



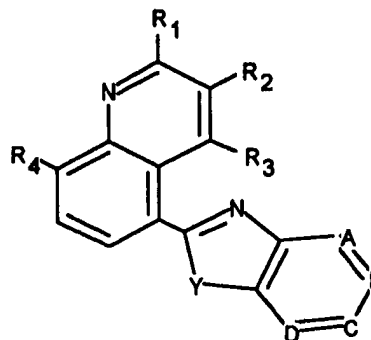
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<p>(21) International Application Number: PCT/GB97/03047</p> <p>(22) International Filing Date: 6 November 1997 (06.11.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>9623163.4</td> <td>6 November 1996 (06.11.96)</td> <td>GB</td> </tr> <tr> <td>9714298.8</td> <td>7 July 1997 (07.07.97)</td> <td>GB</td> </tr> </table> <p>(71) Applicant: DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).</p> <p>(72) Inventors: DYKE, Hazel, Joan; Chiroscience Limited, Cam- bridge Science Park, Milton Road, Cambridge CB4 4WE (GB). MONTANA, John, Gary; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).</p> <p>(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p>	9623163.4	6 November 1996 (06.11.96)	GB	9714298.8	7 July 1997 (07.07.97)	GB	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
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(54) Title: QUINOLINES AND THEIR THERAPEUTIC USE

(57) Abstract

Compounds of formula (i) have therapeutic utility *via* inhibition of PDE and TNF, e.g. in the treatment of inflammatory conditions.



(i)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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QUINOLINES AND THEIR THERAPEUTIC USE

Field of the Invention

The present invention relates to novel quinoline compounds and to their formulation and use as pharmaceuticals.

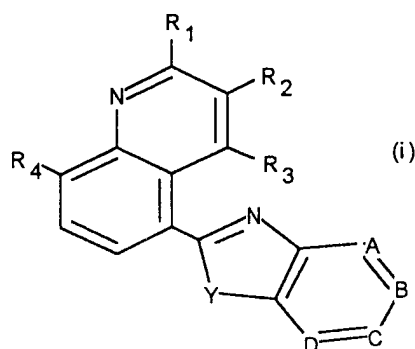
5 Background of the Invention

EP-A-0498722 generically describes quinolines having amide and alkoxy substituents. US-A-5340811 discloses quinoline-5-sulfonamides as bronchodilators, for the treatment of asthma. US-A-4910193 discloses quinolines for the treatment of serotonin-induced gastrointestinal disturbances. US-A-4867301 generically discloses
10 quinoline-5-sulfonamides as anti-allergy agents, e.g. for use in the treatment of asthma and chronic obstructive lung disease. JP-A-2/184673 also discloses quinoline-5-sulfonamides.

WO-A-9412461 discloses catechol diethers as selective phosphodiesterase (PDE) IV inhibitors. The modes of action of phosphodiesterases and also tumour necrosis factors (TNF), and the therapeutic utilities of inhibitors thereof, are described in WO-A-9720833
15 and PCT/GB97/01359-60, the contents of which are incorporated herein by reference. The two PCT Applications disclose quinoline derivatives.

Summary of the invention

This invention provides novel compounds having therapeutic utility, in particular for the treatment of disease states associated with proteins which mediate cellular activity,
20 for example by inhibiting TNF and/or PDE IV. According to the invention, the compounds are of formula (i):



25

30

wherein A, B, C and D are the same or different and are each N, NO or CR₅, provided that not more than two are N or NO;

Y represents NR₇, O or S;

R₁, R₂ and R₃ are the same or different and each represents H, R₆, OR₁₁, COR₆,
 5 C(=NOR₆)R₆, C(=NOH)R₆, alkyl-C(=NOH)R₆, alkyl-C(=NOR₆)R₆, NR₉R₁₀,
 CONHR₆, CON(R₆)₂, CONH₂, halogen, CF₃, CN, CO₂R₁₀ or CONR₁₂R₁₃;

