BENZOFURAN CARBOXAMIDES AND THEIR THERAPEUTIC USE

Field of the Invention

The present invention relates to novel benzofuran carboxamides and thioamides, and to their formulation and use as pharmaceuticals.

Background of the Invention

EP-A-0637586 discloses benzofuran derivatives, including 4-carboxamides, as acetylcholine esterase inhibitors.

WO-A-9408962 discloses benzofuran analogues as fibrinogen receptor antagonists.

WO-A-9203427 discloses benzofuran-2-carboxamides, with a 3-substituent selected from hydroxy, acyloxy, alkoxy, optionally alkyl-substituted aminoalkoxy, alkylsulphonylamino, optionally alkyl-substituted aminoalkylsulphonyl or arylsulphonylamino, as a remedy for osteoporosis.

EP-A-0685475 discloses benzofuran-2-carboxamides as anti-inflammatory agents.

WO-A-9603399 discloses dihydrobenzofuran-4-carboxamides as inhibitors of phosphodiesterases.

WO-A-9636624 (published 21.11.96; EP-A-0771794) discloses compounds of formula (i) as defined below, of which some may be entitled to a priority date earlier than 20.05.96. In such compounds of earlier date, and with respect to formula (i):

R_1 is optionally-substituted alkoxy;

R_2 and R_3 are each H, optionally-substituted alkyl (e.g. cycloalkyl-substituted alkyl), aryl or heteroaryl, alkanoyl, alkoxycarbonyl or CN; and

R_4 is 4-pyridyl optionally substituted at the 2 and 6 positions by alkyl, alkoxy, COOH, alkanoyl, alkoxycarbonyl, CF_3, NH_2, CN, NO_2 or halogen; and

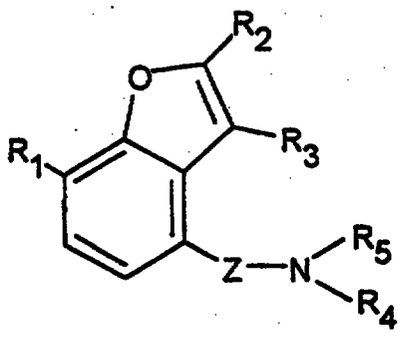
R_5 is H, alkyl, cycloalkyl, aryl, heteroaryl or aralkyl.

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 benzofuran derivatives 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 Z is CO or CS;

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

R_2 and R_3 are the same or different and are each H, R_6, OR_{10}, COR_6, $C(=NOR_6)R_6$, alkyl-$C(=NOR_6)R_6$, alkyl-$C(=NOH)R_6$, $C(=NOH)R_6$, halogen, NR_8R_9, CF_3, CN, CO_2H, CO_2R_{10}, $CONH_2$, $CONHR_6$ or $CON(R_6)_2$;

R_4 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, $S(O)_mR_{10}$ or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy, CO_2R_7, $SO_2NR_{11}R_{12}$, $CONR_{11}R_{12}$, CN, carbonyl oxygen, NR_8R_9, COR_{10} and $S(O)_nR_{10}$;

R_5 represents aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

in R_4 and/or R_5, the aryl/heteroaryl/heterocyclo portion is optionally substituted with one or more substituents alkyl-R_{13} or R_{13};

R_6 represents R_{10} optionally substituted at any position with (one or more) R_{14};

R_7 represents H, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_8 represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

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

R_9, R_{11} and R_{12} are the same or different, and are each H or R_{10};

R_{13} represents alkyl optionally substituted with halogen, alkoxy optionally substituted by halogen, aryl, heteroaryl, heterocyclo, hydroxy, aryloxy, heteroaryloxy, heterocyclooxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, CO_2R_7, $CONR_{11}R_{12}$, $SO_2NR_{11}R_{12}$, halogen, -CN, $-NR_8R_9$, COR_{10}, $S(O)_nR_{10}$, or carbonyl oxygen;

R_{14} represents OH, OR_{10}, carbonyl oxygen, NR_8R_9, CN, CO_2H, CO_2R_{10}, $CONR_{11}R_{12}$ or COR_{10};

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. Heteroarylalkyloxy means a heteroaryl-alkyl-O group and heterocycloalkyloxy means a heterocyclo-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-Sgroup. 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-alkylgroup 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 amd 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 heterocyclosulphonyl means a heterocyclo-SO_2- group. Alkoxycarbonyl means an alkyloxy-CO- group in which the alkoxy group is as previously described. 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 be 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. 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 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-l, 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.

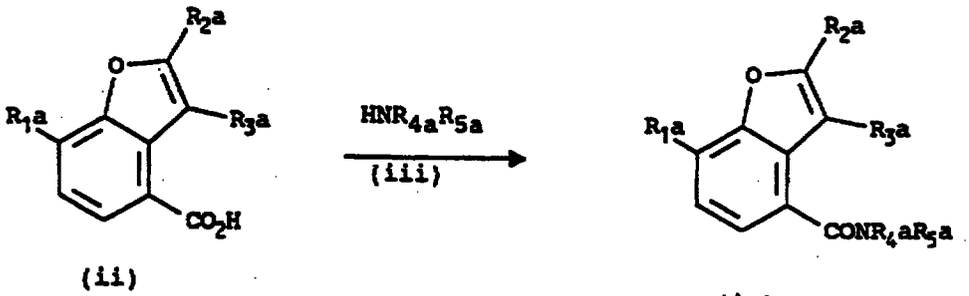
The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, of a pharmaceutically-acceptable

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_4 contains an -OH comprises deprotecting (for example by hydrogenolysis or hydrolysis) a compound of formula (i) in which R_4 contains an appropriate -OP wherein P represents a suitable protecting group (e.g. benzyl or acetyl).

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.

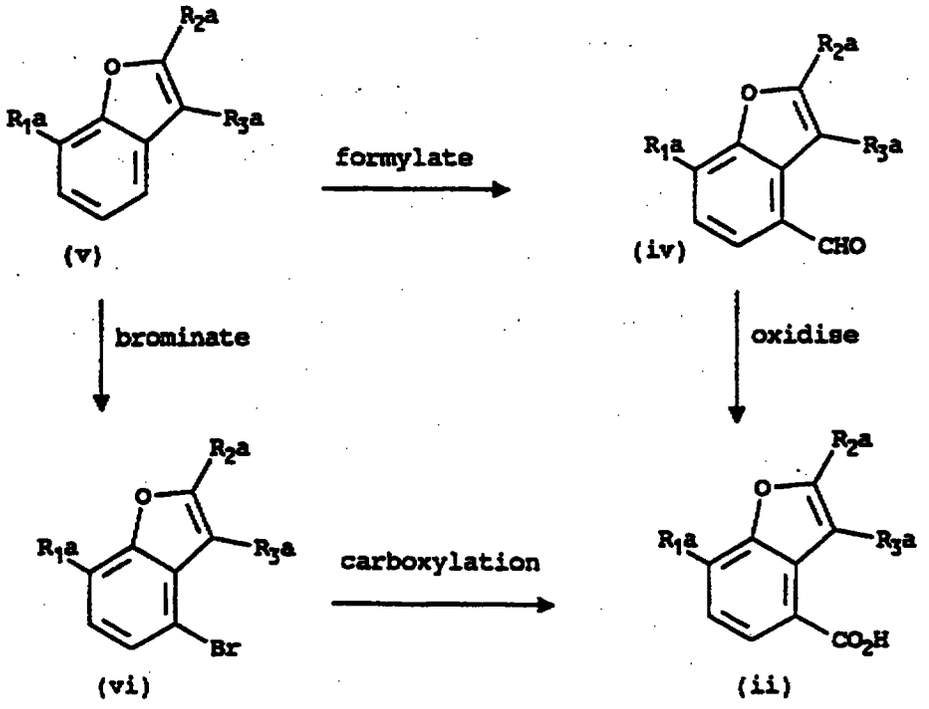
A process for the preparation of a compound of formula (i) wherein Z is CO comprises reaction of an appropriate carboxylic acid of formula (ii) with a suitable amine of formula (iii)



(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_{5a}, similarly represent R_2-R_5 or groups convertible to R_2-R_5 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 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. 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 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, will be required. 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).

Carboxylic acids of formula (ii) and amines of formula (iii) 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) is conveniently prepared from an appropriate benzofuran of formula (v), using standard procedures known to those skilled in the art. For example, a benzofuran of formula (v) can be formulated to provide an aldehyde of formula (iv), which can then be oxidised to provide the corresponding acid of formula (ii). Alternatively, a benzofuran of formula (v) can be brominated to provide a bromide of formula (vi), which can then be converted into a carboxylic acid of formula (ii), for example by organometal-catalysed carboxylation, such as palladium-catalysed reaction.



