QUINOLINE CARBOXAMIDES AS TNF INHIBITORS AND AS PDE-IV INHIBITORS

Field of the Invention

The present invention relates to novel quinolines, and to their formulation and use as pharmaceuticals.

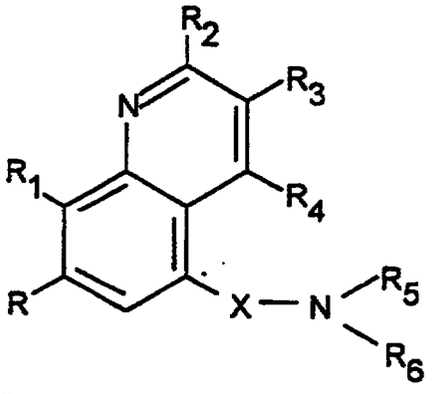
Background of the Invention

EP-A-0498722 discloses quinoline amides as angiotensin A_2 and endothelin inhibitors.

Phosphodiesterases (PDE) and Tumour Necrosis Factor (TNF), their modes of action and the therapeutic utilities of inhibitors thereof, are described in WO-A-9636595, WO-A-9636596 and WO-A-9636611, the contents of which are incorporated herein by reference. The same documents disclose amides having utility as PDE and TNF inhibitors.

Summary of the Invention

This invention is based on the discovery of novel compounds that can be used to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):



(i)

wherein X is CO or CS;

R is H, halogen or alkyl;

R_1 represents OH, alkoxy optionally substituted with one or more halogens, or thioalkyl;

R_2, R_3 and R_4 are the same or different and are each H, R_7, OR_{11}, COR_7, $C(=NOR_7)R_7$, alkyl-$C(=NOR_7)R_7$, halogen, CF_3, alkyl-$C(=NOH)R_7$, $C(=NOH)R_7$, CN,

CO_2H, CO_2R_{11}, $CONH_2$, $CONHR_7$, $CON(R_7)_2$, NR_9R_{10} or $CONR_{12}R_{13}$ where $NR_{12}R_{13}$ is a heterocyclic ring (such as morpholine or piperidine) optionally substituted with one or more R_{15};

R_5 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, $S(O)_mR_{11}$ or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy, CO_2R_8, $SO_2NR_{12}R_{13}$, $CONR_{12}R_{13}$, CN, carbonyl oxygen, NR_9R_{10}, COR_{11} and $S(O)_nR_{11}$;

R_6 represents aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

in R_5 and/or R_6, the aryl/heteroaryl/heterocyclo portion is optionally substituted with one or more substituents alkyl-R_{14} or R_{14};

R_7 represents R_{11} optionally substituted at any position with (one or more) R_{16};

R_8 represents H, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 represents H, aryl, heteroaryl, heterocyclo, cycloalkyl, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

R_{10} represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

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

R_{12} and R_{13} are the same or different and are each H or R_{11}, or $NR_{12}R_{13}$ represents a heterocyclic ring as defined above;

R_{14} represents alkyl (optionally substituted by one or more halogens), cycloalkyl, aryl, heteroaryl, heterocyclo, hydroxy, alkoxy (optionally substituted by one or more halogens), thioalkyl, aryloxy, heteroaryloxy, heterocyclooxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, CO_2R_8, $CONR_{12}R_{13}$, $SO_2NR_{12}R_{13}$, halogen, -CN, $-NR_9R_{10}$, COR_{11}, $S(O)_nR_{11}$, or (where appropriate) carbonyl oxygen;

R_{15} represents alkyl, arylalkyl or heteroarylalkyl;

R_{16} represents alkyl, OH, OR_{11}, NR_9R_{10}, CN, CO_2H, CO_2R_{11}, $CONR_{12}R_{13}$ or COR_{11};

m represents 1-2; and

n represents 0-2;

and pharmaceutically-acceptable salts.

Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

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 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 be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted atoms. The presence of one or more of these asymmetric centers 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. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Aryloxy means an aryl-O- group in which the aryl group is as defined below. Heteroaryloxy means a heteroaryl-O- group and heterocyclooxy means a heterocyclo-O- group in which the heteroaryl and heterocyclo group are as defined below. Arylalkyloxy means an aryl-alkyl-O- group. Alkylamino means an alkyl-N- group in which the alkyl group is as previously defined, arylamino means aryl-N- and heteroarylamino means an

heteroaryl-N- group (aryl and heteroaryl defined below). Thioalkyl means an alkyl-S-group. Cycloalkyl includes a non-aromatic cyclic or multicyclic ring system of about 3 to 10 carbon atoms. The cyclic alkyl may optionally be partially unsaturated. Aryl indicates carbocyclic radicals 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-SO_2- group in which the aryl group is as previously described. Heteroarylsulphonyl means a heteroaryl-SO_2- group and heterocyclosulponyl means a heterocyclo-SO_2- group. Alkoxycarbonyl means an alkyloxy-CO- group in wich the alkoxy group is as previously desribed. Alkylsulphonyl means an alkyl-SO_2- group in which the alkyl group is as previously described. Carbonyl oxygen means a -CO- group. It will be appreciated that a carbonyl oxygen can not be a substituent on an aryl or heteroaryl ring. Carbocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system which may saturated or partially unsaturated. Heterocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system (which may saturated or partially unsaturated) wherein one or more of the atoms in the ring system is an element other than carbon chosen from amongst nitrogen, oxygen or sulphur atoms. 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; if desired, a N atom may be in the form of an N-oxide. 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. Examples include morpholine and piperidine. Halogen means fluorine, chlorine, bromine or iodine.

Compounds of the invention are useful for the treatment of TNF mediated disease states. "TNF mediated disease or disease states" means 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 biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are considered to be inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically indicated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, chronic obstructive airways disease, 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, sepsis, 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. PDE IV inhibitors may also be useful in the treatment of tardive dyskinesia, ischaemia and Huntingdon's disease. 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 elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

Compounds of the invention may also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

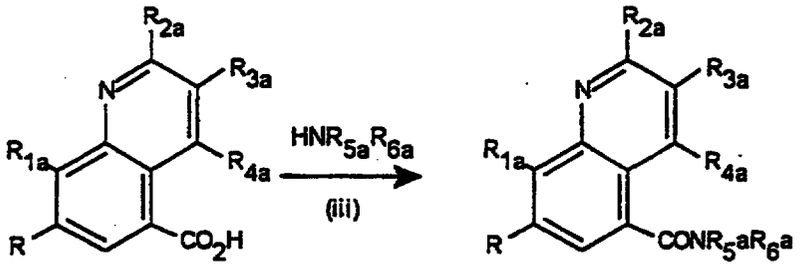
The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, of a pharmaceutically-acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (i), in which R_1 etc, m and n are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various

compounds described below, 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 sequence. 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 the process for preparing compounds of formula (i) in which R_3 contains an -OH comprises of deprotecting (for example by hydrogenolysis or hydrolysis) a compound of formula (i) in which R_3 contains an appropriate -OP wherein P represents a suitable protecting group (e.g. benzyl or acetate).

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 by performed using the appropriate homochiral starting material.

A process for the preparation of a compound of formula (i) wherein X is CO comprises reaction of an appropriate carboxylic acid of formula (ii) with a suitable amine of formula (iii)

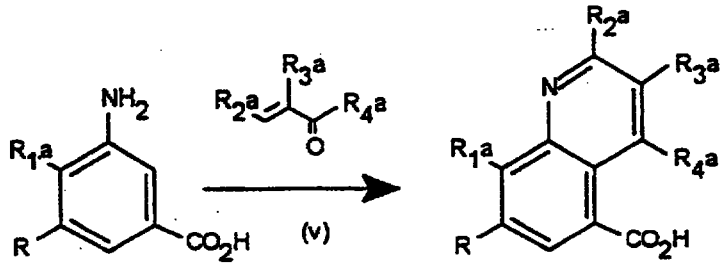


(ii) (Ia)

wherein R_{1a} represents R_1 as defined in relation to formula (i) or a group convertible to R_1 and R_{2a}-R_{6a} similarly represent R_2-R_6 or groups convertible to R_2-R_6 respectively; and thereafter, if required, converting any group R_{1a} to R_1 and/or R_{2a} to R_2 and/or R_{3a} to R_3 and/or R_{4a} to R_4 and/or R_{5a} to R_5 and/or R_{6a} to R_6. The reaction of a carboxylic acid of formula (ii) with an amine of formula (iii) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the carboxylic acid is converted into an acid chloride, mixed anhydride or other activated intermediate prior to reaction with an amine of formula (iii). Preferably, the reaction with the amine of formula (iii) is carried out in the

presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane. In some cases a stronger base, such as sodium hydride, and a polar solvent such as dimethylformamide, will be required.