R₄ represents OH, thioalkyl, or C₁₋₆ alkoxy or cycloalkoxy optionally substituted with one or more halogens;

R₅ represents H, halogen, alkyl, CF₃, hydroxy, OR₁₀, COR₁₁, SO₂R₁₁, SO₂NR₁₂R₁₃,
 10 NR₉R₁₀, CN, CO₂R₁₀, CONR₁₂R₁₃, NHSO₂CF₃ or tetrazolyl;

R₆ represents R₁₁ optionally substituted at any position with R₈;

R₇ represents H or C₁₋₆ alkyl;

R₈ represents OR₁₀, NR₉R₁₀, CN, CO₂R₁₀, CONR₁₂R₁₃ or COR₁₁;

R₉ represents H, alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl,
 15 heterocycloalkyl, alkylcarbonyl, alkoxy carbonyl, arylcarbonyl, heteroarylcarbonyl,
 heterocyclocarbonyl, alkylsulphonyl, arylsulphonyl, heteroarylsulphonyl or
 heterocyclosulphonyl;

R₁₀, R₁₂ and R₁₃ are the same or different and each represents H or R₁₁, or NR₁₂R₁₃
 represents a heterocyclic ring (such as morpholine or piperidine) optionally substituted
 20 with R₁₄;

R₁₁ represents alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or
 heterocycloalkyl; and

R₁₄ represents aryl, arylalkyl or heteroarylalkyl;

and include pharmaceutically-acceptable salts thereof.

25 Description of the Invention

Suitable pharmaceutically-acceptable salts are pharmaceutically-acceptable base
 salts and pharmaceutically-acceptable acid addition salts. Certain of the compounds of
 formula (i) which contain an acidic group form base salts. Suitable pharmaceutically-
 acceptable base salts include metal salts, such as alkali metal salts for example sodium
 30 salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (i) which contain an amino group form acid addition salts. Suitable acid addition salts include pharmaceutically-acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide, and pharmaceutically-acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphate, α -ketoglutarate, α -glycerophosphate and glucose-1-phosphate. The pharmaceutically-acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that some of the compounds of formula (i) may exist in more than one tautomeric form. This invention extends to all tautomeric forms.

It will also be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (i) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures including racemic mixtures thereof.

When used herein, the term alkyl whether used alone or when used as a part of another group includes straight and branched chain alkyl groups containing up to 6 atoms. Cycloalkoxy means a cyclic alkyl group containing up to 6 carbon atoms and cycloalkoxy means a cycloalkyl-O- group. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Aryl means an aromatic monocyclic or multicyclic carbocyclic group containing about 6 to 10 carbon atoms. Arylalkyl means an aryl-alkyl- group wherein the aryl and alkyl are as described herein. Heteroarylalkyl means a heteroaryl-alkyl group and heterocycloalkyl means a heterocyclo-alkyl group. Alkylcarbonyl means an alkyl-CO- group in which the alkyl group is as previously described. Arylcarbonyl means an aryl-CO- group in which the aryl group is as previously described. Heteroarylcarbonyl means a heteroaryl-CO- group and heterocyclocarbonyl means a heterocyclo-CO- group. Arylsulphonyl means an aryl-SO₂- group in which the aryl group is as previously described. Heteroarylsulphonyl means a heteroaryl-SO₂- group and heterocyclosulphonyl means a heterocyclo-SO₂- group. Alkoxy carbonyl means an alkyloxy-CO- group in which the alkoxy group is as previously described. Alkylsulphonyl means an alkyl-SO₂- group in

which the alkyl group is as previously described. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Heterocyclo means about a 5 to about a 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Halogen means fluorine, chlorine, bromine or iodine.