A compound of formula (ia) may also be prepared by reaction of a carboxylic acid of formula (ii) with an amine (iii) to provide a compound of formula (ia) in which R_{4a} is H, followed by reaction with an agent $R_{4a}Y$ (vii) in which Y is a suitable leaving group such as a halogen. The first reaction can be carried out as described above. Preferably, the carboxylic acid is converted into an acid chloride, mixed anhydride or other activated intermediate prior to reaction with the amine (iii). The reaction with agent (vii) may be carried out under any suitable conditions known to those skilled in the art. It may be carried out in the presence of a suitable base, e.g. sodium hydride, preferably in an appropriate solvent such as dimethylformamide. Agents (vii) are known or commercially available, or are prepared using standard procedures known to those skilled in the art. Such compounds include alkylating agents such as propyl bromide, acylating agents such as benzoyl chloride and sulphonylating agents such as methanesulphonyl chloride.

Compounds of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which R_4 contains an alkoxy group may be prepared by appropriate alkylation of a compound in which R_4 contains a hydroxy group. Compounds of formula (i) in which Z is CS may be prepared from compounds of formula (i) in which Z is CO using any appropriate conditions known to those skilled in the art, for example by using Lawesson's reagent.

By way of further example, compounds in which R_2 and/or R_3 contain an oxime may be prepared from compounds in which R_2 and/or 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_2 and/or 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_2 and/or R_3 contains an alcohol group. Compounds in which R_2 and/or R_3 is alkyl may be prepared by reduction of compounds in which R_2 and/or 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_2 and/or R_3 contains a carbonyl group. Such transformations include, but are not limited to, reductive amination and alkylation. Compounds in which R_2 or R_3 contains a CO-alkyl, CO-aryl, CO-heteroaryl, CO-alkylaryl, CO-alkylheterocyclo or CO-alkylheteroaryl group may be prepared from compounds in which R_2 and R_3 contain a CN group by addition of a suitable organometallic reagent (such as a Grignard reagent). Any of the above transformations may be carried out either at the end of the synthesis or on an appropriate intermediate.

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 techniques. 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 **2-Acetyl-7-methoxybenzofuran-4-carbonyl chloride**

2-Acetyl-7-methoxybenzofuran-4-carboxylic acid (0.12g) was suspended in anhydrous dichloromethane (4ml) at room temperature under nitrogen and oxalyl chloride (0.1ml) added followed by 3 drops of *N,N*-dimethylformamide. Evaporation *in vacuo* after 2 hours afforded the title compound as a yellow solid (~0.5g).

TLC R_f 0.60 (50%ethyl acetate in hexane)

Intermediate 2 **2-Acetyl-7-methoxybenzofuran-4-carboxylic acid**

A mixture of 2-acetyl-4-bromo-7-methoxybenzofuran (5g), triphenylphosphine (98mg), bis(triphenylphosphine)palladium(II)chloride (261 mg), triethylamine (2.85ml) and water (1ml) in tetrahyrofuran (25ml) was purged with carbon monoxide gas in a Parr pressure reactor at 110psi. This was heated to 110°C (pressure now 220psi) and left for a week. On cooling and release of pressure the mixture was dissolved in 50% dichloromethane-water (200ml) and taken to pH12 using aqueous sodium hydroxide(1M). The separated aqueous phase was acidified to pH1 using dilute hydrochloric acid(1M) and the resultant slurry extracted with dichloromethane (3x100ml) then ethyl acetate (100ml). These combined organic extracts were dried over magnesium sulphate, filtered and evaporated *in vacuo* to afford a yellow solid (2.58g).

TLC R_f 0.61 (ethyl acetate)

Intermediate 3 **2-Acetyl-4-bromo-7-methoxybenzofuran**

A solution of bromine (5.5ml) in methanol (100ml) was added dropwise to a suspension of 2-acetyl-7-methoxybenzofuran (20g) in methanol (300ml) at 0°C. The ice bath was removed immediately and the mixture allowed to warm to room temperature. After 1 hour conversion was incomplete, so further bromine (0.75ml) in methanol (25ml) was added and the mixture stirred overnight. The reaction was quenched using aqueous sodium metabisulphite solution (300ml) producing a precipitate that was filtered off and dried *in vacuo* to afford a brown solid (17.4g).

TLC R_f 0.90 (ethyl acetate)

Intermediate 4 **2-Ethyl-7-methoxybenzofuran-4-carboxylic acid**

2-Methyl-2-butene (9g) was added to a solution of 2-ethyl-7-methoxybenzofurancarboxaldehyde (5g) in 2-methyl-2-propanol (125ml). A solution of sodium dihydrogen phosphate monohydrate (20.7g) in water (15ml) was added, followed by sodium chlorite (11.05g). The resultant heterogeneous mixture was stirred vigorously for 30 minutes and then diluted with water (125ml). The mixture was adjusted to pH 4 by the addition of 2M hydrochloric acid. The mixture was extracted with ethyl acetate (3x200ml) and the combined organic extracts were washed with water (2x200ml). The organic solution was concentrated to about 100ml and then cooled to 10°C. The resultant precipitate was collected by filtration and dried at 50°C *in vacuo* to afford a beige solid (4g).

mp 215- 216°C

The following compound was prepared using the above procedure.

Intermediate 5 **2-[1-(2,2-Dimethylpropyl)]-7-methoxybenzofuran-4-carboxylic acid**

Prepared from 2-[1-(2,2-dimethylpropyl)]-7-methoxybenzofuran-4-carboxaldehyde (2.14g). The title compound (1.81g) was obtained as a pale yellow solid.

mp 173-174°C

Intermediate 6 **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 white solid produced was obtained by filtration and air dried to afford a white solid (4.9g).

R_f 0.36 (ethyl acetate).

mp 65-67°C.

Intermediate 7 **4-*N*-(Propylamino)pyridine**

4-Aminopyridine (0.499g) and propionaldehyde (0.5g) in dichloromethane (50ml) under an inert atmosphere were stirred at ambient temperature for 1.5 hours. Sodium triacetoxyborohydride (2.7g) was added and left overnight. The reaction mixture was washed with aqueous sodium bicarbonate (2x40ml) and extracted into dilute hydrochloric acid (2x40ml). These acidic extracts were basified using potassium hydroxide pellets and extracted into dichloromethane (2x80ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo* to yield an oily residue (0.11g).

TLC R_f 0.49 (10%methanol in ethyl acetate).

Intermediate 8 **2-Ethyl-7-methoxy-4-*N*-(3-carboethoxyphenyl)benzofuran carboxamide**

2-Ethyl-7-methoxybenzofuran-4-carbonyl chloride (1.0g) was added to a solution of ethyl 3-aminobenzoate (0.72g) in dichloromethane (30ml) at room temperature under an inert atmosphere and the reaction mixture stirred at room temperature overnight. The mixture was poured into dilute aqueous hydrochloric acid and extracted with ethyl acetate

(2 x 50ml). The combined organic extracts were washed with water (50ml), brine (50ml), dried (magnesium sulphate) and evaporated *in vacuo* to yield the title compound (1.39g) as a white solid.

mp 159-161°C.

The following compound was prepared according to the above procedure:

Intermediate 9 **2-Ethyl-7-methoxy-4-*N*-(4-carboethoxyphenyl)benzofuran carboxamide**

Prepared from 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (1.3g) and ethyl 4-aminobenzoate (1.0g) to yield the title compound (0.76g) as a white solid.

TLC R_f 0.18 (25% ethyl acetate in hexane)

Intermediate 10 **2-[1-(2,2-Dimethylpropyl)]-7-methoxybenzofuran-4-carboxaldehyde**

Phosphorus oxychloride (1.64ml) was added dropwise to DMF (1ml) at 0°C under nitrogen and stirred for 10 minutes. A solution of 2-[1-(2,2-dimethylpropyl)]-7-methoxybenzofuran (1.92g) in DMF (3.5ml) was then added. A pale yellow solid formed and the reaction mixture was heated to 100°C for 2h. The reaction mxture was allowed to cool to room temperature overnight. A solution of 50% aqueous sodium acetate trihydrate (20ml) was added cautiously and the resultant mixture was extracted with MTBE (3 x 25ml). The combined organic phases were washed with water (2 x 20ml), saturated aqueous sodium hydrogen carbonate solution (20ml) and brine (30ml). The solution was dried (magnesium sulphate) and concentrated *in vacuo* to provide the title compound (2.14g) as a light brown oil.

TLC R_f 0.25 (5% ethyl acetate in hexane)

Intermediate 11 **2-[1-(2,2-Dimethylpropyl)]-7-methoxybenzofuran**

Sodium hydroxide (2.89g) was added to a solution of *o*-vanillin (l0g) in ethanol (230ml) at 40°C. After 10 minutes, l-bromopinacolone (9.7ml) was added and the resultant mixture was heated at 60°C for 4h then at reflux for a further 4h. The reaction mixture was cooled to room temperature and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100ml) and 0.2% aqueous sodium hydroxide solution (100ml). The aqueous layer was extracted with ethyl acetate (2 x 75ml) and the combined organic extracts were washed with water (100ml) and brine (100ml). The

solution was dried (magnesium sulphate) and concentrated *in vacuo* to furnish 2-[1-(2,2-dimethyl-1-oxopropyl)]-7-methoxybenzofuran as a brown oil.