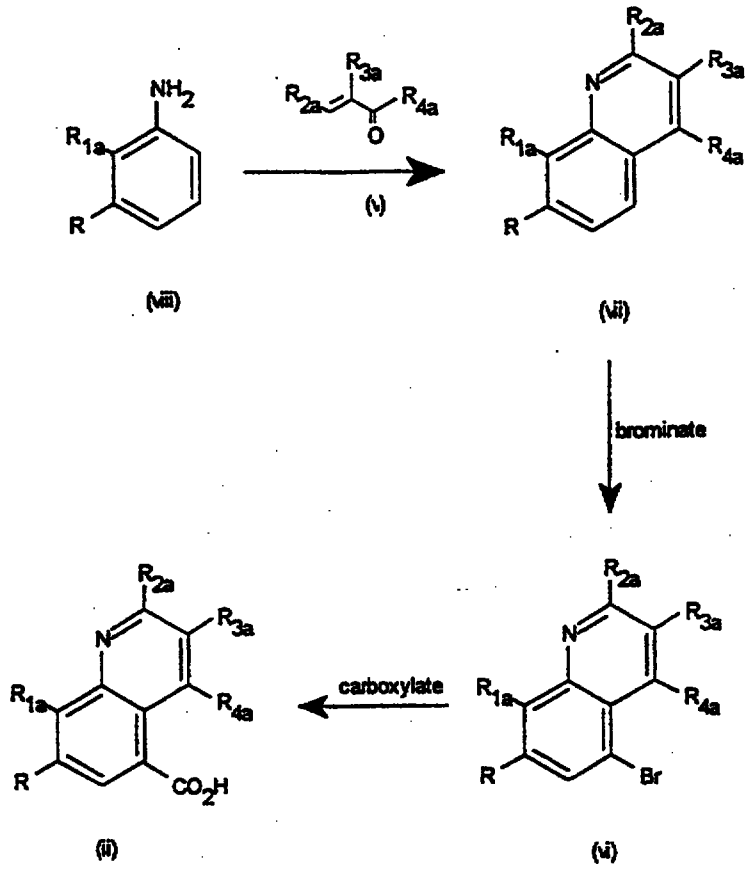
Carboxylic acids of formula (ii) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. For example, a carboxylic acid of formula (ii) can conveniently be prepared from an appropriately substituted aminobenzoic acid of formula (iv) and a ketone (or aldehyde) of formula (v) using a Skraup reaction (Z.H. Skraup, Ber. 13: 2086 (1880)). The reaction can be carried out using standard conditions known to those skilled in the art.



(iv) (ii)

Acids of formula (iv) and ketones (or aldehydes) of formula (v) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art.

Acids of formula (ii) may alternatively be prepared by carboxylation of bromides of formula (vi). Such carboxylations may be carried out using any standard conditions known to those skilled in the art, for example under organometal catalysis (e.g. palladium catalysis). Bromides of formula (vi) may be prepared by bromination of quinolines of formula (vii) under standard conditions know to those skilled in the art, for example by using bromine in methanol. Quinolines of formula (vii) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. For example, quinolines of formula (vii) may be conveniently prepared by a Skraup reaction of an appropriate aniline of formula (viii) with a ketone (or aldehyde) of formula (v). An alternative method for the preparation of quinolines of formula (vii) is the Combes reaction (A. Combes, Bull. Soc. Chim. France 49:89 (1888)).



A compound of formula (ia) may also be prepared by reaction of a carboxylic acid of formula (ii) with an amine of the formula H_2NR_{6a} (ix), to provide a compound of formula (ia) in which R_{5a} is H, followed by reaction with an appropriate agent of the formula $R_{5a}Y$ (x), wherein R_{1a}-R_{6a} are as defined earlier and Y represents a suitable leaving group such as a halogen. The reaction of a carboxylic acid of formula (ii) with an amine of formula (ix) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the carboxylic acid is converted into an acid chloride, mixed anhydride or other activated intermediate prior to reaction with an amine of formula (ix). Preferably, the reaction is carried out in the presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane. In some cases a stronger base such as sodium hydride, and a polar solvent such as dimethylformamide, may be required.

Amines of formula (iii) and (ix) and agents of formula (x) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. The reaction of a compound of formula (ia) in which R_5

is H with an agent of formula (x) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the reaction is carried out using an appropriate base, such as sodium hydride, preferably in an appropriate solvent such as dimethylformamide. Agent (x) can be an alkylating agent such as propyl bromide, an acylating agent such as benzoyl chloride or a sulphonylating agent such as methanesulphonyl chloride.

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which R_3 contains an alkoxy group may be prepared by appropriate alkylation of a compound in which R_3 contains a hydroxy group.

Compounds in which R_2-R_4 contain a CO-alkyl, CO-aryl, CO-heteroaryl, CO-alkylaryl, CO-alkylheteroaryl, CO-alkylheterocyclo may be prepared from compounds in which R_2-R_4 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_2-R_4 contain an oxime may be prepared from compounds in which R_2-R_4 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_2-R_4 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_2-R_4 contains an alcohol group. Compounds in which R_2-R_4 is alkyl may be prepared by reduction of compounds in which R_2-R_4 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_2-R_4 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.

Compounds of formula (i) in which X is CS may be prepared from compounds of formula (i) in which X is CO using any appropriate conditions known to those skilled in the art, for example by using Lawesson's reagent.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered *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-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 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 tecniques. In addition to the treatment 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.

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-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting 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.

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 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.

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 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 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; 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 70kg adult is in the range of about 0.1 to 1000mg, 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 0.5mg/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.

When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

The following Examples illustrate the invention.

Intermediate 1 **8-Methoxyquinoline-5-carboxylic acid**

A mixture of 3-amino-4-methoxybenzoic acid (5.0g), glycerol (4.16g), and iodine (135mg) in concentrated sulphuric acid (5ml) was heated at 180°C for 2 hours. The reaction was allowed to cool, diluted with water (170ml), made basic to pH8/9 with 0.88 ammonia and stirred with activated charcoal (2.0g). The mixture was filtered through Celite and the filtrate acidified to pH4/5 with acetic acid. The precipitate was obtained by filtration and dried in a dessicator to yield the desired product (4.21g) as a tan solid.

TLC R_f 0.35 (1% Acetic acid, 5% methanol in ethyl acetate)

Intermediate 2 **8-Methoxy-2-methylquinoline**

A mixture of 8-hydroxyquinaldine (5.0g) and tetrabutyl ammonium iodide (1.1g) in tetrahydrofuran (90ml) was treated at room temperature with sodium hydroxide (4.5g) in water (45ml). Methyl iodide (3.7ml) was added and the reaction stirred overnight. The THF was removed *in vacuo* and the remaining solution partitioned between ethyl acetate (100ml) and water (100ml). The aqueous layer was re-extracted with ethyl acetate and the organic extracts combined. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (100ml) and saturated aqueous sodium chloride (100ml). The organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo* to yield the desired product as an off-white solid (5.85g).

TLC R_f 0.46 (ethyl acetate)

The following Intermediates were prepared in a similar manner.

Intermediate 3 **8-Methoxyquinoline-2-carbonitrile**

The title compound was isolated as a white solid (325mg).

TLC R_f 0.27 (50% ethyl acetate in hexane)

Intermediate 4 **2-Bromo-8-methoxyquinoline**

Purification by flash chromatography on silica, eluting with 50% ethyl acetate in hexane afforded the title compound (1.45g) as a pale yellow crystalline solid.