Compounds of the invention may be prepared by generally known processes from starting materials that are known or can readily be prepared by methods known to those of ordinary skill in the art. For example, procedures described in WO-A-9412461 and *Biorganic & Med. Chem. Letters* (1995) 5(17):1969, may be used, substituting for the catechol nucleus an appropriately substituted quinoline. The quinoline nucleus may be prepared as described in PCT/GB97/01359-60. Reference may also be made to the procedures given in *J. Indian Chem. Soc.* LXIV:42-45 (1987), and in the Examples below. Appropriate modifications will be evident to those of ordinary skill in the art.

It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups, and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see *Protective Groups in Organic Synthesis*, Wiley Interscience, TW Greene. Thus a process for preparing compounds of formula (i) containing an -OH group comprises deprotecting (for example by hydrogenolysis or hydrolysis) a compound of formula (i) which contains a corresponding -OP group wherein P represents a suitable protecting group (e.g. benzyl).

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which R₃ contains an alcohol function may be prepared by reduction of a compound of formula (i) in which R₃ contains a carbonyl function. Compounds in which R₁-R₃ contain a CO-alkyl, CO-aryl, CO-heteroaryl, CO-alkylaryl, CO-alkylheteroaryl or CO-alkylheterocyclo group may be

prepared from compounds in which R_1 - R_3 contain a CN group by addition of a suitable organometallic agent (such as a Grignard reagent).

By way of further example, compounds in which R_1 - R_3 contain an oxime may be prepared from compounds in which R_1 - R_3 contain a carbonyl group. This transformation may be carried out using any appropriate standard conditions known to those skilled in the art. Compounds of formula (i) in which R_1 - R_3 contain a carbonyl group may be reduced using standard conditions known to those skilled in the art (for example with sodium borohydride in an appropriate solvent) to provide compounds in which R_1 - R_3 contains an alcohol group. Compounds in which R_1 - R_3 is alkyl may be prepared by reduction of compounds in which R_1 - R_3 is CO-alkyl using standard conditions known to those skilled in the art (for example hydrazine hydrate in the presence of a suitable base in an appropriate solvent). Other transformations may be carried out on compounds of formula (i) in which R_1 - R_3 contains a carbonyl group. Such transformations include, but are not limited to, reductive amination and alkylation. Any of the above transformations may be carried out either at the end of the synthesis or on an appropriate intermediate.

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may be performed using the appropriate homochiral starting material.

The invention includes the prevention and treatment of TNF mediated disease or disease states, by which is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin), and since each induces similar biological responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF-inhibiting amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

The compounds of this invention may also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF-mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus

(FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will
5 elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, a pharmaceutically-acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-
10 acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%. When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered
15 *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically-acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, and a pharmaceutically-
20 acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself
25 in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment
30 of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

5 In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-
10 starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending,
15 filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

20 Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated
25 edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia, non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

30 Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for

insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 μm , such as from 0.1 to 50 μm , preferably less than 10 μm , for example from 1 to 10 μm , 1 to 5 μm or from 2 to 5 μm . Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically-acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000 mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70 kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

The following Examples illustrate the invention.

20 Intermediate 1 8-Methoxyquinoline-5-carboxylic acid chloride, hydrochloride

A suspension of 8-methoxyquinoline-5-carboxylic acid (5.0 g) in dichloromethane (50 ml) was cooled to 0°C. Oxalyl chloride (4.29 ml) was added cautiously and then dry dimethylformamide (8 drops) was added dropwise. The mixture was stirred at 0°C for 1h and then at room temperature for 24h. The solvent was removed *in vacuo* and the residue azeotroped with a small amount of toluene. The title compound was obtained as a brown solid (5.18 g).

NMR (200MHz, d_6 -DMSO) δ 9.96(d, 1H), 9.18(dd, 1H), 8.52(d, 1H), 8.12(dd, 1H), 7.61(d, 1H), 4.20(s, 3H).