Hydrazine hydrate (3.2ml) was added to a stirred suspension of 2-[1-(2,2-dimethyl-1-oxopropyl)]-7-methoxybenzofuran (3.0g) in ethylene glycol (38ml). The reaction mixture was heated to 65°C for 1h, then heated at reflux for 1.75h to afford a yellow solution. After cooling to room temperature, water (50ml) was added and the mixture extracted with dichloromethane (3 x 50ml). The combined organic extracts were washed with 2M aqueous hydrochloric acid (15ml), water (3 x 20ml) and brine 50ml). The solution was dried (magnesium sulphate) and concentrated *in vacuo*. Purification by column chromatography on silica, eluting with 5% ethyl acetate in hexane yielded the title compound (1.92g) as a colourless oil.

TLC R_f 0.35 (5% ethyl acetate in hexane)

Intermediate 12 **2-Ethyl-7-methoxybenzofuran-4-carbonyl chloride**

2-Ethyl-7-methoxybenzofuran-4-carboxylic acid (4.05g) was heated in dry toluene (100ml) with thionyl chloride (14ml) under nitrogen at 90°C for 2h. The solution was evaporated to dryness *in vacuo* and azeotroped with dry toluene (2 x 50ml) to afford the title compound (4.4g) as an off-white solid.

mp 100-102°C

Intermediate 13 **Methyl 7-methoxybenzofuran-2-carboxylate**

7-Methoxybenzofuran-2-carboxylic acid (10g) and methanol (110ml) were combined under nitrogen and cooled to 0°C. Acetyl chloride (11ml) was then added and stirring continued for 18h. Removal of the solvent afforded an off-white crystalline solid (10.7g).

TLC R_f 0.94 (10% methanol in dichloromethane)

Intermediate 14 **Methyl 4-formyl-7-methoxybenzofuran-2-carboxylate**

To a suspension of Intermediate 13 (1g) in dichloromethane (14ml) at 0°C was added titanium tetrachloride (1M solution in dichloromethane, 5.3ml) followed by dichloromethyl methyl ether (0.44ml) as a solution in dichloromethane (3ml). The reaction was slowly warmed to room temperature then heated to 35°C for 18h. Upon cooling, the reaction was poured into ice-water and the aqueous phase extracted with dichloromethane. The combined organics were washed with water, dried and concentrated to afford a biscuit coloured solid (0.97g).

TLC R_f 0.86 (10% methanol in dichloromethane)

Intermediate 15 **Methyl 4-carboxy-7-methoxybenzofuran-2-carboxylate**

To a stirred suspension of Intermediate 14 (0.97g) in t-butanol (115ml) was added 2-methyl-2-butene (3ml) followed by sodium phosphate (5.7g in 28ml water) and sodium chlorite (3.74g in 28ml water). Stirring was continued for 4h, the reaction solution concentrated and partitioned between ethyl acetate and 10% aqueous hydrochloric acid solution. The organics were dried and concentrated to give a beige solid. Purification by trituration with ether afforded a pale yellow solid (0.62g).

TLC R_f 0.64 (10% methanol in dichloromethane)

Intermediate 16 **7-Methoxy-2-methoxycarbonylbenzofuran-4-carbonyl chloride**

Intermediate 15 (0.62g) was heated in dry toluene (23ml) with thionyl chloride (2ml) under nitrogen at 90°C for 2h. The solution was evaporated to dryness *in vacuo* and azeotroped with dry toluene (2 x 50ml) to afford the title compound (0.51g) as a pale brown solid.

TLC R_f 0.0 (10% methanol in dichloromethane)

Intermediate 17 **2-(1-(t-Butyldimethylsilyloxy)iminoethyl)-7-methoxy-4-[N-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

To a solution of 2-acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (0.5g) in toluene (50ml) was added O-(*t*-butyldimethylsilyl)hydroxylamine (0.39g). The reaction mixture was heated under a nitrogen atmosphere under Dean Stark conditions for 3 days then left stirring at room temperature for 2 days. The reaction mixture was concentrated to dryness giving the crude product. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded a white solid (0.22g).

TLC R_f 0.53 (50% ethyl acetate in hexane)

Intermediate 18 **2-[(Pyridin-4-yl)carbonyl]-7-methoxybenzofuran-4-carbonyl chloride hydrochloride**

The title compound was prepared in a similar manner to Intermediate 1.

Intermediate 19 **7-Methoxy-2-[(pyridin-4-yl)carbonyl]benzofuran-4-carboxylic acid**

2-[(Pyridin-4-yl)carbonyl]-4-bromo-7-methoxybenzofuran (3.3g), triphenylphosphine (1g), bis(triphenylphosphine)palladium (II) chloride (0.47g), triethylamine (14ml), tetrahydrofuran (150ml) and H_2O (57ml) were combined in a Parr pressure reactor. The vessel was purged with carbon monoxide, charge to 180psi with carbon monoxide and then heated to 80°C with stirring for 3 days. On cooling and release of pressure the tetrahydrofuran was removed *in vacuo* The remaining aqueous mixture was basified to pH14 with 1N NaOH solution (250ml) and washed with ethyl acetate (200ml). The aqueous layer was then acidified to pH5 with acetic acid under ice bath cooling. The resulting precipitate was collected by filtration and dried to give a beige solid (2.97g).

M.S. M+H observed

The following Intermediate was prepared by a similar procedure.

Intermediate 20 **7-Methoxy-2-(2-thiazolocarbonyl)benzofuran-4-carboxylic acid**

The title compound was obtained as a cream solid (625mg).

M.S. [M+H] observed

Intermediate 21 **4-Bromo-7-methoxy-2-[(pyridin-4-yl)carbonyl]benzofuran**

Bromine (0.02ml) was added to a mixture of 2-[(pyridin-4-yl)carbonyl]-7-methoxy benzofuran (0.1g) in methanol (7ml) under a nitrogen atmosphere cooled to -78°C. The reaction mixture was allowed to warm to room temperature over 2.5hrs. The reaction was then diluted with ethyl acetate (40ml), washed with 5% sodium metabisulfite solution (2x20ml), saturated sodium bicarbonate solution (40ml), dried over $MgSO_4$ and concentrated to dryness to afford a pale yellow solid (0.05g) as a 2:1 mixture of product:starting material by nmr.

TLC R_f 0.65 (10% methanol in ethyl acetate)

Intermediate 22 **4-Bromo-7-methoxy-2-(2-thiazolocarbonyl)benzofuran**

A stirred solution of 7-methoxy-2-(2-thiazolocarbonyl)benzofuran (3.09g) in methanol (160ml) was cooled to 0°C under an inert atmosphere and bromine (0.61ml) added dropwise. Stirring was continued for 18h at room temperature and the solvent was then removed *in vacuo*. The residue was partitioned between 5N potassium

hydroxide(60ml)/5% sodium metabisulfite (200ml) and ethyl acetate (100ml). The aqueous phase was extracted with ethyl acetate(3 x 60ml), dried (magnesium sulphate) and concentrated *in vacuo* to give the title compound as a beige solid (2.83g).

TLC R_f 0.55 (50% ethyl acetate in hexane)

Intermediate 23 **7-Methoxy-2-[(pyridin-4-yl)carbonyl]benzofuran**

4-(Bromoacetyl)pyridine hydrobromide (5g) and *o*-vanillin (2.11g) were reacted in a similar manner to Intermediate 11 to give the title compound as a yellow solid (0.95g).

TLC R_f 0.53 (ethyl acetate)

Intermediate 24 **7-Methoxy-2-(2-thiazolocarbonyl)benzofuran**

To a stirred solution of *o*-vanillin (2.95g) in ethanol (70ml) at 55°C was added sodium hydroxide (1.7g) and stirring continued for 10 minutes. 2-Bromoacetylthiazole hydrobromide (5.57g) was then added portionwise and heating was continued for 5h. The solution was allowed to cool and concentrated *in vacuo*. The residue was partitioned between water (200ml) and ethyl acetate (100ml) and extracted with ethyl acetate (3x70ml), the combined organic phases were dried over magnesium sulphate and concentrated *in vacuo* to give a brown solid. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane gave the title compound as orange needles (3.09g).