TLC R_f 0.55 (50% ethyl acetate in hexane)

Intermediate 5 **3-Ethyl-8-methoxyquinoline**

Freshly distilled 2-ethyl acrolein (1.7ml) was added, over 20 minutes, to a solution of o-anisidine (1.5g) and iodine (20mg) in 70% sulphuric acid (10ml) stirring at 110°C. After 2 hours the reaction was cooled to 0°C and basified with 25% aqueous sodium hydroxide (pH 13). The aqueous layer was extracted with ethyl acetate (2x100ml) and the extracts combined. The organic layer was extracted with 2M hydrochloric acid (2x100ml) and the combined acidic extracts basified once again with 25% sodium hydroxide. The aqueous layer was extracted with ethyl acetate (2x100ml), the extracts combined, dried over magnesium sulphate, filtered, and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography, eluting with 25%-50% ethyl acetate in hexane, to yield the title product as a tan oil (0.42g).

TLC R_f 0.17 (50% ethyl acetate in hexane)

Intermediate 6 **2-Ethyl-8-methoxyquinoline**

n-Butyllithium (1ml, 1.6M in hexanes) was added dropwise to a stirred solution of 8-methoxy-2-methylquinoline (0.25g) in tetrahydrofuran (4ml) at -60°C under an inert atmosphere. The resulting red solution was stirred at -60°C for 15 minutes, and then warmed to -40°C. Iodomethane (0.27ml) was then added dropwise and the reaction warmed slowly to room temperature with continued stirring for 12 hours. The reaction was quenched with brine (50ml) and extracted with dichloromethane (2x50ml). The organic phases were combined, dried over magnesium sulphate and preadsorbed onto silica. Purification was achieved by column chromatography eluting with ethyl acetate to afford the title compound as a pale yellow solid (0.16g).

TLC R_f 0.53 (ethyl acetate).

Intermediate 7 **7-Fluoro-8-methoxyquinoline**

A solution of 3-fluoro-2-methoxyaniline (5.0g) in 1,2-dichlorobenzene (50ml) was heated to 170°C and treated with *p*-toluenesulphonic acid (0.7g). A solution of acrolein (4.0g) in 1,2-dichlorobenzene (20ml) was added dropwise over 20 minutes. The reaction was stirred for 1 hour at 170°C before being allowed to cool. The mixture was extracted with 2N hydrochloric acid (3 x 200ml) and the combined extracts washed with dichloromethane (20ml), basified with 25% aqueous sodium hydroxide, and extracted with ethyl acetate (3 x 200ml). The combined extracts were dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column

chromatography on silica gel eluting with 50% ethyl acetate in hexane to yield the desired product (2.6g) as a clear oil.

TLC R_f 0.21 (50% ethyl acetate in hexane).

Intermediate 8 **5-Bromo-8-methoxy-2-methylquinoline**

A solution of 8-methoxy-2-methylquinoline (1.0g) in methanol (30ml) was treated at room temperature with bromine (0.31ml). The mixture was heated at 45°C for 2 hours and the reaction quenched with 5% aqueous sodium metabisulphite (50ml). The solution was basified with 25% aqueous sodium hydroxide to pH13 and the product extracted with ethyl acetate (2x100ml). The extracts were combined, dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in ethyl acetate and passed through a silica pad. The solution was evaporated *in vacuo* to yield the desired product as an off-white solid (0.43g).

TLC R_f 0.57 (ethyl acetate)

The following Intermediates were prepared in a similar manner.

Intermediate 9 **5-Bromo-3-ethyl-8-methoxyquinoline**

The title compound was isolated as a tan solid (0.501g).

TLC R_f 0.125 (50% ethyl acetate in hexane).

Intermediate 10 **5-Bromo-2-ethyl-8-methoxyquinoline**

The title compound was isolated as a brown oily solid (3.3g).

TLC R_f 0.67 (15% ethyl acetate in dichloromethane).

Intermediate 11 **5-Bromo-8-methoxy-2-(trifluoromethyl)quinoline**

The title compound (4.15g) was obtained as a white solid.

mp 84-85°C

Intermediate 12 **5-Bromo-7-fluoro-8-methoxyquinoline**

Bromine (0.48ml) was added dropwise to a solution of 7-fluoro-8-methoxyquinoline (1.6g) in glacial acetic acid (24ml). The mixture was heated to 40°C for 4 h and the reaction quenched with 5% aqueous sodium metabisulphite (100ml). The solution was basified with 25% aqueous sodium hydroxide to pH13 and the product extracted with ethyl acetate (3x150ml). The extracts were combined, dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 25% ethyl acetate in hexane to yield the desired product as a white solid (0.50g).

TLC R_f 0.46 (50% ethyl acetate in hexane).

Intermediate 13 **5-Bromo-8-methoxyquinoline-2-carbonitrile**

Sodium acetate (690mg) was added to a solution of Intermediate 3(310mg) in glacial acetic acid (10ml). Bromine (0.1ml) was added dropwise, and the mixture stirred at room temperature for 17 h. It was quenched with 5% aqueous sodium metabisulphite (20ml), then basified with 25% aqueous sodium hydroxide to pH13 and extracted with ethyl acetate (3 x 60ml). The extracts were combined, dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 33% ethyl acetate in hexane to yield the desired product as a white solid (365mg).

TLC R_f 0.63 (50% ethyl acetate in hexane).

Intermediate 14 **Methyl 5-bromo-8-methoxyquinoline-2-carboxylate**

Purification by flash chromatography gave the title compound (0.48g) as a white solid.

TLC R_f 0.37 (ethyl acetate in hexane)

Intermediate 15 **5-Bromo-8-difluoromethoxyquinoline**

Aqueous sodium hydroxide (47%, 15ml) and benzyltriethylammonium chloride (0.25g) were added to a suspension of 5-bromo-8-hydroxyquinoline (2.74g) in dioxane (150ml). The vigorously stirred mixture was heated to 75°C and chlorodifluoromethane gas was bubbled through the reaction mixture with a diffuser for 50 minutes. The solution was allowed to cool to room temperature and the reaction mixture was poured into water (250ml) and extracted with ethyl acetate (3 x 200ml). The combined organic extracts were washed with water (2 x 150ml), dried (magnesium sulphate) and evaporated *in vacuo*. The residue was purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to furnish the title compound (1.64g) as a yellow solid.

TLC R_f 0.70 (50% ethyl acetate in hexane)

Intermediate 16 **5-Bromo-8-difluoromethoxyquinaldine**

Purification by recrystallisation from aqueous methanol afforded the title compound as an offwhite solid (4.8g).

TLC R_f 0.86 (50% ethyl acetate in hexane).

Intermediate 17 **8-Methoxy-2-methylquinoline-5-carboxylic acid**

A mixture of 5-bromo-8-methoxy-2-methylquinoline (2.0g), triethylamine (11ml), triphenylphosphine (0.79g), and bis(triphenylphosphine)palladium (II) chloride (1.56g) in tetrahydrofuran (200ml) and water (90ml) was stirred in a pressurised reaction vessel and charged with carbon monoxide to a pressure of 160psi. The vessel was heated to 80°C and stirred for 72 hours. The reaction was allowed to cool and depressurised. The mixture was filtered and the organic solvent was removed *in vacuo*. The aqueous residue was basified with 1M sodium hydroxide and washed with ethyl acetate (300ml). The aqueous solution was acidified to pH 5 with glacial acetic acid and extracted with ethyl acetate (2x400ml). The organic extracts were combined, dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo* to yield the title product (1.0g) as an off-white solid.

TLC R_f 0.17 (ethyl acetate).

The following Intermediates were prepared in a similar manner:-

Intermediate 18 **3-Ethyl-8-methoxyquinoline-5-carboxylic acid**

The title compound was obtained from 5-bromo-3-ethyl-8-methoxyquinoline and isolated as an off-white solid (0.6g).

TLC R_f 0.7 (10% methanol in ethyl acetate).

Intermediate 19 **2-[(*t*-Butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline-5-carboxylic acid**

The title compound (0.311g) was prepared from 5-bromo-2[(*t*-butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline (1.18g).