Intermediate 2 8-Methoxyquinoline-5-[N-(2-amino-5-carbomethoxyphenyl)]-carboxamide

A solution of methyl 3,4-diaminobenzoate (1.27 g) in dry pyridine (10 ml) was cooled to 0°C under nitrogen. A suspension of 8-methoxyquinoline-5-carbonyl chloride, hydrochloride (1.97 g) in dry tetrahydrofuran was added, the resultant suspension was allowed to warm to room temperature and then stirred for 16h. The resultant suspension was heated at 60°C for 16h and then cooled to room temperature. The mixture was concentrated *in vacuo* and ethyl acetate (100 ml) and 2M hydrochloric acid (50 ml) were added. The resultant precipitate was collected by filtration to provide the title compound as a brown solid (919 mg).

TLC R_f 0.52 (10% methanol in dichloromethane).

Intermediate 3 8-Methoxy-2-trifluoromethylquinoline-5-[N-(2-amino-5-carbomethoxyphenyl)]carboxamide

A solution of methyl 3,4-diaminobenzoate (1.0 g) in dry pyridine (25 ml) and triethylamine (1.7 ml) was cooled to 0°C under nitrogen. A suspension of 8-methoxy-2-trifluoromethylquinoline-5-carbonyl chloride, hydrochloride (1.8 g; Intermediate 35 of PCT/GB97/01359) in dry tetrahydrofuran (40 ml) was added; the resultant suspension was allowed to warm to room temperature and then stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (200 ml) and water (200 ml). The solid precipitate was removed by filtration and dried *in vacuo* at 45°C to yield the title compound as an off white solid (1.34 g).

Mass spectrum (EI) 420 [M+H]⁺

Intermediate 4 8-Methoxy-2-methylquinoline-5-[N-(2-hydroxy-5-methoxyphenyl)]carboxamide

A solution of 2-amino-4-methoxyphenol (3.8 g) in dry dimethylformamide (200 ml) was stirred at room temperature under nitrogen. Sodium hydride (3.9 g) was added and stirring continued for 2h. 8-Methoxy-2-methylquinoline-5-carbonyl chloride, hydrochloride (6.2 g; Intermediate 28 of PCT/GB97/01359) was added, and the resultant mixture was stirred overnight. The solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with ethyl acetate to give the title compound as a brown solid (0.86 g).

TLC R_f 0.30 (ethyl acetate)

Intermediate 5 **2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester**

8-Methoxy-2-trifluoromethylquinoline-5-[N-(2-amino-5-carbomethoxyphenyl)]carboxamide (1.3 g) was suspended in phosphorus oxychloride (10 ml) and heated at reflux for 4h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was neutralised by the addition of 46% aqueous sodium hydroxide solution and the resultant solid was collected by filtration and dried *in vacuo*. The title compound was obtained as a grey solid (1.3 g).

10 TLC R_f 0.55 (ethyl acetate)

Example 1 **2-(8-Methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester**

8-Methoxyquinoline-5-[N-(2-amino-5-carbomethoxyphenyl)]carboxamide (919 mg) was suspended in phosphorus oxychloride (10 ml) and heated at reflux for 4h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was basified to pH 8 by the addition of saturated aqueous sodium hydrogen carbonate solution and the resultant solid was collected by filtration and dried *in vacuo*. The title compound was obtained as a light brown solid (850 mg).

15 NMR (400MHz, d₆-DMSO) δ 9.79(d, 1H), 8.94(d, 1H), 8.38(d, 1H), 8.25(d, 1H), 7.88(d, 1H), 7.73(d, 1H), 7.70(d, 1H), 7.40(d, 1H), 4.08(s, 3H), 3.89(s, 3H).

Example 2 **2-(8-Methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester dihydrochloride**

A sample of 2-(8-methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester (45 mg) was dissolved in 2M hydrochloric acid (3 ml), the resultant solution filtered and the filtrate concentrated *in vacuo*. The residue was triturated with dichloromethane and dried *in vacuo* to provide the title compound as a yellow solid (34 mg).