TLC R_f 0.55 (50% ethyl acetate in hexane)

Intermediate 25 **4-(Bromoacetyl)pyridine hydrobromide**

4-Acetylpyridine (10g) was combined with 48% HBr solution (18ml) and heated to 70°C. Bromine (4.7ml) dissolved in 48% HBr solution (5ml) was then added dropwise and heating then continued for 2.5hrs. The precipitate which had formed was collected by filtration, washed with 1:1 methanol:hexane (20ml) and dried to give a cream solid (19.5g) as 2:1 mixture of product:starting material by nmr.

mp 170-172°C

The following Intermediate was prepared in a similar manner.

Intermediate 26 **2-Bromoacetylthiazole hydrobromide**

The title compound was obtained as a pale yellow solid (5.57g).

^{1}H NMR (d_6-DMSO) δ 5.00 (2H, CH_2), 8.2 (1H, aromatic), 8.4 (1H, aromatic).

Intermediate 27 **4-Nitrophenyl 7-methoxy-2-(2-thiazolocarbonyl)-benzofuran-4-carboxylate**

To a stirred solution of 7-methoxy-2-(2-thiazolocarbonyl)benzofuran-4-carboxylic acid (625mg) in dichloromethane (40ml) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (593mg), 4-nitrophenol (430mg) and 4-dimethylaminopyridine (catalytic amount). Stirring was continued for 20h, then the precipitate was filtered off, washed with dichloromethane and dried *in vacuo* to give the title compound as a white solid (720mg).

^{1}H NMR ($CDCl_3$) δ 4.2 (3H, OCH_3), 7.1(1H, aromatic), 7.6(2H, aromatic), 7.8(1H, aromatic), 8.2(1H, aromatic), 8.3(1H, aromatic), 8.5(2H, aromatic), 9.2(1H, aromatic)

The following Intermediate was prepared by a similar procedure.

Intermediate 28 **4-Nitrophenyl 2-ethyl-7-methoxybenzofuran-4-carboxylate**

The title compound (1.26g) was obtained as a white solid.

TLC R_f 0.3 (50% ethyl acetate in hexane)

Intermediate 29 ***t*-Butyl 2-acetyl-7-methoxybenzofuran-4-carboxylate**

A solution of 2-acetyl-7-methoxybenzofuran-4-carboxylic acid (100mg) in dichloromethane (4ml) was stirred at room temperature under an atmosphere of nitrogen. *t*-Butyl-2,2,2-trichloroacetimidate (0.16ml) followed by boron trifluoride etherate (0.012ml) were added and the mixture stirred at room temperature for 2h. The reaction was quenched by the addition of a saturated solution of sodium bicarbonate (1ml). The mixture was extracted with dichloromethane (3x10ml) and the combined organic phases dried over magnesium sulphate. Removal of the solvent *in vacuo* and purification by flash chromatography eluting with dichloromethane gave the product as a white solid (130mg).

TLC R_f 0.25 (dichloromethane)

Intermediate 30 ***(Z)*-*t*-Butyl 2-(1-methoxyiminoethyl)-7-methoxybenzofuran-4-carboxylate**

A mixture of *(Z)*-*t*-butyl 2-acetyl-7-methoxybenzofuran-4-carboxylate (0.54g), methoxylamine (0.31g), pyridine (0.46ml) and toluene (50ml) was refluxed under Dean and Stark conditions overnight. The mixture was then cooled and the toluene removed *in vacuo*. The residue was taken up in ethyl acetate (100ml) and washed with water (50ml) then brine (50ml). Drying over magnesium sulphate followed by removal of the

solvent *in vacuo* and purification by flash chromatography eluting with dichloromethane gave the product as a colourless oil.

TLC R_f 0.52 (dichloromethane)

Intermediate 31 ***(Z)*-2-(1-Methoxyiminoethyl)-7-methoxybenzofuran-4-carboxylic acid**

A solution of *(Z)*-*t*-butyl 2-(1-methoxyiminoethyl)-7-methoxybenzofuran-4-carboxylate (100mg) and trifluoroacetic acid (0.05ml) in dichloromethane (5ml) was stirred at room temperature for 4h. A further aliquot of trifluoroacetic acid (0.1ml) was added and stirring continued overnight. The solvent was removed *in vacuo* and the residue was evapourated *in vacuo* from toluene (2x5ml) and dichloromethane (2x5ml) to remove excess trifluoroacetic acid. The product was obtained as a white solid (72mg).

TLC R_f 0.22 (dichloromethane)

mp 233-234°C

Intermediate 32 ***(Z)*-4-Nitrophenyl 2-(1-methoxyiminoethyl)-7-methoxybenzofuran-4-carboxylate**

A solution of *(Z)*-2-(1-methoxyiminoethyl)-7-methoxybenzofuran-4-carboxylic acid (70mg), 4-nitrophenol (41mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (56mg) and 4-dimethylaminopyridine (catalytic) in dichloromethane (20ml) was stirred at room temperature for 6h under an atmosphere of nitrogen. The reaction mixture was diluted with dichloromethane (20ml) and washed with water (3x20ml). Drying over magnesium sulphate followed by concentration to dryness *in vacuo* gave a pale yellow solid. Purifcation by flash chromatography eluting with dichloromethane gave the product as a white solid (53mg).

TLC R_f 0.42 (dichloromethane)

mp 195-196°C

Example 1 **2-Acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4yl)]benzofuran-carboxamide (Method A)**

Sodium hydride (0.03g) was added to a solution of 4-amino-3,5-dichloropyridine (0.08g) in anhydrous *N,N*-dimethylformamide (1ml) at room temperature under nitrogen. This stirred mixture was warmed to 60°C for 1 hour before addition of 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (generated from 2-acetyl-7-methoxybenzofuran-4-carboxylic acid, 0.12g) washed in with anhydrous

N,N-dimethylformamide (2ml). The brown mixture was heated at 60°C for 4 hours, allowed to cool, poured into water(100ml) and extracted into ethyl acetate (2x50ml). These organic extracts were washed with water (50ml) and saturated brine(50ml) then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a crude residue (0.17g). Purification by column chromatography on silica eluting with a 20-80% ethyl acetate in hexane gradient afforded a white solid (0.04g).

TLC R_f 0.20 (50% ethyl acetate in hexane)

mp 252-254°C

Example 2 **2-Ethyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (Method B)**

A suspension of 2-ethyl-7-methoxybenzofuran-4-carboxylic acid (300mg) in dry toluene (50ml) under an inert atmosphere was treated with thionyl chloride (2ml) and heated to reflux for 2 hours. The cooled reaction mixture was evaporated *in vacuo* and the residue azeotroped with dry toluene (2x 10ml) to afford the acid chloride as a white solid (325mg). 4-Amino-3,5-dichloropyridine (230mg) in dry *N,N*-dimethylformamide (20ml) under an inert atmosphere was treated with sodium bis(trimethylsilyl)amine (1.5ml; 1.0M in tetrahydrofuran) at ambient temperature for 30 minutes. The aforementioned solid acid chloride (325mg) was added to this mixture and heated at 50°C for 3 hours then allowed to cool overnight. It was evaporated *in vacuo*, saturated aqueous sodium bicarbonate (50ml) added and extracted into dichloromethane (2x50ml). These extracts were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a crude residue. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a white solid (210mg).

TLC R_f 0.15 (25% ethyl acetate in hexane)

mp 199-200°C

Example 3 **2-Acetyl-7-methoxy-4-[*N*-(pyrid-4-yl)]benzofurancarboxamide (Method C)**

A solution of 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (164mg) in anhydrous dichloromethane (10ml) under nitrogen at 0°C, was treated with 4-aminopyridine (0.07g), triethylamine (0.12g) and 4-dimethylaminopyridine (2mg). This solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with saturated aqueous sodium bicarbonate (10ml), water (10ml) and

saturated brine(10ml) then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a crude residue. Purification by column chromatography on silica eluting with 5% methanol in dichoromethane afforded a pale yellow solid (85mg).

TLC R_f 0.27 (5% methanol in dichloromethane)

mp 247-248°C (dec)

Example 4 **2-Acetyl-7-methoxy-4-[*N*-(pyrid-4-yl)-*N*-propyl] benzofuran-carboxamide**

4-[N-(Propylamino)]pyridine (0.08g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.15g) as in method C to afford a pale yellow foam (129mg).

TLC R_f 0.57 (5% methanol in dichloromethane)

IR (film); 1292, 1587, 1647, 1685 cm^{-1}

Example 5 **2-Acetyl-7-methoxy-4-[*N*-(2-chlorophenyl)]benzofuran-carboxamide**

2-Chloroaniline (0.42ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a solid (137mg).

mp 179- 181°C

Example 6 **2-Acetyl-7-methoxy-4-[*N*-(2,6-dimethylphenyl)]benzofuran-carboxamide**

2,6-Dimethylaniline (0.49ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a solid (255mg).

TLC R_f 0.23 (50% ethyl acetate in hexane)

mp 225 - 226°C

Example 7 **2-Acetyl-7-methoxy-4-[*N*-(4-methoxyphenyl)]benzofuran-carboxamide**

4-Methoxyaniline (567mg) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.19g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in heptane afforded a yellow solid (103mg).