Mass spectrum (EI) 233 $[M\text{-}Boc+H]^+$

The following Intermediates were prepared in a similar manner, but on acidification of the aqueous phase to pH4-5 with glacial acetic acid, the title compounds were precipitated. They were removed by filtration and dried *in vacuo*.

Intermediate 20 **8-Difluoromethoxyquinoline-5-carboxylic acid**

The title compound was isolated as a beige solid (0.85g).

mp 280°C (dec.)

Intermediate 21 **8-Difluoromethoxyquinaldine-5-carboxylic acid**

The title compound was isolated as a beige solid (2.9g).

TLC R_f 0.6 (10% methanol in dichloromethane)

Intermediate 22 **7-Fluoro-8-methoxyquinoline-5-carboxylic acid**

The title compound was isolated as an off-white solid (0.58g).

TLC R_f 0.1 (ethyl acetate).

Intermediate 23 **8-Methoxy-2-(pyrid-3-yl)-quinoline-5-carboxylic acid**

The title compound was obtained as a beige powder (366mg).

mp 264°C (dec.)

The following Intermediates were prepared in a similar manner, but using dimethylformamide as the solvent instead of tetrahydrofuran:-

Intermediate 24 **2-Cyano-8-methoxyquinoline-5-carboxylic acid**

The title compound was isolated as an off-white solid (0.304g).

TLC R_f 0.1 (ethyl acetate).

Intermediate 25 **8-Methoxy-2-(trifluoromethyl)quinoline-5-carboxylic acid**

The title compound (3.10g) was obtained as a white solid.

mp 248-249°C

Intermediate 26 **2-Ethyl-8-methoxyquinoline-5-carboxylic acid**

A mixture of 5-bromo-2-ethyl-8-methoxyquinoline (3.3g), sodium hydroxide (3.1g, 46% solution in water), triphenylphosphine (0.22 g), and bis(triphenylphosphine)palladium (II) chloride (0.14g) in tetrahydrofuran (14ml) and water (7ml) was stirred in a pressurised reaction vessel and charged with carbon monoxide to a pressure of 160psi. The vessel was heated to 105°C and stirred for 24 hours. The reaction was allowed to cool and depressurised. The mixture was filtered and the solid collected washed with tetrahydrofuran (2x10ml). The solid was dissolved in hot methanol (10ml) and water (10ml), and the solution filtered to remove any remaining solids. The hot solution was treated with glacial acetic acid (2ml) and cooled in ice. The resulting precipitate was filtered off and dried over silica gel under vacuum to afford the title compound as a white solid (0.44g).

TLC R_f 0.2 (ethyl acetate).

Intermediate 27 **8-Methoxyquinoline-5-carbonyl chloride, hydrochloride**

A suspension of 8-methoxyquinoline-5-carboxylic acid (1.5g) in dichloromethane (12ml) was cooled to 0°C and treated with oxalyl chloride (1.3ml) followed by DMF (8 drops). The reaction was allowed to warm to room temperature and stirred overnight. The

solvent was removed *in vacuo* and the residue azeotroped with toluene (2x10ml) to yield the desired product (1.61g) as an off-white powder.

The following acid chlorides were prepared in a similar manner from the appropriate carboxylic acid:-

Intermediate 28 **8-Methoxy-2-methylquinoline-5-carbonyl chloride, hydrochloride**

The title compound was isolated as an off-white solid (0.5g).

Intermediate 29 **3-Ethyl-8-methoxyquinoline-5-carbonyl chloride, hydrochloride**

The title compound was isolated as an off-white solid (0.68g).

Mp 185-186°C (dec.)

Intermediate 30 **7-Fluoro-8-methoxyquinoline-5-carbonyl chloride, hydrochloride**

The title compound was isolated as a brown solid (0.64g).

Intermediate 31 **2-Cyano-8-methoxyquinoline-5-carbonyl chloride, hydrochloride**

The title compound was isolated as a brown solid (0.32g).

Intermediate 32 **8-Difluoromethoxyquinoline-5-carbonyl chloride, hydrochloride**

The title compound was obtained as a beige solid (853mg).

Intermediate 33 **2-Ethyl-8-methoxyquinoline-5-carbonyl chloride, hydrochloride**

The title compound was isolated as a deep red oily solid (0.48g).

Intermediate 34 **8-Methoxy-2-(3-pyridyl)-quinoline-5-carbonyl chloride, hydrochloride**

The title compound was obtained as a beige solid (0.39g).

Intermediate 35 **8-Methoxy-2-(trifluoromethyl)quinoline-5-carbonyl chloride, hydrochloride**

The title compound was obtained as a pale yellow solid.

Intermediate 36 **4-Amino-3-chloropyridine**

A solution of 4-aminopyridine (4.0g) in concentrated hydrochloric acid (50ml) was treated at 80-85°C with an aqueous solution of hydrogen peroxide (13.5% w/v). The

solution was cooled to 0°C. After 30 minutes, the solution was carefully treated with an aqueous sodium hydroxide solution (50%w/v) maintaining the temperature below 15°C. The precipitate was filtered off and air dried to afford the title compound as a white solid (4.9g).

TLC R_f 0.36 (ethyl acetate).

Mp 65-67°C.

Intermediate 37 **8-Methoxy-2-(3-pyridyl)quinoline**

Powdered potassium hydroxide (675mg) was added to a stirred mixture of 2-bromo-8-methoxyquinoline (956mg), diethyl(3-pyridyl)borane (590mg), tetrakis(triphenylphosphine)-palladium(0) (250mg) and tetra-*n*-butylammonium iodide (740mg) in anhydrous tetrahydrofuran (60ml). The stirred mixture was refluxed under an inert atmosphere for 1.25h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (100ml) and water (80ml). The aqueous phase was reextracted with dichloromethane (2 x 50ml) and the combined organic phases were dried (magnesium sulfate), filtered through a small pad of Celite and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate to yield the title compound (780mg) as a clear oil.

TLC R_f 0.25 (ethyl acetate)

Intermediate 38 **5-Bromo-8-methoxy-2-(3-pyridyl)quinoline**

Bromine (200µl) was added in a dropwise manner to a stirred and cooled (0-5°C) solution of 8-methoxy-2-(3-pyridyl)quinoline (780mg) in methanol (30ml) under a nitrogen atmosphere. The reaction mixture was stirred for 15 minutes then quenched by the addition of 5% aqueous sodium metabisulfite solution (7ml). The reaction mixture was evaporated *in vacuo* and the residue partitioned between 0.5N sodium hydroxide solution (65ml) and dichloromethane (75ml). The aqueous phase was reextracted with dichloromethane (2 x 75ml) and the combined organic phases were dried (magnesium sulfate), filtered and evaporated *in vacuo*. Trituration with diethyl ether afforded the title compound (570mg) as a pale brown solid.

TLC R_f 0.2 (ethyl acetate)

Intermediate 39 **5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-2-trimethylstannyl-2H-tetrazole**

2-Cyano-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]-carboxamide (390mg) and trimethyltin azide (480mg) in toluene (20ml) and tetrahydrofuran (20ml) were heated to reflux for 16 hours. The reaction was cooled to room temperature and the resulting precipitate filtered off, washed with toluene (2x5ml) and dried *in vacuo* at 40°C to yield the title compound as a pale yellow solid (299mg).

Mp 229-231°C

Intermediate 40 **Methyl 8-hydroxyquinoline-2-carboxylate**

8-Hydroxyquinoline-2-carboxylic acid (2.08g) and tetrahydrofuran (200ml) were combined and stirred with ice bath cooling. Diazomethane (approx. 16.6mmol in solution in diethyl ether) was then added and the whole stirred for 1.5h as it slowly warmed to room temperature. Nitrogen was blown through the reaction mixture to purge any excess diazomethane and the solution was evaporated *in vacuo* to give the title compound (1.6g).

TLC R_f 0.12 (50% ethyl acetate in hexane)

Intermediate 41 **Methyl 8-methoxyquinoline-2-carboxylate**

Methyl 8-hydroxyquinoline-2-carboxylate (1.6g), acetone (15ml), potassium carbonate (1.3g) and iodomethane (0.6ml) were combined and stirred at room temperature for 48h. The solvents were removed *in vacuo* and the resulting white residue suspended in water (25ml) which was extracted with ethyl acetate (3 x 25ml). The combined organic layers were dried (magnesium sulphate) and the solvents removed *in vacuo* to give the title compound as a white solid (1.72g).