25 NMR (200MHz, d₆-DMSO) δ 9.82(d, 1H), 9.10(d, 1H), 8.40(d, 1H), 8.32(bs, 1H), 7.90(bd, 2H), 7.87(d, 1H), 7.66(d, 1H), 4.18(s, 3H), 3.91(s, 3H).

Example 3 **2-(8-Methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid dihydrochloride**

A mixture of 2-(8-methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester (730 mg), 1M sodium hydroxide solution (40 ml) and ethanol (40 ml) was heated at reflux for 2h and then stirred at room temperature for 16h. The mixture was concentrated *in vacuo* and the residue acidified to pH 1 with concentrated hydrochloric acid and diluted with water (20 ml). The resultant solid was collected by filtration and then dissolved in methanol (30 ml). The solution was concentrated *in vacuo* and the resultant yellow solid dried over silica to provide the title compound (600 mg).

5 TLC R_f 0.15 (1% acetic acid, 5% methanol in ethyl acetate)

Mass spectrum (CI) 320 [M+H]⁺

Example 4 **2-(8-Methoxy-2-methylquinolin-5-yl)-5-methoxy-1H-benzimidazole**

A solution of 4-methoxy-1,2-phenylenediamine (3.0 g) in dry pyridine (50 ml) and triethylamine (5.5 ml) was cooled to 0°C under nitrogen. A suspension of 8-methoxy-2-methylquinoline-5-carbonyl chloride, hydrochloride (5.4 g; Intermediate 28 of PCT/GB97/01359) in dry tetrahydrofuran (60 ml) was added; the resultant suspension was allowed to warm to room temperature and then stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (2x200 ml) and water (300 ml). The solid precipitate was removed by filtration and dried *in vacuo* at 50°C to yield an off white solid (4.25 g). The crude amide (1.0 g) was suspended in phosphorus oxychloride (10 ml) and heated at reflux for 4h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with water and left to stand for 2 days. The solution was basified to pH14 by the addition of 46% aqueous sodium hydroxide solution and the resultant brown solid was collected by filtration and dried *in vacuo* to give a brown solid. Purification by flash chromatography eluting with 10% methanol/1% triethylamine/ethyl acetate followed by trituration with hexane gave the title compound as a beige solid (0.12 g).

15 TLC R_f 0.32 (10% methanol in ethyl acetate)

20 m.p. 145.5-147.5°C

25

30

The following compounds were prepared in a similar manner using the appropriate starting materials.

Example 5 **2-(8-Methoxy-2-methylquinolin-5-yl)-5-aza-1H-benzimidazole**

Prepared from 3,4-diaminopyridine; the title compound was obtained as a light
5 brown solid (0.37 g).

TLC R_f 0.54 (12% methanol in dichloromethane)

m.p. 150°C (dec.)

Example 6 **2-(8-Methoxy-2-methylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester**

10 Prepared from methyl 3,4-diaminobenzoate; purification by flash chromatography eluting with ethyl acetate gave the title compound as a pale orange solid (0.17 g).

TLC R_f 0.25 (ethyl acetate)

m.p. 165-167°C

Example 7 **2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-5-methoxy-1H-benzimidazole**

15

Prepared from 8-methoxy-2-trifluoromethylquinoline-5-carbonyl chloride, hydrochloride (Intermediate 35 of PCT/GB97/01359) and 4-methoxy-1,2-phenylenediamine; purification by column chromatography eluting with 50%-70% ethyl acetate in hexane afforded the title compound as a pale yellow solid (1.32 g).

20 TLC R_f 0.14 (50% ethyl acetate in hexane)

m.p. 131-133°C.

Example 8 **2-(8-Methoxy-2-methylquinolin-5-yl)-5-methoxybenzoxazole**

8-Methoxy-2-methylquinoline-5-[N-(2-hydroxy-5-methoxyphenyl)]carboxamide (0.86 g) was suspended in phosphorus oxychloride (8.8 ml) and heated at reflux for 5h.

