (external bath temperature) for 2h. The resulting yellow solution was cooled to room temperature and evaporated *in vacuo* to give a yellow solid. This was azeotroped with toluene to give an orange oil which was treated with dioxane (100ml). The resulting orange viscous solution was added carefully and slowly to ice cooled 880 ammonia over ca. 30min. (the acid chloride started to crystallise out during the addition, so the final part was added as a slurry). (Note this is quite a violent reaction accompanied by an exotherm). The cooling bath was removed and stirring continued for 1h. The precipitate was filtered, washed with water and dried *in vacuo* to obtain the title compound as a cream-coloured solid (69.0g).

LC/MS R_t 3.32 min, m/z 381/383 [MH^+]

Intermediate 7. 2-Chloro-4-[(3-cyanophenyl)amino]-6-iodo-8-methyl-3-quinolinecarboxamide



3-Aminobenzonitrile (0.059g, available from Aldrich) was dissolved in anhydrous *N,N*-dimethylformamide (5ml) and sodium hydride (0.04g, 60% dispersion in mineral oil) was

added. After 5 minutes, Intermediate 6 (0.15g) in anhydrous *N,N*-dimethylformamide (5ml) was added and the mixture was heated at 60°C, under nitrogen for 30 minutes. After cooling, the reaction was quenched by the addition of water (20ml) and the mixture extracted with dichloromethane (2x20ml). The organic layer was dried using a hydrophobic frit and the solvent was evaporated. The residue was purified by solid phase extraction (5g SCX cartridge), eluting with methanol and 2M ammonia solution in methanol (available from Aldrich). The product eluted with the methanol. The methanol fraction was evaporated, and the resulting residue was triturated with methanol to give the title compound as a pale yellow solid (0.021g).

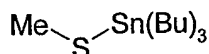
LC/MS R_t 3.32 min, m/z 463/465 [MH^+]

Intermediate 7 (alternative procedure). 2-Chloro-4-[(3-cyanophenyl)amino]-6-iodo-8-methyl-3-quinolinecarboxamide

A stirred solution of 3-aminobenzonitrile (available from Aldrich, 17g) in dry *N,N*-dimethylformamide (500ml), under nitrogen, was treated with sodium hydride (8.62g of a 60% dispersion in mineral oil) portionwise over 15min – no exotherm observed. The resulting deep purple solution was treated with a solution of Intermediate 6 (from alternative procedure, 49.8g) in dry *N,N*-dimethylformamide (400ml) over 1h. A slight/moderate exotherm accompanied the addition but the rate of addition maintained the reaction temperature below 33°. The resulting yellow/brown solution was stirred for 4h then concentrated *in vacuo* to ca. 250ml. The mixture was poured slowly into water (4l) with stirring, causing a yellow precipitate. The pH of the mixture was adjusted to pH7 by the addition of 2N hydrochloric acid, then the mixture was filtered under reduced pressure. The cake was washed with 4:1 water: *N,N*-dimethylformamide (250ml) then water (2x250ml) and dried *in vacuo* at 55° to give a pale yellow solid (60g). The solid was treated with acetonitrile (1l) and heated to reflux on a steam bath. The mixture was filtered hot and the solid was dried *in vacuo* to a pale yellow solid (45.5g). This solid was treated with ethyl acetate (1l) and heated to reflux on a steam bath. The mixture was filtered hot and the solid was dried *in vacuo* to give the title compound as a pale yellow solid (40g).

LC/MS R_t 3.28 min, m/z 463/465 [MH^+]

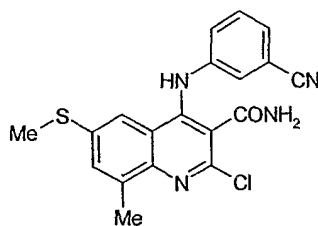
Intermediate 8. Tributyl(methylthio)stannane



To a solution of tributyltin chloride (82g) in anhydrous carbon tetrachloride (500ml) was added sodium thiomethoxide (19.4g, available from Aldrich) and the resulting mixture was stirred for 72h under nitrogen. The mixture was filtered through Celite® filter agent and concentrated *in vacuo* to give the title compound as a colourless oil (88.4g).