TLC R_f 0.22 (50% ethyl acetate in hexane)

Intermediate 42 **5-Bromo-8-methoxyquinoline-2-carboxylic acid**

Methyl 5-bromo-8-methoxyquinoline-2-carboxylate (1.54g), tetrahydrofuran (40ml), water (40ml) and lithium hydroxide monohydrate (0.436g) were combined and stirred at room temperature for 1.5h. The tetrahydrofuran was removed *in vacuo* and the resulting aqueous mixture was acidified with hydrochloric acid. The resulting white precipitate was collected by filtration and dried *in vacuo* to give the title compound (1.33g) as a white solid.

Mass spectrum (EI) 296 & 298 $[M+H]^+$

Intermediate 43 **5-Bromo-2-*t*-butyloxycarbonylamino-8-methoxyquinoline**

5-Bromo-8-methoxyquinoline-2-carboxylic acid (2g), *t*-butanol (25ml) and triethylamine (1.48ml) were combined under a nitrogen atmosphere and heated to 80°C. Diphenylphosphorylazide (2.29ml) was added to the solution and heating was continued for 60h by which time a white preciptate was present. The reaction mixture was evaporated *in vacuo* onto silica and purified by flash chromatography to give the title compound (1.21g) as an off white solid.

TLC R_f 0.50 (50% ethyl acetate in hexane)

Intermediate 44 **5-Bromo-2[(*t*-butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline**

5-Bromo-2-*t*-butyloxycarbonylamino-8-methoxyquinoline (1.21g) and tetrahydrofuran (20ml) were combined at room temperature under a nitrogen atmosphere. Sodium hydride (60% dispersion in oil) (164mg) was added and the reaction mixture stirred for 2h whilst effervescence occurred and a yellow colour appeared. Iodomethane (0.43ml) was then added and stirring was continued for 2h after which time the reaction was diluted with ethyl acetate (100ml), washed successively with water, saturated aqueous sodium bicarbonate and brine, then dried (magnesium sulphate) and evaporated *in vacuo* to give the title compound (1.18g) as a yellow solid.

TLC R_f 0.60 (50% ethyl acetate in hexane)

Intermediate 45 **4-Nitrophenyl 2-[(*t*-butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline-5-carboxylate**

2-[(*t*-Butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline-5-carboxylic acid (0.311g), ethyldimethylaminopropylcarbodiimide hydrochloride (0.269g), 4-nitrophenol (0.195g), *N,N*-dimethylaminopyridine (20mg) and dichloromethane (20ml) were combined and then stirred at room temperature for 17h. The reaction mixture was evaporated *in vacuo* onto silica and purified by flash chromatography to give the title compound (0.384g) as a pale yellow solid.

TLC R_f 0.50 (50% ethyl acetate in hexane)

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

Intermediate 46 **4-Nitrophenyl 8-difluoromethoxyquinaldine-5-carboxylate**

Purification by column chromatography eluting with 50% ethyl acetate in hexane yielded the title compound as a cream solid (0.63g).

TLC R_f 0.76 (10% methanol in dichloromethane).

Intermediate 47 **8-*t*-Butyldimethylsilyloxyquinaldine**

8-Hydroxyquinaldine (10g), *t*-butyldimethylsilyl chloride (10g) and imidazole (8.6g) were dissolved in N,N-dimethylformamide (150ml) and stirred at ambient temperature overnight. Further *t*-butyldimethylsilyl chloride (4.7g) was added and the reaction stirred for another 30 minutes. The reaction was diluted with water (600ml) and extracted with dichloromethane (3x300ml). The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound as an orange oil (17g).

TLC R_f 0.9 (10% methanol in ethyl acetate).

Intermediate 48 **5-Bromo-8-*t*-butyldimethylsilyloxyquinaldine**

N-bromosuccinimde (14g) was added in one portion to a stirred solution of 8-*t*-butyldimethylsilyloxyquinaldine (15g) in chloroform at -40°C under an inert atmosphere. The reaction was warmed to room temperature and then heated to reflux for 6 h. Further N-bromosuccinimide (6g) was added to the reaction at room temperature and stirring continued for 3 days. The reaction mixture was poured into 5% aqueous sodium metabisulphite solution (300ml) and extracted with chloroform (3x300ml). The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound as an orange oil (16.4g).

TLC R_f 0.8 (dichloromethane).

Intermediate 49 **5-Bromo-8-hydroxyquinaldine**

Tetrabutylammonium fluoride (54ml, 1M in tetrahydrofuran) was added dropwise to a stirred solution of 5-bromo-8-*t*-butyldimethylsilyloxyquinaldine (16.3g) in tetrahydrofuran (500ml). After stirring for 10 minutes the reaction was diluted with dichloromethane (500ml) and extracted with water (3x200ml). The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. Purification by recrystallisation from aqueous methanol afforded the title compound as an off white solid (7.7g).

TLC R_f 0.58 (10% methanol in dichloromethane).

Example 1 **8-Methoxyquinoline-5-[N-(pyridin-4-yl)]carboxamide**

A suspension of 8-methoxyquinoline-5-carbonyl chloride hydrochloride (0.5g) in dichloromethane (3ml) was added to a solution of 4-aminopyridine (94mg) and triethylamine (140µl) in dichloromethane (3ml) at 0°C under nitrogen. The reaction was stirred at room temperature for 16 hours and then diluted with dichloromethane. The organic solution was washed with saturated aqueous sodium hydrogen carbonate (20ml), water (5ml) and the aqueous layer extracted with dichloromethane (25ml). The organic extracts were combined and dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 15% methanol in dichloromethane to yield the title compound as an off-white solid (130mg).

TLC R_f 0.4 (15% methanol in dichloromethane)

Mp 257-258°C

The following Examples were prepared from 8-methoxyquinoline-5-carbonyl chloride, hydrochloride and the appropriate amine using a similar procedure to the one described above.

Example 2 **8-Methoxyquinoline-5-[N-(thiazol-2-yl)]carboxamide**

The title compound was obtained as an off-white solid (80mg).

TLC R_f 0.32 (10% methanol in ethyl acetate)

Mp 249-251°C

Example 3 **8-Methoxyquinoline-5-[N-(2-trifluoromethoxyphenyl)]carboxamide**

The title compound was obtained as an off-white solid (125mg).

TLC R_f 0.54 (10% methanol in ethyl acetate)

Mp 206-208°C

Example 4 **8-Methoxyquinoline-5-[N-2-(piperidin-1-yl)phenyl]carboxamide**

The title compound was obtained as an off-white solid (100mg).

TLC R_f 0.50 (10% methanol in dichloromethane)

Mp 214-216°C

Example 5 **8-Methoxyquinoline-5-[N-(2-fluorophenyl)]carboxamide**

The title compound was obtained as an off-white solid (90mg).

TLC R_f 0.41 (10% methanol in ethyl acetate)

Mp 190-192°C

Example 6 **8-Methoxyquinoline-5-[N-(2-methylphenyl)]carboxamide**

The title compound was obtained as an off-white solid (630mg).

TLC R_f 0.46 (10% methanol in dichloromethane)

Mp 215-216°C

Example 7 **8-Methoxyquinoline-5-[N-(2,6-dimethylphenyl)]carboxamide**

The title compound was obtained as an off-white solid (550mg).

TLC R_f 0.43 (10% methanol in dichloromethane)

Mp 273-275°C

Example 8 **8-Methoxyquinoline-5-[N-(2-chlorophenyl)]carboxamide**

The title compound was obtained as an off-white solid (490mg).

TLC R_f 0.47 (5% methanol in dichloromethane)

Mp 196-197°C

Example 9 **8-Methoxyquinoline-5-[N-(2-methoxyphenyl)]carboxamide**

The title compound was obtained as an off-white solid (150mg).

TLC R_f 0.60 (10% methanol in dichloromethane)

Example 10 **8-Methoxyquinoline-5-[N-(4-methoxyphenyl)]carboxamide**

The title compound was obtained as an off-white solid (780mg).