TLC R_f 0.26 (50% ethyl acetate in heptane)

Example 8 **2-Acetyl-7-methoxy-4-[*N*-(3-bromo-5-methylpyrid-2-yl)]-benzofurancarboxamide (Method D)**

2-Amino-3-bromo-5-methylpyridine (0.64g) in dry tetrahydrofuran (20ml) was treated with sodium hydride (0.15g; 60% dispersion in oil) under an inert atmosphere at ambient temperature for 15 minutes. A solution of 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.86g) in dry tetrahydrofuran (10ml) was added and then stirred overnight before evaporation *in vacuo*. Aqueous sodium bicarbonate (50ml) was added and the mixture extracted with ethyl acetate (2x50ml). These extracts were dried over magnesium sulphate, filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to afford a pale yellow powder (95mg).

TLC R_f 0.5 (50% ethyl acetate in hexane)

Example 9 **2-Acetyl-7-methoxy-4-[*N*-(3-methylphenyl)]benzofuran-carboxamide**

m-Toluidine (0.42ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a yellow solid (200mg).

TLC R_f 0.5 (50% ethyl acetate in hexane)

mp 193- 195°C

Example 10 **2-Acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-2-yl)]benzofuran-carboxamide**

2-Amino-3,5-dichloropyridine (0.758g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.17g) as in method D using *N,N*-dimethylformamide as a cosolvent. Purification by column chromatography on silica eluting with 3% methanol in dichloromethane afforded a yellow solid (13mg).

TLC R_f 0.5 (50% ethyl acetate in hexane)

Example 11 **2-Acetyl-7-methoxy-4-[*N*-(2-methylphenyl)]benzofuran-carboxamide**

2-Methylaniline (0.21ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.5g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a yellow solid (128mg).

TLC R_f 0.24 (50% ethyl acetate in hexane)

mp 174- 175°C

Example 12 **2-Acetyl-7-methoxy-4-[*N*-(4-methoxy-2-methylphenyl)]-benzofurancarboxamide**

4-Methoxy-2-methylaniline (0.56ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.0g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a yellow solid (235mg).

TLC R_f 0.25 (50% ethyl acetate in hexane)

mp 217 - 218°C

Example 13 **2-Acetyl-7-methoxy-4-[*N*-(pyrimidin-4-yl)]benzofuran-carboxamide**

4-Aminopyrimidine (0.376g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by column chromatography on silica eluting with a 0-10% methanol in ethyl acetate gradient afforded a yellow solid (0.14g).

TLC R_f 0.49 (10% methanol in ethyl acetate)

mp 212 - 214 °C

Example 14 **2-Acetyl-7-methoxy-4-[*N*-(2-trifluoromethylphenyl)]-benzofurancarboxamide**

2-Aminobenzotrifluoride (0.5ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.0g) as in method D. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a yellow solid (0.12g).

mp 164 - 166°C

Example 15 **2-Acetyl-7-methoxy-4-[*N*-(3-chloropyrid-4-yl)]benzofuran-carboxamide**

4-Amino-3-chloropyridine (0.26g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.5g) as in method A except that the initial anion generation was performed at ambient temperature and using 15-crown-5 (0.90g). Purification by column chromatography on silica eluting with 5% methanol in dichloromethane afforded an off-white solid (0.08g).

TLC R_f 0.65 (5% methanol in dichloromethane)

mp 197 - 200°C

Example 16 **2-Acetyl-7-methoxy-4-[*N*-(2-trifluoromethoxyphenyl)]-benzofurancarboxamide**

2-Trifluoromethoxyaniline (0.49g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.7g) as in method C. Purification by column chromatography on silica eluting with 50% ethyl acetate in hexane afforded a yellow solid (0.065g).

TLC R_f 0.49 (50% ethyl acetate in hexane)

mp 163 - 165°C

Example 17 **2-Acetyl-7-methoxy-4-[*N*-(2-ethylphenyl)]benzofuran-carboxamide**

2-Ethylaniline (0.48g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.0g) as in method C. Purification by column chromatography on silica eluting with 25% ethyl acetate in hexane afforded an off-white solid (310mg).

TLC R_f 0.13 (25% ethyl acetate in hexane)

mp 174 - 175°C

Example 18 **2-Acetyl-7-methoxy-4-[*N*-(3-methylpyrid-2-yl)]benzofuran-carboxamide**

2-Amino-3-picoline (0.32ml) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (0.73g) as in method C. Purification by column chromatography on silica eluting with 5% methanol in dichloromethane afforded a yellow solid (0.12g).

TLC R_f 0.40 (5% methanol in dichloromethane)

Example 19 **2-Ethyl-7-methoxy-4-[*N*-(2-chloropyrid-3-yl)]benzofuran-carboxamide**

3-Amino-2-chloropyridine (0.88g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (1.8g) as in method A except that the anion generation was performed at ambient temperature for 1.5hours. Purification by flash chromatography on silica eluting with hot ethyl acetate then trituration with diethyl ether afforded a beige solid (0.53g).

TLC R_f 0.35 (50% ethyl acetate in hexane)

mp 124 - 125°C

Example 20 **2-Acetyl-7-methoxy-4-[*N*-(2-methoxyphenyl)]benzofuran-carboxamide**

o-Anisidine (0.49g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by column chromatography on silica eluting with 30% ethyl acetate in hexane afforded a yellow solid (160mg).

Example 21 **2-Acetyl-7-methoxy-4-[*N*-(2-chloropyrid-3-yl)]benzofuran-carboxamide**

3-Amino-2-chloropyridine (509mg) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1.0g) as in method D. Purification by column chromatography on silica eluting with 25% ethyl acetate in hexane afforded a yellow solid (205mg).

Example 22 **2-Acetyl-7-methoxy-4-[*N*-(2-chloro-6-methylphenyl)]-benzofurancarboxamide**

2-Chloro-6-methylaniline (0.56g) was treated with 2-acetyl-7-methoxybenzofuran-4-carbonyl chloride (1g) as in method C. Purification by recrystallisation from dichloromethane afforded a brown solid (160mg).

TLC R_f 0.4 (5%methanol in dichloromethane)

Example 23 **2-(1-Hydroxyethyl)-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]-benzofurancarboxamide**

2-Acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (0.50g) was suspended in dry methanol (20ml) and treated with sodium borohydride (196mg) at ambient temperature. Some external ice cooling was required then stirred overnight.The reaction mixture was poured into water and extracted into ethyl acetate. Evaporation *in vacuo* yielded a solid that was purified by column chromatography using 5% methanol in dichloromethane to afford a white solid (400mg).

TLC R_f 0.52 (80% ethyl acetate in heptane)

mp 229 - 231°C

Example 24 **2-[3-(Pyrid-3-yl)-1-oxopropyl]-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

A solution of 2-acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (0.40g) in dry *N,N*-dimethylformamide (5ml) under an inert atmosphere was cooled to -10°C and sodium hydride (60%dispersion in oil, 0.11g) added

over 30 minutes. After 1 hour at -10°C, 3-picolyl chloride hydrochloride (0.20g) was added and the mixture stirred for a further 2 hours before allowing to warm to room temperature overnight. It was poured into water and extracted into ethyl acetate. These extracts were washed with water and saturated brine then dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The resultant residue was purified by column chromatography using a 3-10% methanol in dichloromethane gradient then triturated with diethyl ether to yield a beige powder (15.5mg).

TLC R_f 0.27 (10% methanol in dichloromethane).

Example 25 **2-(1-Benzyloxyimino)ethyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

2-Acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (100mg) was refluxed under Dean-Stark conditions in dry toluene (40ml) with dry pyridine (64 µl) and O-benzylhydroxylamine hydrochloride (126mg) under an inert atmosphere. After 2 hours the mixture was allowed to cool and left stirring overnight. Addition of methanol and acetone formed a precipitate. This was filtered off to afford a solid (26mg).

TLC R_f 0.45 (50% ethyl acetate in hexane).

Example 26 **2-Ethyl-7-methoxy-4-[*N*-(3-carboxyphenyl)]benzofurancarboxamide**

A solution of 2-ethyl-7-methoxy-4-[*N*-(3-carboethoxyphenyl)]-benzofurancarboxamide (0.78g) in THF (25ml) was treated with a solution of lithium hydroxide monohydrate (0.18g) in water (25ml) and the reaction mixture stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, diluted with water (100ml) and acidified with dilute aqueous hydrochloric acid. The resulting white precipitate was collected, washed with water and dried *in vacuo* to afford the title compound (0.68g) as a white solid.

TLC R_f 0.35 (5% methanol in dichloromethane)

mp 265-267°C

The following compound was prepared according to the above procedure:

Example 27 **2-Ethyl-7-methoxy-4-[*N*-(4-carboxyphenyl)]benzofurancarboxamide**

Prepared from 2-ethyl-7-methoxy-4-[*N*-(4-carboethoxyphenyl)]-benzofurancarboxamide (0.67g) to afford the title compound (0.59g) as a white solid.