25 The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with water and neutralised by the addition of 1N aqueous sodium hydroxide solution. The aqueous phase was extracted with dichloromethane (5x50 ml), dried (magnesium sulphate) and the solvent removed *in vacuo* to give a brown glass. Purification by flash chromatography eluting with ethyl acetate followed by trituration with
30 acetone gave the title compound as a white solid (1.3 mg).

TLC R_f 0.37 (ethyl acetate)

NMR (200MHz, CDCl₃) δ 2.9 (s, 3H), 3.9 (s, 3H), 4.2 (s, 3H), 7.0 (dd, 1H), 7.2 (d, 1H), 7.4 (d, 1H), 7.6 (dd, 2H), 8.4 (d, 1H), 9.9 (d, 1H).

Example 9 **2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-5-methoxy-1-methyl-benzimidazole and 2-(8-Methoxy-2-trifluoromethyl-quinolin-5-yl)-6-methoxy-1-methyl-benzimidazole**

Sodium hydride (32 mg) was added to 2-[8-methoxy-2-trifluoromethylquinolin-5-yl]-5-methoxy-1H-benzimidazole (0.25 g) in *N,N*-dimethylformamide (5 ml) at room temperature under an inert atmosphere. After stirring for 25 minutes iodomethane (0.06 ml) was added and the reaction stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (2x45 ml) and water (45 ml). The combined organic phases were dried over magnesium sulphate and preadsorbed onto silica *in vacuo*. Purification by column chromatography eluting with 75% ethyl acetate in hexane afforded the title compound as a pale yellow solid (0.23 g) as a 1:1 mixture of the two isomers.

TLC R_f 0.49 (75% ethyl acetate in hexane)

Mass spectrum (CI) 388 [M+H]⁺

Example 10 **2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid**

Sodium hydroxide (1M, 40 ml) was added to a stirred suspension of 2-(2-trifluoromethyl-8-methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester (1 g) in ethanol (40 ml) at room temperature. The reaction was heated to 80°C for 4h and cooled to room temperature. The ethanol was removed *in vacuo* and the remaining aqueous phase acidified to pH 5 with glacial acetic acid. The resulting solid was collected by filtration and dried *in vacuo* to give the titled compound as a brown solid (0.88 g).

m.p. 249°C (dec.)

Mass spectrum (CI) 388 [M+H]⁺

The following compound was prepared in a similar manner using the appropriate starting materials.

Example 11 **2-(8-Methoxy-2-methylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid**

Prepared from 2-(8-Methoxy-2-methylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester; the title compound was obtained as a white solid (35 mg).

5 TLC R_f 0.16 (10% methanol in dichloromethane)

m.p. 205-207°C (dec.)

Example 12 **2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxamide**

Ammonia (0.5M in 1,4-dioxane, 3.9 ml) was added to a stirred solution of 2-(8-methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid (0.15 g) in
10 1,4-dioxane (30 ml) at room temperature under an inert atmosphere. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.11 g) was added followed by 4-dimethylaminopyridine (36 mg) and the reaction stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl
15 acetate (2x40 ml) and water (50 ml). The combined organic phases were dried over magnesium sulphate and preadsorbed onto silica *in vacuo*. Purification by column chromatography eluting with 10% methanol in ethyl acetate afforded the title compound as a cream solid (20 mg).

TLC R_f 0.62 (10% methanol in ethyl acetate)

20 m.p. 205-207°C

Assay Methods

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (I) are standard assay procedures as disclosed by Schilling *et al*,
Anal. Biochem. 216:154 (1994), Thompson and Strada, Adv. Cycl. Nucl. Res. 8:119
25 (1979) and Gristwood and Owen, Br. J. Pharmacol. 87:91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

The ability of compounds of formula (i) to inhibit TNF production in human
30 peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are prepared from freshly taken blood or "Buffy coats" by standard procedures. Cells are

plated out in RPMI1640 +1% foetal calf serum in the presence and absence of inhibitors. LPS (100 ng/ ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere of 95% air/5% CO₂. Supernatants are tested for TNF α by ELISA using commercially available kits.