Mass spectrum (EI) 309 $[M+H]^+$

Example 11 **8-Methoxyquinoline-5-[N-(2-chloro-6-methylphenyl)]carboxamide**

The title compound was obtained as a off-white solid (700mg).

Mass spectrum (EI) 327 $[M+H]^+$

The following Example was prepared from 8-methoxy-2-methylquinoline-5-carbonyl chloride hydrochloride and 2-chloroaniline using a procedure similar to that described above.

Example 12 **8-Methoxy-2-methylquinoline-5-[N-(2-chlorophenyl)]carboxamide**

Purification by flash chromatography on silica eluting with 50% ethyl acetate in dichloromethane afforded the title compound (50mg) as a pale brown solid.

TLC R_f 0.4 (50% ethyl acetate in dichloromethane)

mp 225-226°C

Example 13 **8-Methoxyquinoline-5-[N-(2, 5-dichloropyridin-3-yl)]carboxamide**

A solution of 3-amino-2,5-dichloropyridine (504mg) in anhydrous DMF (5ml) was carefully added to a suspension of sodium hydride (272mg, 60% dispersion in oil) in anhydrous DMF (5ml) at room temperature under nitrogen. The resultant mixture was stirred for 10 minutes and then treated dropwise with a solution of 8-methoxyquinoline-5-carbonyl chloride hydrochloride (800mg) in anhydrous DMF (10ml). The reaction was stirred for two hours at 50°C and 18 hours at room temperature. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane (50ml) and saturated aqueous sodium hydrogen carbonate solution (50ml). The aqueous layer was extracted with dichloromethane (30ml). The organic extracts were combined and washed with saturated aqueous sodium chloride (10ml), dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to yield the title compound as an off-white solid (230mg).

TLC R_f 0.30 (10% methanol in ethyl acetate)

Mp 251-252°C

The following Examples were prepared from 8-methoxyquinoline-5-carbonyl chloride, hydrochloride and the appropriate amine using a similar procedure to the one described above.

Example 14 **8-Methoxyquinoline-5-[N-(pyrimidin-4-yl)]carboxamide**

The title compound was obtained as an off-white solid (130mg).

TLC R_f 0.39 (15% methanol in ethyl acetate)

Mp 225-226°C

Example 15 **8-Methoxyquinoline-5-[N-(3,5-dichloropyridin-2-yl)]carboxamide**

The title compound was obtained as an off-white solid (89mg).

Example 16 **8-Methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

The title compound was obtained as an off-white solid (452mg).

TLC R_f 0.45 (10% methanol in dichloromethane)

Mp 258-260°C

Example 17 **8-Methoxyquinoline-5-[N-(4,6-dichloropyrimidin-5-yl)]carboxamide**

The title compound was obtained as an off-white solid (264mg).

TLC R_f 0.39 (10% methanol in ethyl acetate)

Mp 249-251°C

Example 18 **8-Methoxyquinoline-5-[N-(4-chloropyridin-4-yl)]carboxamide**

The title compound was obtained as an off-white solid (40mg).

TLC R_f 0.35 (10% methanol in dichloromethane)

Mp 232-234°C

Example 19 **8-Methoxyquinoline-5-[N-(2-trifluoromethylphenyl)]carboxamide**

The title compound was obtained as an off-white solid (470mg).

TLC R_f 0.50 (15% methanol in ethyl acetate)

Mp 247-248°C

Example 20 **8-Methoxyquinoline-5-[N-(3-bromo-5-methylpyridin-2-yl]carboxamide**

The title compound was obtained as an off-white solid (250mg).

TLC R_f 0.15 (3% methanol in dichloromethane)

Example 21 **8-Methoxyquinoline-5-[N-(2-chloropyridin-3-yl)]carboxamide**

The title compound was obtained as an off-white solid (60mg).

TLC R_f 0.15 (3% methanol in ethyl acetate)

The following Examples were prepared from 8-methoxy-2-methylquinoline-5-carbonyl chloride hydrochloride and the appropriate amine using a procedure similar to that described above.

Example 22 **8-Methoxy-2-methylquinoline-5-[N-(3-chloropyridin-4-yl)]carboxamide**

Purification by flash chromatography on silica eluting with 10% methanol in ethyl acetate furnished the title compound (190mg) as a pale yellow solid.

TLC R_f 0.35 (10% methanol in ethyl acetate)

mp 222-223.5°C

Example 23 **8-Methoxy-2-methylquinoline-5-[N-(5-chloropyrimidin-4-yl)]-carboxamide**

Purification by flash chromatography on silica eluting with 10% methanol in ethyl acetate and trituration with diethyl ether afforded the title compound (110mg) as a pale yellow solid.

TLC R_f 0.38 (10% methanol in ethyl acetate)

mp 192-193.5°C

Example 24 **8-Methoxy-2-methylquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

The title compound was obtained as an off-white solid (20mg).

TLC R_f 0.58 (5% methanol in ethyl acetate)

Mp 273-275°C (dec.).

The following Examples were prepared from the appropriate quinoline carbonyl chloride hydrochloride and 4-amino-3,5-dichloropyridine using a procedure similar to that described in Example 13.

Example 25 **3-Ethyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]-carboxamide**

The title compound was obtained as an off-white solid (50mg).

TLC R_f 0.34 (5% methanol in dichloromethane)

Mass spectrum (EI) 376 $[M+H]^+$

Example 26 **7-Fluoro-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

The title compound was obtained as an off-white solid (210mg).

TLC R_f 0.48 (ethyl acetate)

Mass spectrum (EI) 366 $[M+H]^+$

Example 27 **2-Cyano-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]-carboxamide**

The title compound was obtained as an off-white solid (72mg).

TLC R_f 0.48 (ethyl acetate)

Mass spectrum (EI) 373 $[M+H]^+$

Example 28 **2-Ethyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)carboxamide**

Purification was achieved by column chromatography eluting with ethyl acetate to afford the title compound as a peach solid (0.14g).

TLC R_f 0.35 (ethyl acetate)

mp 256.5-257.5°C

Example 29 **8-Difluoromethoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl]carboxamide**

The title compound was obtained as a white solid (530mg).

TLC R_f 0.25 (50% ethyl acetate in hexane)

mp 200-202°C

Example 30 **8-Methoxy-2-(3-pyridyl)quinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

Purification by flash chromatography on silica, eluting with 10% methanol in ethyl acetate yielded the title compound (175mg) as a white powder.

TLC R_f 0.4 (10% methanol in ethyl acetate)

mp 258-259°C

Example 31 **8-Methoxy-2-(trifluoromethyl)quinoline-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide**

The title compound (0.94g) was obtained as a white solid.

mp 254-255°C

TLC R_f 0.24 (50% ethyl acetate in hexane)

Example 32 **8-Hydroxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

Sodium hydride (1.6g, 60% dispersion in oil) was washed with diethyl ether under nitrogen and dried *in vacuo*. Anhydrous N,N-dimethylformamide (20ml) was added followed by the careful addition of a solution of ethanethiol (3ml) in DMF (3ml). A solution of 8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)] carboxamide (100mg) in DMF (5ml) was added to the mixture and the reaction refluxed for 1.5 hours. The solvent was removed *in vacuo* and the residue partitioned between saturated aqueous ammonium chloride solution (50ml) and dichloromethane (50ml). The aqueous phase was re-extracted with dichloromethane (75ml) and the organic extracts combined. The organic phase was dried over magesium sulphate, filtered, and the filtrate evaporated *in vacuo*. The residue was partitioned between dichloromethane (20ml) and 0.5M aqueous sodium hydroxide solution. The aqueous phase was separated and acidified to pH 4/5 with glacial acetic acid. The preciptate was collected by filtration and dried *in* vacuo to yield the title compound as an off-white solid (20mg).

Mass spectrum (EI) 334 $[M]^+$

Example 33 **8-Methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide, dihydrochloride**

A solution of 8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)] carboxamide (114mg) in methanol (50ml) was treated with hydrogen chloride gas for 5 minutes at

25°C. The solution was evaporated *in vacuo* to yield the title compound as an off-white solid (138mg).