^1H NMR (400MHz, CDCl_3) δ 0.92 (t, $J=7\text{Hz}$, 9H), δ 1.15 (m, $J=7\text{Hz}$, 6H), δ 1.35 (m, $J=7\text{Hz}$, 6H), δ 1.58 (m, $J=7\text{Hz}$, 6H), δ 2.09 (m, $J=14\text{Hz}$, 3H)

Intermediate 9. 2-Chloro-4-[(3-cyanophenyl)amino]-8-methyl-6-(methylthio)-3-quinolinecarboxamide



5

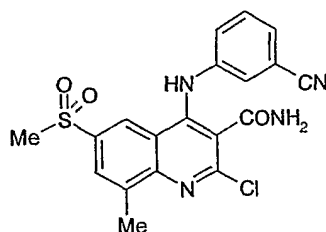
Intermediate 7 (0.021g) was suspended in anhydrous toluene (5ml) and Intermediate 8 (0.018g) was added, followed by the addition of tetrakis(triphenylphosphine) palladium(0) (0.005g, available from Aldrich). Anhydrous *N,N*-dimethylformamide (few drops) was added to aid solubility and the mixture was heated under reflux for 4h. After cooling, the solvent was evaporated and the residue triturated with cyclohexane. The precipitate was filtered off to give the title compound as a yellow solid (0.017g, ca. 85% purity). LC/MS R_t 3.12 min, m/z 383/385 [MH^+]

Intermediate 9 (alternative procedure). 2-Chloro-4-[(3-cyanophenyl)amino]-8-methyl-6-(methylthio)-3-quinolinecarboxamide

To Intermediate 7 (from alternative procedure, 40.3g) in dry *N,N*-dimethylformamide (200ml) under nitrogen was added Intermediate 8 (32.25g), washed in with more *N,N*-dimethylformamide (150ml). Tetrakis(triphenylphosphine) palladium(0) (1.61g) was added (washed in with more *N,N*-dimethylformamide (50ml), and the mixture was stirred and heated at ca. 105° for 2.5h. The mixture was filtered from some un-dissolved solid and the filtrate evaporated. The residue was triturated with methanol (2x250ml), which was decanted off. The residue was further triturated with isopropanol (500ml) overnight, and the solid filtered off, washed with isopropanol and dried to give the title compound (27.3g). LC/MS R_t 3.17 min, m/z 383/385 [MH^+]

More solid precipitated out from the methanol filtrate; this was filtered off, washed with methanol and dried to give further title compound (3.41g). After standing for several days, still more solid precipitated out from the methanol filtrate; this was filtered off and dried to give further title compound (1.6g).

Intermediate 10. 2-Chloro-4-[(3-cyanophenyl)amino]-8-methyl-6-(methylsulfonyl)-3-quinolinecarboxamide



Intermediate 9 (0.017g) was dissolved in *N,N*-dimethylformamide (2ml) and oxone (0.055g, available from Aldrich) was added. The mixture was stirred at room temperature for 2h. The reaction was quenched by the addition of 10% aqueous sodium sulphite solution (1ml) and extracted with dichloromethane. The organic layer was dried using a hydrophobic frit and the solvent evaporated to give the title compound as a pale yellow solid (0.02g, ca. 77% purity).

LC/MS R_t 2.58 min, m/z 415/417 [MH^+]

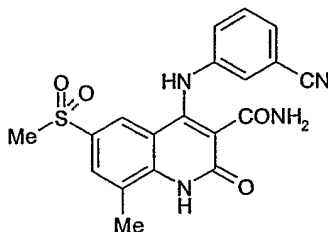
10 **Intermediate 10 (alternative procedure).** 2-Chloro-4-[(3-cyanophenyl)amino]-8-methyl-6-(methylsulfonyl)-3-quinolinecarboxamide

Intermediate 9 (from alternative procedure, 30.0g) was stirred under nitrogen with dry *N,N*-dimethylformamide (450ml), and oxone (119.5g) was added in portions over ca. 45min., with cooling in a water bath to which ice was occasionally added to keep the reaction temperature below 25°. After the addition stirring under nitrogen was continued at ca. 20° for a further 5h, followed by stirring at room temperature under nitrogen overnight. More oxone (20g) was added and stirring at room temperature was continued for a further 2.5h. More oxone (20g) was added and stirring at room temperature was continued for 2h (reaction complete) followed by stirring overnight. The mixture was poured cautiously in portions onto stirred aqueous 10% sodium sulphite solution (1.5l) with cooling in ice. The mixture was stirred for a further 0.5h. Dichloromethane (ca. 1l) was added, the mixture was filtered, and the residue was washed with water and dichloromethane. The residue was then stirred with more water (ca 1.5l), and the solid filtered off and dried *in vacuo* at 45° to give the title compound (19.3g).