TLC R_f 0.4 (5% methanol in dichloromethane)

mp 279-280°C

Example 28 **2-[1-(2,2-Dimethylpropyl)]-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

Thionyl chloride (1.65ml) was added to a suspension of 2-[1-(2,2-dimethylpropyl)]-7-methoxybenzofurancarboxylic acid (0.59g) in toluene (10ml) and the mixture heated at reflux for 3h. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was azeotroped several times with toluene to furnish 2-[1-(2,2-dimethylpropyl)]-7-methoxybenzofuran-4-carbonyl chloride (0.63g). Sodium hexamethyldisilazide (1M solution in THF, 4.5ml) was added to a solution of 4-amino-3,5-dichloroaminopyridine (0.74g) in dry DMF (2ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 0.5h, then warmed to 50°C. A solution of 2-[1-(2,2-dimethylpropyl)]-7-methoxybenzofuran-4-carbonyl chloride (0.63g) in DMF was added and the reaction mixture stirred for a further 3h, then at room temperature for 16h. Water (20ml) was added and the resultant precipitate was collected and dried *in vacuo*. Purification by column chromatography on silica, eluting with 25% ethyl acetate in hexane afforded the title compound (0.29g) as a pale yellow solid.

TLC R_f 0.4 (50% ethyl acetate in hexane)

mp 164-165°C

Example 29 **2-(1-Methoxyiminoethyl)-7-methoxybenzofuran-4-[N-3,5-dichloropyrid-4-yl)]carboxamide**

To a suspension of 2-acetyl-7-methoxy-4-[N-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide (0.07g) in dry toluene (40ml) was added pyridine (0.09ml) and methoxylamine hydrochloride (0.056g) and the mixture heated under Dean-Stark conditions for 24h. Evaporation of the solvent and purification by flash chromatography on silica eluting with dichloromethane then 5% methanol in dichloromethane followed by preparative tlc (5% methanol in dichloromethane) afforded a white solid (0.03g) as a mixture of E and Z isomers by nmr.

TLC R_f 0.27-0.34 (50% ethyl acetate in hexane)

Example 30 **N-(3,5-Dichloropyrid-4-yl)-2-carboxy-7-methoxybenzofuran-4-carboxamide**

4-Amino-3,5-dichloropyridine (0.31g) was treated with methyl 7-methoxy-2-methoxycarbonylbenzofuran-4-carbonyl chloride as in Example 19. Purification by flash chromatography on silica eluting with 10% methanol in dichloromethane afforded a pale yellow solid (0.15g).

TLC R_f 0.1 (10% methanol in dichloromethane)

mp greater that 350°C

Example 31 **2-Ethyl-7-methoxy-4-[N-(2,5-dimethylpyrid-4-yl)]benzofurancarboxamide**

4-Amino-2,5-dimethylpyridine (0.3g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.59g) as in Example 19. Purification by flash chromatography on silica eluting with 10% methanol in dichloromethane then trituration with hexane afforded an off-white solid (0.11g)

TLC R_f 0.33 (10% methanol in dichloromethane)

mp 164-165°C

Example 32 **N-(5-Chloropyrimidin-4-yl)-2-ethyl-7-methoxybenzofuran-4-carboxamide**

4-Amino-5-chloropyrimidine (0.25g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.46g) as in Method B. Purification by recrystallisation afforded an off-white solid (0.12g)

TLC R_f 0.25 (3:2 Ethyl Acetate:Hexane)

mp 161-163°C

Example 33 **2-Ethyl-7-methoxy-4-[N-(3-methylthiotriazin-5-yl)]-benzofurancarboxamide**

5-Amino-3-methylthiotriazine (0.3g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.50g) as in Example 19. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded a cream solid (0.1g)

TLC R_f 0.47 (50% ethyl acetate in hexane)

M.S. [M+H] observed

Example 34 **2-Ethyl-7-methoxy-4-[N-(4-aminopyrido[3,2-b]pyridinyl)]-benzofurancarboxamide**

4-Aminopyrido[3,2-b]pyridine (0.36g) was treated with 2-ethyl-7-methoxybenzofuran-4carbonyl chloride (0.59g) as in Example 21. Purification by flash chromatography on silica eluting with 10% methanol in ethyl acetate followed by trituration with hexane afforded a pale yellow solid (0.23g)

TLC R_f 0.52 (10% methanol in ethyl acetate)

mp 155-157°C

Example 35 **2-Ethyl-7-methoxy-4-[N-(3-fluoropyridin-4-yl)]benzofuran-carboxamide**

4-Amino-3-fluoropyridine (0.25g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.53g) as in Method B. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded an off-white solid (0.13g)

TLC R_f 0.15 (50% ethyl acetate in hexane)

mp 150-151°C

Example 36 **Z-2-(1-Hydroxyiminoethyl)-4-[N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide**

To a suspension of 2-acetyl-7-methoxy-4-[N-(3,5-dichloropyrid-4-yl)]benzofuran carboxamide (0.5g) in dry toluene (30ml) were added pyridine (1g) and hydroxylamine (0.9g) and the mixture heated under Dean-Stark conditions for 48h. Evaporation of the solvent and washing with water afforded an off-white solid (0.2g)

TLC R_f 0.22 (50% ethyl acetate in hexane)

mp 250°C (decomp)

Example 37 **2-Ethyl-7-methoxy-4-[N-(2-chloro-5-carboxyl)phenyl]-benzofurancarboxamide**

5-Carboxymethyl-2-chloroaniline (0.566g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.50g) as in Example 19. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded 2-ethyl-7-methoxy-4-[N-(2-chloro-5-methoxycarbonyl)phenyl]benzofurancarboxamide as a white solid (0.497g; TLC R_f 0.5 (50% ethyl acetate in hexane); mp 174-176°C). This product (0.31 g) was treated as in Example 26, to afford the title compound (0.282g) as a white solid.

TLC R_f 0.6 (ethyl acetate)

mp 278-279°C

Example 38 **Z-2-(1-Hydroxyiminoethyl)-4-[N-methyl-N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide**

To a solution of Z-2-(1-hydroxyiminoethyl)-4-[N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide (50mg) in tetrahydrofuran (10ml) was added Bu_4NI (cat. amount) followed by a solution of NaOH (6mg) in H_2O (1ml). The whole was stirred for 20mins then MeI (45mg) was added and stirring continued for 12hrs. The mixture was concentrated to dryness, diluted with EtOAc (20ml), washed with H_2O (10ml), brine (10ml), dried over $MgSO_4$ and concentrated to dryness again giving the crude product. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded a white solid (24mg).

TLC R_f 0.37 (50% ethyl acetate in hexane)

mp 97-98°C

Example 39 **Z-2-(1-(4-Pyridylmethoxy)iminoethyl)-7-methoxybenzofuran-4-[N(3,5-dichloropyrid-4-yl)]carboxamide**

To a solution of Z-2-(1-hydroxyiminoethyl)-4-[N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide (50mg) in tetrahydrofuran (10ml) was added Bu_4NI (cat. amount) followed by a solution of NaOH (17mg) in H_2O (1ml). The whole was stirred for 20mins then 4-chloromethylpyridine hydrochloride (46mg) was added and stirring continued for 48hrs. The mixture was concentrated to dryness, diluted with EtOAc (20ml), washed with H_2O (10ml), brine (10ml), dried over $MgSO_4$ and concentrated to dryness again giving the crude product. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded an off-white solid (10mg).

TLC R_f 0.26 (ethyl acetate)

mp 217-218°C

Example 40 **2-(1-Hydroxyiminoethyl)-4-[N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide**

Tetrabutylammonium fluoride (1M solution in tetrahydrofuran) (0.48ml) was added to a solution of 2-(1-(t-butyldimethylsilyloxy)iminoethyl)-7-methoxy-4-[N-3,5-dichloropyrid-4-yl]benzofurancarboxamide in tetrahydrofuran (10ml) under a nitrogen atmosphere. Stirring was continued for 20 mins then the reaction mixture was

concentrated to dryness giving the crude product. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded an off-white solid (0.1g) as a 2:1 mixture of E:Z isomers by nmr.

TLC R_f 0.22 (50% ethyl acetate in hexane)

mp 280°C (dec.)