5 *In vivo* activity in a skin eosinophilia model is determined by using the methods described by Hellewell *et al*, Br. J. Pharmacol. 111:811 (1994) and Br. J. Pharmacol. 110:416 (1993). Activity in a lung model is measured using the procedures described by Kallos and Kallos, Int. Archs. Allergy Appl. Immunol. 73:77 (1984), and Sanjar *et al*, Br. J. Pharmacol. 99:679 (1990).

10 An additional lung model, which allows measurement of inhibition of the early and late-phase asthmatic responses and also the inhibition of airway hyperreactivity, is described by Broadley *et al*, Pulmonary Pharmacol. 7:311 (1994), J. Immunological Methods 190:51 (1996) and British J. Pharmacol. 116:2351 (1995). Compounds of the invention show activity in this model.

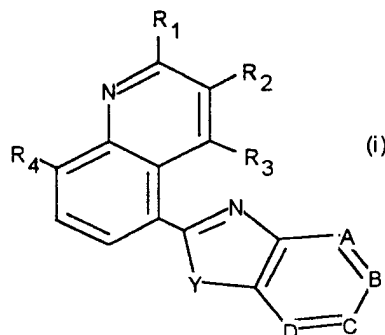
15 Abbreviations

LPS	Lipopolysaccharide (endotoxin)
ELISA	Enzyme linked immunosorbent assay

CLAIMS

1. A compound of formula (i)

5



10

wherein A, B, C and D are the same or different and are each N, NO or CR₅, provided that not more than two are N or NO;

Y represents NR₇, O or S;

15

R₁, R₂ and R₃ are the same or different and each represents H, R₆, OR₁₁, COR₆, C(=NOR₆)R₆, C(=NOH)R₆, alkyl-C(=NOH)R₆, alkyl-C(=NOR₆)R₆, NR₉R₁₀, CONHR₆, CON(R₆)₂, CONH₂, halogen, CF₃, CN, CO₂R₁₀ or CONR₁₂R₁₃;

R₄ represents OH, thioalkyl, or C₁₋₆ alkoxy or cycloalkoxy optionally substituted with one or more halogens;

20

R₅ represents H, halogen, alkyl, CF₃, hydroxy, OR₁₀, COR₁₁, SO₂R₁₁, SO₂NR₁₂R₁₃, NR₉R₁₀, CN, CO₂R₁₀, CONR₁₂R₁₃, NHSO₂CF₃ or tetrazolyl;

R₆ represents R₁₁ optionally substituted at any position with R₈;

R₇ represents H or C₁₋₆ alkyl;

R₈ represents OR₁₀, NR₉R₁₀, CN, CO₂R₁₀, CONR₁₂R₁₃ or COR₁₁;

25

R₉ represents H, alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxy carbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl, alkylsulphonyl, arylsulphonyl, heteroarylsulphonyl or heterocyclosulphonyl;

30

R₁₀, R₁₂ and R₁₃ are the same or different and each represents H or R₁₁, or NR₁₂R₁₃ represents a heterocyclic ring (such as morpholine or piperidine) optionally substituted with R₁₄;

R_{11} represents alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl; and

R_{14} represents aryl, arylalkyl or heteroarylalkyl;
or a pharmaceutically-acceptable salt thereof.

5 2. A compound of claim 1, wherein none of R_1 , R_2 and R_3 is OR_{11} ; R_4 is OH, thioalkyl or optionally-substituted alkoxy; and A, B, C and D are each N or CR_5 , provided that not more than one is N.

3. A compound of claim 2, wherein R_1 , R_2 and R_3 are the same or different and are each H, CF_3 , COR_6 , $C(=NOH)R_6$, CN, R_6 , alkyl, alkyl- $C(=NOR_6)R_6$ or alkyl- $C(=NOH)R_6$.

10 4. A compound of any preceding claim, wherein R_4 is optionally-substituted alkoxy.