25 LC/MS R_t 2.60min, m/z 415/417 [MH^+]

The dichloromethane filtrate and initial water washings were separated, and the aqueous layer extracted with more dichloromethane (2x500ml). The combined dichloromethane extracts were washed with water (500ml) and brine (500ml); the organic layer was dried ($MgSO_4$) and evaporated to give a residual yellow oil, which was triturated with isopropanol (600ml) with stirring and heating to 60°. The mixture was filtered while hot, and the filtrate allowed to stand in the refrigerator. The resulting yellow precipitate was filtered off and dried *in vacuo* to give further title compound (2.1g).

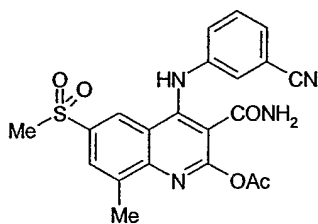
35 **Example 1.** 4-[(3-Cyanophenyl)amino]-8-methyl-6-(methylsulfonyl)-2-oxo-1,2-dihydro-3-quinolinecarboxamide



Intermediate 10 (0.019g) was suspended in acetic acid (2ml) and sodium acetate (0.008g) was added. The mixture was heated at 180°C under microwave irradiation for 15 minutes. LC-MS of the crude reaction mixture showed a 1:1 mixture of the title compound and a compound with *m/z* consistent with structure A. The mixture was partitioned between ethyl acetate (10ml) and water (10ml). The organic layer was evaporated to give a yellow solid. The solid was dissolved in water (10ml) and methanol (1ml), lithium hydroxide (0.002g) was added, and the mixture was heated at 40°C for 30 minutes. The mixture was extracted with ethyl acetate (2x10ml), the organic layers were dried using a hydrophobic frit, and the solvent was evaporated. The resulting residue was purified by mass directed preparative HPLC to give the title compound as a white solid (0.0025g).

LC/MS R_t 2.49 min, *m/z* 397 [MH^+]

1H NMR (400MHz, DMSO) δ 2.50 (3H, br.s, $-CH_3$), δ 2.94 (3H, s, SO_2CH_3), δ 7.39 (1H, ddd, aromaticCH), δ 7.46 (1H, dd, aromaticCH), δ 7.54 (1H, ddd, aromaticCH), δ 7.59 (1H, dd, aromaticCH), δ 7.66 (1H, d, aromaticCH), δ 7.84 (1H, m, aromaticCH), δ 7.89 (1H, br.d, $-CONH_2$), δ 9.63 (1H, br.d, $-CONH_2$, $J=4.0$ Hz), δ 12.75 (1H, br.s, NH).



Structure A

Example 1 (alternative procedure). 4-[(3-Cyanophenyl)amino]-8-methyl-6-(methylsulfonyl)-2-oxo-1,2-dihydro-3-quinolinecarboxamide

A suspension of Intermediate 10 (alternative procedure, 0.9g) in acetic acid (12ml) and water (4ml) was heated with stirring under microwave irradiation at 180° for 15 mins. The mixture was allowed to cool and combined with other reactions (x 18) conducted under identical conditions on the same scale. The collective reaction mixture was filtered and the solid product washed with water and methanol and dried *in vacuo* at 40° to give the crude product (12.4g).

The crude product (11.9g) was stirred in *N,N*-dimethylformamide (550ml) at 100° for ca. 1h. The mixture was filtered hot to remove undissolved solid. The filtrate was warmed to 85° with stirring and treated dropwise with acetonitrile:water (1:1) (approx 260ml) until the mixture started to go cloudy. The mixture was warmed at 100° for 0.5h and allowed to cool slowly to ambient temperature with stirring over the weekend. The yellow solid was collected by filtration and washed sparingly with *N,N*-dimethylformamide, stirred with methanol (200ml) and collected by filtration. The product was dried overnight *in vacuo* at 40° to give a yellow solid (6.8g) (purity 87.3% by HPLC). This material was stirred with

dichloromethane (200ml) and formic acid (10ml) for ca. 1h. Un-dissolved material was filtered off and dried (2.2g); the filtrate was diluted with more dichloromethane and formic acid, and the solution applied to a silica gel (Biotage) column (800g), pre-conditioned with dichloromethane: formic acid: methanol 100:1:1.5. The column was eluted with
5 dichloromethane: formic acid: methanol 100:1:1.5 and product fractions evaporated to give the title compound (2.0g).