Example 41 **2-[(Pyridin-4-yl)carbonyl]-7-methoxybenzofuran-4-[N-(3,5-dichloropyridin-4-yl)]carboxamide**

Sodium hydride (0.3g) was added to a solution of 4-amino-3,5-dichloropyridine (0.56g) in dimethylformamide (10 ml) under an atmosphere of nitrogen. The reaction mixture was heated to 55°C for 1hr, then 2-[(pyridin-4-yl)carbonyl]-7-methoxybenzofuran-4-carbonyl chloride was added in one portion. Heating at 55°C was continued for 2hrs then at room temperature for 12hrs. The reaction mixture was concentrated to dryness to give the crude product. Purification by flash chromatography on silica eluting with ethyl acetate and then 20% methanol in ethyl acetate afforded a cream solid (0.3g).

TLC R_f 0.36 (ethyl acetate)

mp 250-252°C

Example 42 **2-[Methoxyimino(4-pyridyl)methyl]-7-methoxybenzofuran-4-[N-(3,5dichloropyridin-4-yl)]carboxamide**

2-[(Pyridin-4-yl)carbonyl]-7-methoxybenzofuran-4-[N-(3,5-dichloropyridin-4-yl)]-carboxamide (0.25g) was treated with methoxylamine hydrochloride (0.165g) as in Example 29. The crude product was washed with H_2O and then diethyl ether to give a white solid (0.217g) as a 5.5:4.5 mixture of E:Z isomers by nmr.

mp 245-247°C

M.S. [M+H] observed

Example 43 **E-2-(1-(4-Pyridylmethoxy)iminoethyl)-7-methoxybenzofuran-4-[N(3,5-dichloropyrid-4-yl)]carboxamide**

Sodium (9mg) was added to a suspension of 2-(1-hydroxyiminoethyl)-4-[N-(3,5-dichloropyridin-4-yl)]-7-methoxybenzofurancarboxamide (50mg) in ethanol (2ml) under a nitrogen atmosphere. Once all solids had gone into solution 4-chloromethylpyridine hydrochloride (21mg) was added and the reaction mixture was stirred at room temperature for 3 days. More sodium (6mg) and 4-chloromethylpyridine hydrochloride (21mg) were

added and the reaction mixture was heated to 85°C for 6hrs. The reaction was quenched with H_2O (20ml), extracted with ethyl acetate (3 x 20ml). The combined organic layers were washed with H_2O (20ml), brine (20ml), dried over $MgSO_4$ and concentrated to dryness to give the crude product. Purification by flash chromatography on silica eluting with ethyl acetate afforded an off-white solid (18mg).

TLC R_f 0.43 (ethyl acetate)

mp 231-232°C

Example 44 **2-(4-Morpholino)acetyl-7-methoxybenzofuran-4-[N-(3,5-dichloropyrid-4-yl)carboxamide**

Bromine (0.01ml) was added to a solution of 2-acetyl-7-methoxy-4-[N-(3,5-dichloropyridin-4-yl)]benzofurancarboxamide (0.1g) in 45% HBr/AcOH (4ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 12hrs then quenched with H_2O (20ml) and extracted with ethyl acetate (3 x 20ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (20ml), brine (20ml), dried over $MgSO_4$ and concentrated to dryness to give the crude 2-bromoacetyl-7-methoxybenzofuran-4-[N-(3,5-dichloropyrid-4-yl)]carboxamide. Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane afforded an impure yellow solid (20mg) which was used without further purification.

Morpholine (0.09ml) and triethylamine (10mg) were added to a solution of 2-bromoacetyl-7-methoxybenzofuran-4-[N-(3,5-dichloropyrid-4-yl)]carboxamide (20mg) in dichloromethane (5ml) under a nitrogen atmosphere. Stirring was continued for 1.5hrs. The reaction mixture was then diluted with more dichloromethane washed with H_2O, dried over $MgSO_4$ and concentrated to dryness to give the crude product. Purification by flash chromatography on silica eluting with ethyl acetate afforded a yellow solid (10mg).

TLC R_f 0.38 (ethyl acetate)

mp 130°C (dec.)

Example 45 **N-(2,6-Dichloro-4-carboxyphenyl)-2-ethyl-7-methoxybenzofuran-4-carboxamide**

Ethyl 4-amino-3,5-dichlorobenzoate (0.815g) was treated with 2-ethyl-7-methoxybenzofuran-4-carbonyl chloride (0.754g) as in Example 19. Purification by triturating the crude product with dichloromethane afforded N-[2,6-dichloro-4-(ethoxycarbonyl)phenyl]-2-ethyl-7-methoxybenzofuran-4-carboxamide

a white solid (338mg; TLC R_f 0.15 (20% ethyl acetate in hexane); mp 165-166°C). This product (292 mg) was treated as in Example 26 to afford the title compound (230mg) as a white solid.

TLC R_f 0.6 (6% methanol in dichloromethane)

mp 274-275°C

Example 46 **7-Methoxy-2-(2-thiazolocarbonyl)-4-[*N*-(5-chloropyrimidin-4-yl)]benzofurancarboxamide**

To a stirred solution of 4-amino-5-chloropyrimidine (220mg) in dimethylformamide (20ml) under nitrogen was added sodium hydride (60% dispersion in oil) (135mg) and stirring was continued for 3h. 4-Nitrophenyl 7-methoxy-2-(2-thiazolocarbonyl)-benzofuran-4-carboxylate (720mg) was then added and stirring was continued for a further 18 h. The solvent was removed *in vacuo* and the resulting residue was triturated with ethyl acetate then purified by flash chromatography eluting with 2% ammonium hydroxide/20% methanol in ethyl acetate. Further trituration with methanol yielded the title compound as a cream solid (165mg).

M.S. [M+H] observed

mp 262-264°C (dec)

The following examples were prepared from 4-nitrophenyl 2-ethyl-7-methoxybenzofuran-4-carboxylate and the appropriate amine according to the above procedure.

Example 47 **2-Ethyl-7-methoxy-4-[(*N*-(2,5-difluoropyrimidin-4-yl)]benzofurancarboxamide**

Prepared from 4-amino-2,5-difluoropyrimidine (190mg) to give the title compound (95mg) as an off-white solid.

TLC R_f 0.6 (50% ethyl acetate in hexane)

mp 175-176°C

Example 48 **2-Ethyl-7-methoxybenzofuran-4-[(*N*-(1,3,5-trimethylpyrazol-4-yl)]carboxamide**

Prepared from 4-amino-1,3,5-trimethylpyrazole (165mg) to give the title compound (222mg) as a white solid.

TLC R_f 0.27 (10% methanol in ethyl acetate)

mp 182-184°C

Example 49 **2-[2-(4-Morpholino)-(2-methoxy)iminoethyl]-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

Prepared from 2-(4-morpholino)acetyl-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide by a similar procedure to that of Example 4. Purification by flash chromatography on silica eluting with ethyl acetate afforded the product as a yellow solid as a 1:1 mixture of isomers (20mg).

TLC R_f 0.66 and 0.53 (ethyl acetate)

mp 140°C (dec.)

Example 50 ***(Z)*-2-[1-(2-Methylthiazol-4-ylmethoxy)iminoethyl]-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

A solution of *(Z)*-2-(1-hydroxyiminoethyl)-7-methoxy-4-[*N*-(3,5-dichloropyridin-4-yl)]benzofurancarboxamide (0.75g) in dimethylformamide (30ml) was stirred at room temperature under an atmosphere of nitrogen. Sodium hydride (60% dispersion in oil) (0.17g) was added and stirring continued for 1h. 4-Chloromethyl-2-methylthiazole (0.84g) was added (generated from the hydrochloride salt using sodium bicarbonate) and the mixture stirred for 1h. The mixture was poured onto water (100ml) and extracted with ethyl acetate (3x100ml). The combined organic washings were washed with water (100ml) and brine (50ml), dried over magnesium sulphate and the solvent removed *in vacuo* to give creamy solid. The solid was triturated with ether to removed unreacted alkylating agent and purified by flash chromatography eluting with 0-10% methanol in ethyl acetate to give the product as a white solid (0.69g).

TLC R_f 0.62 (ethyl acetate)

mp 221-222°C

The following Example was prepared by a similar procedure.

Example 51 ***(Z)*-2-(1-(4-Morpholinoethoxy)iminoethyl)-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

Purification by recrystallisation from ethyl acetate/hexane gave the product as a white solid (0.22g)

TLC R_f 0.50 (10% methanol in dichloromethane)

mp 178-179°C

Example 52 ***(Z)*-2-(1-Methoxyiminoethyl)-7-methoxy-4-[*N*-(3,5-dichloropyrid-4-yl)]benzofurancarboxamide**

A solution of 4-amino-3,5-dichloropyridine (23mg) in dimethylformamide (5ml) was stirred at room temperature under an atmosphere of nitrogen. Sodium hydride (60% dispersion in oil) (9mg) was added and the resulting suspension stirred for 1h. A solution of 4-nitrophenyl 2-(1-methoxyiminoethy)]-7-methoxybenzofuran-4-carboxylate (50mg) in dimethylformamide (2ml) was added and stirring continued overnight. The reaction was quenched by the addition of water (1ml) and the mixture concentrated to dryness *in vacuo*. Purification by flash chromatography eluting with 50% ethyl acetate in hexane gave the product as a white solid (23mg).