Elemental Analysis

Calculated	45.64% C	3.11% H	9.98% N
Observed	44.51% C	3.09% H	9.67% N

Example 34 **8-Methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide, dihydrobromide**

Cooled methanol (50ml) was carefully treated with acetyl bromide (0.25ml) and the mixture stirred at below 5°C for 30 minutes. The solution was allowed to warm to room temperature and 8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)] carboxamide (105mg) was added. After 30 minutes the solution was evaporated *in vacuo* to yield the title compound as an off-white solid (148mg).

Example 35 **5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-2H-tetrazole dihydrochloride salt**

Hydrogen chloride (0.6ml, 1M in diethyl ether) was added to a stirred suspension of 5-[8-methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-2-trimethylstannyl-2H-tetrazole (150mg) in tetrahydrofuran (10ml) at room temperature under an inert atmosphere with immediate dissolution being observed. The reaction was stirred at room temperature for 90 minutes and the resulting precipitate filtered off, washed with diethyl ether and dried *in vacuo* at 40°C to afford the title compound as a white solid (92mg).

Mp 242-244°C.

Mass spectrum (EI) 416 $[M+H]^+$ free base

Example 36 **5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonyl-quinolin-2-yl]-2-methyltetrazole and 5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-1-methyl-tetrazole**

5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-2-trimethylstannyl-2H-tetrazole (153mg) and iodomethane (1.0ml) were dissolved in methanol (2.5ml) and stirred under an inert atmosphere at room temperature for 5 days. The solvent was removed *in vacuo* and the resulting solid suspended in diethyl ether, filtered and washed with diethyl ether (3 x 10ml). Purification by column chromatography

eluting with 5% methanol in dichloromethane afforded a 7:1 mixture of the title compounds respectively as a white solid (55mg).

TLC R_f 0.71(10% methanol in dichloromethane)

Mp 273-275°C

Example 37 **2-Acetyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]-carboxamide**

Methyl magnesium bromide (0.6ml, 3.0M in diethyl ether) was added dropwise to a stirred solution of 2-cyano-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide (300mg) in tetrahydrofuran (20ml) at room temperature under an inert atmosphere. The reaction was stirred at room temperature for 1 hour then poured into brine (25ml) and extracted with ethyl acetate (4x25ml). The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography eluting with 5% methanol in dichloromethane afforded the title compound as a pale yellow solid (180mg).

TLC R_f 0.42 (ethyl acetate)

Mp 257-259°C

Example 38 **2-(1-Methoxyiminoethyl)-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

2-Acetyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide (100mg), methoxylamine hydrochloride (75mg) and pyridine (0.12ml) in toluene (50ml) were heated to reflux under Dean-Stark conditions for 3 days. The cooled reaction mixture was evaporated to dryness *in vacuo* and passed through a silica column eluting with 66% ethyl acetate in hexane to afford the title compound as a white solid (20mg).

TLC R_f 0.29 (66% ethyl acetate in hexane)

Mp 273-275°C

Example 39 **2-(1-Hydroxyethyl)-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

Sodium borohydride (50mg) was added to a stirred solution of 2-acetyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide (180mg) in methanol (10ml) at ambient temperature. The reaction was stirred for 90 minutes, quenched with water (dropwise) and the methanol removed *in vacuo*. The residue was partitioned between ethyl acetate (4x20ml) and water (10ml). The combined organic phases were

dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography eluting with 4% methanol in dichloromethane yielded the title compound as an orange solid (68mg).

TLC R_f 0.28(10% methanol in dichloromethane)

Mp 252-254°C.

Example 40 **2-[(*t*-Butyloxycarbonyl)-(methyl)amino]-8-methoxyquinoline-5-[N-(3,5-dichloropyrid-4-yl)]carboxamide**

4-Amino-3,5-dichloropyridine (138mg) and dimethylformamide (10ml) were combined under a nitrogen atmosphere at room temperature. Sodium hydride (60% dispersion in oil) (51mg) was added and stirring was continued for 3h. 4-Nitrophenyl 2-[(*t*-butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline-5-carboxylate (384mg) was then added as a solution in dimethylformamide (10ml) and stirring was continued for 16h. The reaction mixture was evaporated *in vacuo* onto silica and purified by flash chromatography to give the title compound (217mg) as a white solid.

TLC R_f 0.20 (50% ethyl acetate in hexane)

Mp 184-186°C

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

Example 41 **8-Difluoromethoxyquinaldine-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide**

Purification by column chromatography eluting with 5% methanol in dichloromethane and trituration with ethyl acetate afforded the title compound as a white solid (0.3g).

TLC R_f 0.24 (5% methanol in dichloromethane)

mp 210-212°C.

Example 42 **2-(*N*-Methyl)amino-8-methoxyquinoline-5-[N-(3,5-dichloropyrid-4-yl)]carboxamide**

2-[(*t*-Butyloxycarbonyl)(methyl)amino]-8-methoxyquinoline-5-[*N*-(3,5-dichloropyrid-4-yl)]carboxamide (195mg), dichloromethane (10ml) and trifluoroacetic acid (6ml) were combined and stirred at room temperature for 5h. The solvents were removed *in vacuo* and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. Extraction was carried out with dichloromethane (3 x 20ml)

which was then evaporated *in vacuo* onto silica and purified by flash chromatography to give the title compound (108mg) as a white solid.

TLC R_f 0.30 (2% ammonium hydroxide in ethyl acetate)

Mp 271-272°C

Example 43 **2-[(Pyridin-2-yl)carbonyl]-8-methoxyquinoline-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide**

n-Butyllithium (0.87ml, 1.6M in hexanes) was added dropwise to a stirred solution of 2-bromopyridine (0.11ml) in tetrahydrofuran (2ml) at -78°C under an inert atmosphere. After stirring at this temperature for 45 minutes, 2-cyano-8-methoxyquinoline-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide (0.2g) in tetrahydrofuran (10ml) was added dropwise and the reaction allowed to warm to room temperature. After stirring at room temperature for 1 hour the reaction was concentrated *in vacuo*. The residue was partitioned between water (45ml) and dichloromethane (3x45ml). The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography eluting with 0.5% triethylamine and 4.5% methanol in dichloromethane afforded the title compound as a pale orange solid(0.54mg).

TLC R_f 0.23 (0.5% triethylamine/4.5% methanol in dichloromethane)

mp 185-187°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 (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 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% CO_2. Supernatants are tested for TNFα by ELISA using commercially available kits.

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).

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.

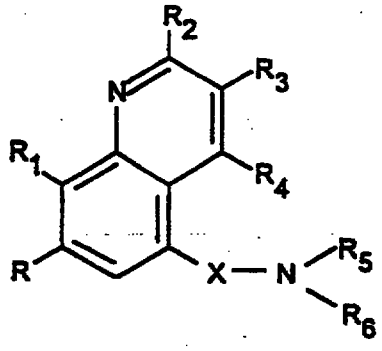
Abbreviations

LPS	Lipopolysaccharide (endotoxin)
ELISA	Enzyme linked immunosorbent assay

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CLAIMS

1. A compound of the general formula (i)



wherein X is CO or CS;

R is H, halogen or alkyl;

R_1 represents OH, alkoxy optionally substituted with one or more halogens, or thioalkyl;

R_2, R_3 and R_4 are the same or different and are each H, R_7, OR_{11}, COR_7, $C(=NOR_7)R_7$, alkyl-$C(=NOR_7)R_7$, halogen, CF_3, alkyl-$C(=NOH)R_7$, $C(=NOH)R_7$, CN, CO_2H, CO_2R_{11}, $CONH_2$, $CONHR_7$, $CON(R_7)_2$, NR_9R_{10} or $CONR_{12}R_{13}$ where $NR_{12}R_{13}$ is a heterocyclic ring optionally substituted with one or more R_{15};

R_5 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, $S(O)_mR_{11}$ or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy, CO_2R_8, $SO_2NR_{12}R_{13}$, $CONR_{12}R_{13}$, CN, carbonyl oxygen, NR_9R_{10}, COR_{11} and $S(O)_mR_{11}$;