LC/MS R_t 2.67 min, m/z 397 [MH^+]

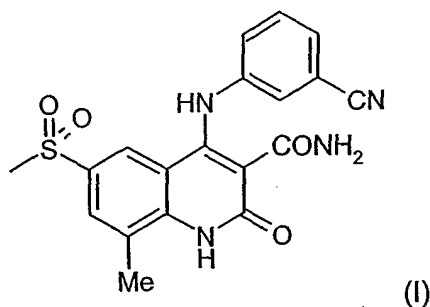
Impure fractions from the column were combined with the 2.2g of material which failed to dissolve in dichloromethane: formic acid (total 3.1g), and dissolved with stirring in 15:1
10 dichloromethane: formic acid (200ml). The material was purified by chromatography on a preconditioned silica column (Biotage 800g), eluting with dichloromethane:formic acid:methanol (100:1:0.5) to give further title compound (2.0g).

LC/MS R_t 2.68 min, m/z 397 [MH^+]

15

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable solvate thereof:

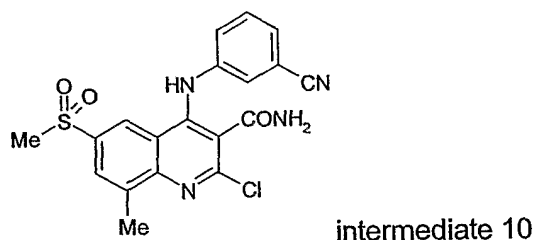


2. A compound of formula (I) selected from the group consisting of:

4-[(3-Cyanophenyl)amino]-8-methyl-6-(methylsulfonyl)-2-oxo-1,2-dihydro-3-quinolinecarboxamide.

3. A process for the preparation of a compound of formula (I) and pharmaceutically acceptable solvates thereof as claimed in claims 1 to 2 which comprises:

(A) reacting intermediate 10 as a suspension in acetic acid



with sodium acetate, under microwave irradiation at a suitable temperature for example 180°C, for a suitable period of time, for example 15 minutes, followed by isolation, followed by treatment with lithium hydroxide in a water/methanol mixture at an elevated temperature, for example 40°C, followed by purification; or

(B) heating intermediate 10 as a suspension in acetic acid/water under microwave irradiation at a suitable temperature, for example 180°C, for a suitable time period, for example 15 minutes, followed by purification; or

(C) deprotecting a protected derivative of a compound of formula (I).

4. A method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable solvate thereof according to any of claims 1 to 2.
5. A compound or a pharmaceutically acceptable solvate thereof, according to claims 1 to 2 for use in therapy.
6. A compound or a pharmaceutically acceptable solvate thereof, according to claims 1 to 2 for use in the treatment or prophylaxis of inflammatory and/or allergic diseases.
7. The use of a compound according to claims 1 to 2, or a pharmaceutically acceptable solvate thereof, in the manufacture of a medicament for the treatment or prophylaxis of inflammatory and/or allergic diseases.
8. A pharmaceutical composition which comprises a compound according to claims 1 to 2 optionally with a pharmaceutically acceptable carrier or excipient.
9. A pharmaceutical composition according to claim 8 which is suitable for inhaled administration.
10. A pharmaceutical composition according to claim 8 which is suitable for oral administration.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/001440

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/54 A61K31/4706 A61K31/4709 A61P11/00

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/103998 A (GLAXO GROUP LIMITED; BALDWIN, IAN, ROBERT; BARKER, MICHAEL, DAVID; DEA) 2 December 2004 (2004-12-02) Activity table on page 57; examples 312,194,242,250,291,304	1-10
A	WO 97/44322 A (CHIROSCIENCE LIMITED; DYKE, HAZEL, JOAN; MONTANA, JOHN, GARY) 27 November 1997 (1997-11-27) the whole document	1-10

☐ 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

20 June 2006

Date of mailing of the international search report

30/06/2006

Name and mailing address of the ISA/

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Authorized officer

Goss, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/001440

Box 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. ☒ 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 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 fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/001440

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004103998 A	02-12-2004	AU 2004240759 A1	02-12-2004
		BR PI0410477 A	30-05-2006
		CA 2526228 A1	02-12-2004
		EP 1633748 A1	15-03-2006
		MA 27808 A1	01-03-2006
WO 9744322 A	27-11-1997	AU 722662 B2	10-08-2000
		AU 2905997 A	09-12-1997
		BR 9709105 A	03-08-1999
		CA 2252501 A1	27-11-1997
		CN 1219168 A	09-06-1999
		EP 0912519 A1	06-05-1999
		JP 2000510866 T	22-08-2000
		US 5834485 A	10-11-1998