TLC R_f 0.40 (50% ethyl acetate in hexane)

mp 238-239°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 (PBMC's) is measured as follows. PBMC'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.

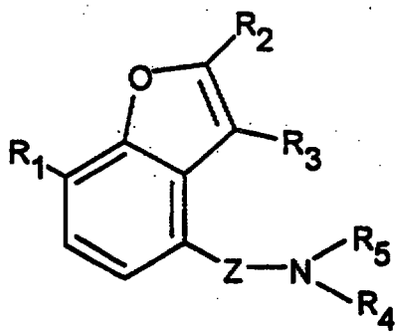
Abbreviations

LPS	Lipopolysaccharide (endotoxin)
ELISA	Enzyme linked immunosorbent assay

CLAIMS

1. A compound of the general formula (i)

(i)



wherein Z is CO or CS;

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

R_2 and R_3 are the same or different and are each H, R_6, OR_{10}, COR_6, $C(=NOR_6)R_6$, alkyl-$C(=NOR_6)R_6$, alkyl-$C(=NOH)R_6$, $C(=NOH)R_6$, halogen, NR_8R_9, CF_3, CN, CO_2H, $C0_2R_{10}$, $CONH_2$, $CONHR_6$ or $CON(R_6)_2$;

R_4 represents H, arylalkyl, heteroarylalkyl, heterocycloalkyl, $S(O)_mR_{10}$ or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy, CO_2R_7, $SO_2NR_{11}R_{12}$, $CONR_{11}R_{12}$, CN, carbonyl oxygen, NR_8R_9, COR_{10} and $S(O)_nR_{10}$;

R_5 represents aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

in R_4 and/or R_5 the aryl/heteroaryl/heterocyclo portion is optionally substituted with one or more substituents alkyl-R_{13} or R_{13};

R_6 represents R_{10} optionally substituted at any position with R_{14};

R_7 represents H, alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_8 represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

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

R_9, R_{11} and R_{12} are the same or different and are each H or R_{10};

* C L M S *

R_{13} represents alkyl optionally substituted with halogen, alkoxy optionally substituted by halogen, aryl, heteroaryl, heterocyclo, hydroxy, aryloxy, heteroaryloxy, heterocyclooxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, CO_2R_7, $CONR_{11}R_{12}$, $SO_2NR_{11}R_{12}$, halogen, -CN, $-NR_8R_9$, COR_{10}, $S(O)_nR_{10}$ or carbonyl oxygen;

R_{14} represents OH, carbonyl oxygen, OR_{10}, NR_8R_9, CN, CO_2H, CO_2R_{10}, $CON_{11}R_{12}$ or COR_{10};

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_2 and R_3 are the same or different and are each H, R_6, COR_6, $C(=NOR_6)R_6$, CN, CO_2H, CO_2R_{10}, $CONH_2$, $CONHR_6$ or $CON(R_6)_2$.

3. A compound of claim 1, wherein

Z is CO;

R_1 is alkoxy optionally substituted by one or more halogens;

R_2 and R_3 are the same or different and are each R_{6a} or alkyl-R_{6a};

R_{6a} is H, aryl, heteroaryl, heterocyclo, hydroxy, alkoxy, aryloxy, heteroaryloxy, heterocyclooxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy, alkylamino, CF_3 or COR_{10};

R_{10} is alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_{13} is aryl, heteroaryl, heterocyclo, hydroxy, alkoxy, aryloxy, heteroaryloxy, heterocyclooxy, arylalkoxy, heteroarylalkyloxy, heterocycloalkyloxy, $C0_2R_7$, $CONR_{11}R_{12}$, $SO_2NR_{11}R_{12}$, halogen, CN, NR_8R_9, COR_{10}, $S(O)_nR_{10}$ or carbonyl oxygen; and

m is 1 or 2.

4. A compound of claim 1, wherein

R_2 and R_3 are each independently selected from H, R_6 and COR_6; and

R_6 is alkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl.

5. A compound of any preceding claim, wherein R_2 is not H.

6. A compound of any preceding claim,wherein R_5 is optionally-substituted aryl or heteroaryl.

7. A compound of any preceding claim, wherein R_1 is alkoxy optionally substituted with one or more halogens.

8. A compound of any preceding claim, wherein R_2 and R_3 are not both H.

9. A compound of any preceding claim, wherein R_2 and R_3 are independently OR_{10}, halogen, NR_8R_9 or CF_3.

10. A compound of any of claims 1 to 8, wherein R_2 and R_3 are independently $C(=NOR_6)R_6$, alkyl-$C(=NOR_6)R_6$, $C(=NOH)R_6$ or alkyl-$C(=NOH)R_6$.

11. A compound of any of claims 1 to 8, wherein R_2 and R_3 are independently heterocyclo, heterocycloalkyl or heteroarylalkyl optionally substituted at any position with (one or more) R_{14}.

12. A compound of any of claims 1 to 8, wherein R_2 and R_3 are independently alkyl substitution at any position with (one or more) OH, OR_{10}, NR_8R_9 or CN.

13. A compound of any of claims 1 to 8, wherein R_2 and R_3 are independently alkyl substituted with one or more COR and R is aryl, heteroaryl, heterocyclo (not attached through nitrogen), arylalkyl, heteroarylalkyl or heterocycloalkyl.

14. A compound of any of claims 1 to 8, wherein R_2 and R_3 are independently COR as defined in claim 13 optionally substituted at any position with (one or more) R_{14}.

15. A compound of any preceding claim, wherein R_4 is H or alkyl.

16. A compound of any preceding claim, wherein R_5 is aryl or heteroaryl, either of which may be optionally substituted with one or more substituents alkyl-R_{13} or R_{13}.

17. A compound of claim 1, selected from 2-acetyl-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide and 2-acetyl-7-methoxy-4-*N*-(pyrid-4-yl)-benzofurancarboxamide.

18. A compound of claim 1, selected from

2-ethyl-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-[*N*-(pyrid-4-yl)-N-propyl]benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-chlorophenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2,6-dimethylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(4-methoxyphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(3-bromo-5-methylpyrid-2-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(3-methylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(3,5-dichloropyrid-2-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-methylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(4-methoxy-2-methylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(pyrimidin-4-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-trifluoromethylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-[2-(piperidin-1-yl)phenyl]benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(3-chloropyrid-4-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-trifluoromethoxyphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-ethylphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-biphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(3-methylpyrid-2-yl)benzofurancarboxamide,

2-ethyl-7-methoxy-4-*N*-(2-chloropyrid-3-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-methoxyphenyl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-chloropyrid-3-yl)benzofurancarboxamide,

2-acetyl-7-methoxy-4-*N*-(2-chloro-6-methylphenyl)benzofurancarboxamide,

2-(1-hydroxyethyl)-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide,

2-(3-pyrid-3-yl-1-oxopropyl)-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide,

2-(1-benzyloxyimino)ethyl-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide,

2-ethyl-7-methoxy-4-*N*-(3-carboxyphenyl)benzofurancarboxamide,

2-ethyl-7-methoxy-4-*N*-(4-carboxyphenyl)benzofurancarboxamide, and

2-[1-(2,2-Dimethylpropyl)]-7-methoxy-4-*N*-(3,5-dichloropyrid-4-yl)benzofurancarboxamide.

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

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

21. Use of a compound of any of claims 1 to 19, 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.

22. The use of claim 21, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

23. The use of claim 22, wherein the pathological condition is selected from asthma, chronic bronchitis, chronic obstructive 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.

24. The use of claim 22, wherein the pathological condition is selected from chronic bronchitis, allergic rhinitis and adult respiratory distress syndrome.

25. The use of claim 21, wherein the disease state is capable of being modulated by TNF inhibition.

26. The use of claim 25, wherein the disease state is an inflammatory disease or autoimmune disease.

27. The use of claim 26, 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.

28. The use of claim 22 or claim 25, wherein the pathological condition or disease state is asthma.

29. The use of claim 27, wherein the disease state is acute respiratory distress syndrome, pulmonary inflammatory disease or pulmonary sarcoidosis.

30. The use of claim 27, wherein the disease state is joint inflammation.

31. The use of claim 22 or claim 25, wherein the disease state is a disease or disorder of the brain, such as brain trauma, stroke, ischaemia, Huntingdon's disease or tardive dyskinesia.

32. The use of claim 25, wherein the disease state is a yeast or fungal infection.

33. Use of a compound of any of claims 1 to 19, for the manufacture of a medicament for use in gastroprotection.

34. Use of a compound of any of claims 1 to 19, 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.

35. Use of a compound of any of claims 1 to 19, in coadministration with another drug such as a bronchodilator, steroid or xanthine, for asthma therapy.

* C L M S *