R_6 represents aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

in R_5 and/or R_6, the aryl/heteroaryl/heterocyclo portion is optionally substituted with one or more substituents alkyl-R_{14} or R_{14};

R_7 represents R_{11} optionally substituted at any position with one or more R_{16};

R_8 represents H, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

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R_{10} represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

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

R_{12} and R_{13} are the same or different and are each H or R_{11}, or $NR_{12}R_{13}$ represents a heterocyclic ring as defined above;

R_{14} represents alkyl (optionally substituted by one or more halogens), cycloalkyl, aryl, heteroaryl, heterocyclo, hydroxy, alkoxy, thioalkyl, aryloxy, heteroaryloxy, heterocyclooxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, CO_2R_8, $CONR_{12}R_{13}$, $SO_2NR_{12}R_{13}$, halogen, -CN, $-NR_9R_{10}$, COR_{11}, $S(O)_nR_{11}$, or carbonyl oxygen;

R_{15} represents alkyl, arylalkyl or heteroarylalkyl;

R_{16} represents alkyl, OH, OR_{11}, NR_9R_{10}, CN, CO_2H, CO_2R_{11}, $CONR_{12}R_{13}$ or COR_{11};

m is an integer of up to 2; and

n represents 0-2;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, wherein R is H or halogen.

3. A compound of claim 1 or claim 2, wherein R_1 is alkoxy optionally substituted with one or more halogens.

4. A compound of any preceding claim, wherein R_2, R_3, R_4 are the same or different and each represent H, CF_3, COR_7, $C(=NOR_7)R_7$, $C(=NOH)R_7$, CN, R_7, alkyl-$C(=NOH)R_7$ or alkyl-$C(=NOR_7)R_7$.

5. A compound of any preceding claim, wherein R_5 is H or alkyl.

6. A compound of any preceding claim, wherein R_6 is aryl or heteroaryl in which the aryl and heteroaryl portions may be optionally substituted with one or more substituents alkyl-R_{14} or R_{14}.

7. A compound of claim 1, wherein

R is H;

R_1 is optionally-substituted alkoxy;

R_2, R_3 and R_4 are independently H, R_7 or alkyl-R_7;

R_7 is H, OH, alkoxy, aryloxy, heteroaryloxy, heterocyclooxy, arylalkoxy, heteroarylalkoxy, heterocycloalkoxy, alkylamino, CF_3 or R_{11};

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R_8 is H, alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 is not cycloalkyl;

R_{10} is not cycloalkyl;

R_{11} is not cycloalkyl; and

R_{14} is not alkyl, substituted alkoxy, thioalkyl, or cycloalkyl.

8. A compound of claim 1, which is

8-methoxyquinoline-5-[N-(pyridin-4-yl)]carboxamide.

9. A compound of claim 1, which is

8-methoxyquinoline-5-[N-(thiazol-2-yl)]carboxamide

8-methoxyquinoline-5-[N-(2-trifluoromethoxyphenyl)]carboxamide

8-methoxyquinoline-5-[N-2-(piperidin-1-yl)phenyl]carboxamide

8-methoxyquinoline-5-[N-(2-fluorophenyl)]carboxamide

8-methoxyquinoline-5-[N-(2-methylphenyl)]carboxamide

8-methoxyquinoline-5-[N-(2,6-dimethylphenyl)]carboxamide

8-methoxyquinoline-5-[N-(2-chlorophenyl)]carboxamide

8-methoxyquinoline-5-[N-(2-methoxyphenyl)]carboxamide

8-methoxyquinoline-5-[N-(4-methoxyphenyl)]carboxamide

8-methoxyquinoline-5-[N-(2-chloro-6-methylphenyl)]carboxamide

8-methoxy-2-methylquinoline-5-[N-(2-chlorophenyl)]carboxamide

8-methoxyquinoline-5-[N-(2, 5-dichloropyridin-3-yl)]carboxamide

8-methoxyquinoline-5-[N-(pyrimidin-4-yl)]carboxamide

8-methoxyquinoline-5-[N-(3,5-dichloropyridin-2-yl)]carboxamide

8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

8-methoxyquinoline-5-[N-(4,6-dichloropyrimidin-5-yl)]carboxamide

8-methoxyquinoline-5-[N-(4-chloropyridin-4-yl)]carboxamide

8-methoxyquinoline-5-[N-(2-trifluoromethylphenyl)]carboxamide

8-methoxyquinoline-5-[N-(3-bromo-5-methylpyridin-2-yl]carboxamide

8-methoxyquinoline-5-[N-(2-chloropyridin-3-yl)]carboxamide

8-methoxy-2-methylquinoline-5-[N-(3-chloropyridin-4-yl)]carboxamide

8-methoxy-2-methylquinoline-5-[N-(5-chloropyrimidin-4-yl)]carboxamide

8-methoxy-2-methylquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

3-ethyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

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7-fluoro-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

2-cyano-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

2-ethyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)carboxamide

8-difluoromethoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl]carboxamide

8-methoxy-2-(3-pyridyl)quinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

8-methoxy-2-(trifluoromethyl)quinoline-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide

8-hydroxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide, dihydrochloride

8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide, dihydrobromide

5-[8-methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-2H-tetrazole dihydrochloride salt

5-[8-methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonyl-quinolin-2-yl]-2-methyltetrazole

5-[8-Methoxy-5-[N-(3,5-dichloropyridin-4-yl)]-aminocarbonylquinolin-2-yl]-1-methyl-tetrazole

2-acetyl-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]-carboxamide

2-(1-methoxyiminoethyl)-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

2-(1-hydroxyethyl)-8-methoxyquinoline-5-[N-(3,5-dichloropyridin-4-yl)]carboxamide

2-[(*t*-butyloxycarbonyl)-(methyl)amino]-8-methoxyquinoline-5-[N-(3,5-dichloropyrid-4-yl)]carboxamide

8-difluoromethoxyquinaldine-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide

2-(*N*-methyl)amino-8-methoxyquinoline-5-[N-(3,5-dichloropyrid-4-yl)]carboxamide

2-[(pyridin-2-yl)carbonyl]-8-methoxyquinoline-5-[*N*-(3,5-dichloropyridin-4-yl)]carboxamide

10. A compound of any preceding claim, in the form of an enantiomer or mixture of enantiomers.

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

12. Use of a compound of any of claims 1 to 10, for the manufacture of a medicament for use in the treatment of a disease state capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor.

13. The use of claim 12, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

14. The use of claim 13, wherein the pathological condition is selected from asthma, chronic bronchitis, chronic destructive airways disease, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis and other arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic eczema, atopic dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke and intermittent claudication.

15. The use of claim 13, wherein the pathological condition is selected from chronic bronchitis, allergic rhinitis and adult respiratory distress syndrome.

16. The use of claim 12, wherein the disease state is capable of being modulated by TNF inhibition.

17. The use of claim 16, wherein the disease state is an inflammatory disease or autoimmune disease.

18. The use of claim 17, wherein the disease state is selected from joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection, malaria, myalgias, HIV, AIDS, ARC, cachexia, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukaemia.

19. The use of claim 14 or claim 18, wherein the pathological condition or disease state is asthma.

20. The use of claim 18, wherein the disease state is acute respiratory distress syndrome, pulmonary inflammatory disease or pulmonary sarcoidosis.

21. The use of claim 18, wherein the disease state is joint inflammation.

22. The use of claim 13 or claim 17, wherein the disease state is a disease or disorder of the brain, such as brain trauma, stroke, ischaemia, Huntingdon's disease or tardive dyskinesia.

23. The use of claim 16, wherein the disease state is a yeast or fungal infection.

24. Use of a compound of any of claim 1 to 10, for the manufacture of a medicament for use in gastroprotection.

25. Use of a compound of any of claims 1 to 10, for the manufacture of a medicament for use as an analgesic, anti-tussive or anti-hyperalgesic in the treatment of neurogenic inflammatory disease associated with irritation and pain.

26. Use of a compound of any of claims 1 to 10, in coadministration with another durg such as a bronchodilator, steroid or xanthine, for asthma therapy.

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