5. A compound of claim 4,

wherein one of A, B, C and D is CR_5 and the others are CH;

R_1 , R_2 and R_3 are the same or different and are each H, R_6 , COR_6 , $C(=NOR_{11})R_6$, CN, $COOR_{10}$ or $CONR_{12}R_{13}$;

15 R_5 is $COOR_{10}$, $CONR_{12}$, $NHSO_2CF_3$ or tetrazolyl; and

R_{12} and R_{13} are each H or R_{11} .

6. A compound of claim 1, which is 2-(8-methoxyquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid as its methyl ester, dihydrochloride or methyl ester dihydrochloride.

7. A compound of claim 1, which is

20 2-(8-methoxy-2-methylquinolin-5-yl)-5-methoxy-1H-benzimidazole,

2-(8-methoxy-2-trifluoromethylquinolin-5-yl)-5-methoxy-1H-benzimidazole,

2-(8-Methoxy-2-trifluoromethylquinolin-5-yl)-5-methoxy-1-methyl-benzimidazole,

or

25 2-(8-Methoxy-2-trifluoromethyl-quinolin-5-yl)-6-methoxy-1-methyl-benzimidazole.

8. A compound of claim 1, which is

2-(8-methoxy-2-methylquinolin-5-yl)-5-aza-1H-benzimidazole,

2-(8-methoxy-2-methylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, methyl ester,

30 2-(8-methoxy-2-methylquinolin-5-yl)-5-methoxybenzoxazole,

2-(8-methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid,
2-(8-methoxy-2-methylquinolin-5-yl)-1H-benzimidazole-5-carboxylic acid, or
2-(8-methoxy-2-trifluoromethylquinolin-5-yl)-1H-benzimidazole-5-carboxamide.

9. A compound of any preceding claim, in the form of an enantiomer thereof.

5 10. A pharmaceutical composition for therapeutic use comprising a compound of any preceding claim and a pharmaceutically-acceptable carrier or excipient.

11. Use of a compound of any of claims 1 to 9, for the manufacture of a medicament for use in the treatment of a disease state that is capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor, or that is a pathological condition
10 associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

12. The use of claim 11, wherein the disease state is an inflammatory disease or autoimmune disease.

13. The use of claim 11, wherein the disease state is selected from asthma, chronic
15 bronchitis, chronic pulmonary inflammatory disease, chronic obstructive airways disease, atopic dermatitis, allergic rhinitis, psoriasis, arthritis, rheumatoid arthritis, joint inflammation, ulcerative colitis, Crohn's disease, atopic eczema, stroke, bone resorption disease, multiple sclerosis and inflammatory bowel disease.

14. The use of claim 11, wherein the disease state is selected from urticaria, allergic
20 conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis and other arthritic conditions, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis,
25 septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever or myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, Bechet's disease,
30 anaphylactoid purpura nephritis, chronic glomerulonephritis, leukaemia, tarditive

dyskinesia, yeast or fungal infection, conditions requiring gastroprotection, and neurogenic inflammatory disease associated with irritation and pain.

15. The use of claim 12, wherein the disease state is asthma.

16. The use of claim 12, wherein the disease state is chronic obstructive airways

5 disease or chronic bronchitis.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/03047

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/04 A61K31/47 C07D413/04 C07D417/04 C07D487/04
 C07D498/04 C07D513/04 C07D473/00 A61K31/495

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)

IPC 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZARIF H. KHALIL ET AL.: "Synthesis of some oxazolo-, imidazolo-, selenadiazolo-, thiadiazolo-, azetidino- and thiazolidinono-8-hydroxyquinolines" JOURNAL INDIAN CHEMICAL SOCIETY, vol. 64, no. 1, 1987, CALCUTTA, pages 42-45, XP002040517 see compounds 4a and 4e	1
A	WO 94 12461 A (PFIZER) 9 June 1994 cited in the application see claims 1,10	1,3

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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- "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
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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 97/03047

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