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(54) Titre : OXOPYRAZOLOCINNOLINES IMMUNOMODULANTES EN TANT QU'INHIBITEURS DE CD80
(54) Title: IMMUNOMODULATING OXOPYRRAZOLOCINNOLINES AS CD80 INHIBITORS

(57) Abrégé/Abstract:
N-(l-Aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3clcinnolin-2-yl)-benzamide is a CD80 antagonist, useful in the treatment of diseases which benefit from immuno-inhibition.

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(54) Title: IMMUNOMODULATING OXOPYRRAZOLOCINNOLINES AS CD80 INHIBITORS

(57) Abstract: N-(l-Aza-bicyclo[2.2.2]oct-3-yI)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3clcinnolin-2-yI)-benzamide is a CD80 antagonist, useful in the treatment of diseases which benefit from immuno-inhibition.

IMMUNOMODULATING OXOPYRRAZOLOCINNOLINES AS CD80 INHIBITORS

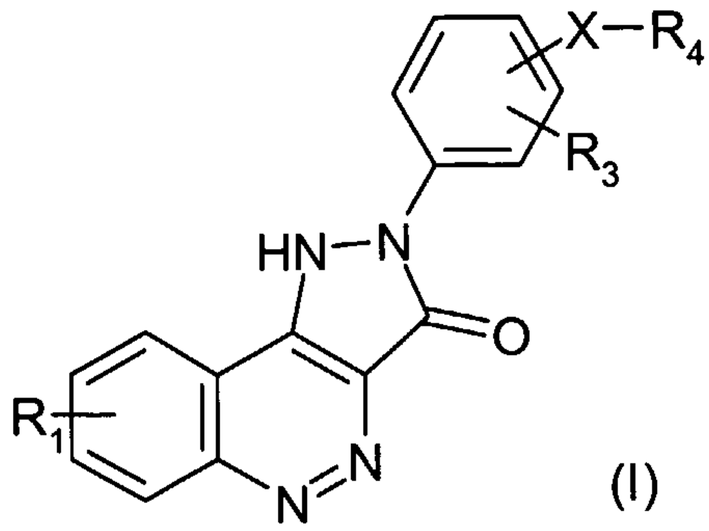
The present invention relates to the immunoinhibitory CD80 antagonist compound N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide, to a method for its preparation, to compositions containing it, and to its for clinical treatment of medical conditions which benefit from immunomodulation, e.g. autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis.

Background to the Invention

The immune system possesses the ability to control the homeostasis between the activation and inactivation of lymphocytes through various regulatory mechanisms during and after an immune response. Among these are mechanisms that specifically inhibit and/or turn off an immune response. Thus, when an antigen is presented by MHC molecules to the T-cell receptor, the T-cells become properly activated only in the presence of additional co-stimulatory signals. In the absence of these accessory signals there is no lymphocyte activation and either a state of functional inactivation termed anergy or tolerance is induced, or the T-cell is specifically deleted by apoptosis.

One such co-stimulatory signal involves interaction of CD80 on specialised antigen-presenting cells with CD28 on T-cells, and this signal has been demonstrated to be essential for full T-cell activation. (Lenschow *et al.* (1996) *Annu. Rev. Immunol.*, **14**, 233-258). It would therefore be desirable to provide compounds which inhibit this CD80/CD28 interaction.

Our copending international patent application PCT/GB2004/001008 relates to compounds of formula (I) and pharmaceutically or veterinarily acceptable salts, hydrates or solvates thereof:



(I)

wherein

R_1 and R_3 independently represent H; F; Cl; Br; -NO_2; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_4 represents a carboxylic acid group (-COOH) or an ester thereof, or –C(=O)NR_6R_7, -NR_7C(=O)R_6, -NR_7C(=O)OR_6, –NHC(=O)NR_7R_6 or –NHC(=S)NR_7R_6 wherein

R_6 represents H, or a radical of formula –$(Alk)_m$-Q wherein

m is 0 or 1

Alk is an optionally substituted divalent straight or branched C_1-C_{12} alkylene, or C_2-C_{12} alkenylene, or C_2-C_{12} alkynylene radical or a divalent C_3-C_{12} carbocyclic radical, any of which radicals may contain one or more –O-, -S- or –N(R_8)- links wherein R_8 represents H or C_1-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_4 alkynyl, or C_3-C_6 cycloalkyl, and

Q represents H; -NR_9R_{10} wherein R_9 and R_{10} independently represents H; C_1-C_4 alkyl; C_3-C_4 alkenyl; C_3-C_4 alkynyl; C_3-C_6 cycloalkyl; an ester group; an optionally substituted carbocyclic or heterocyclic group; or R_9 and R_{10} form a ring when taken together with the nitrogen to which they are attached, which ring is optionally substituted; and

R_7 represents H or C_1-C_6 alkyl; or when taken together with the atom or atoms to which they are attached R_6 and R_7 form an optionally

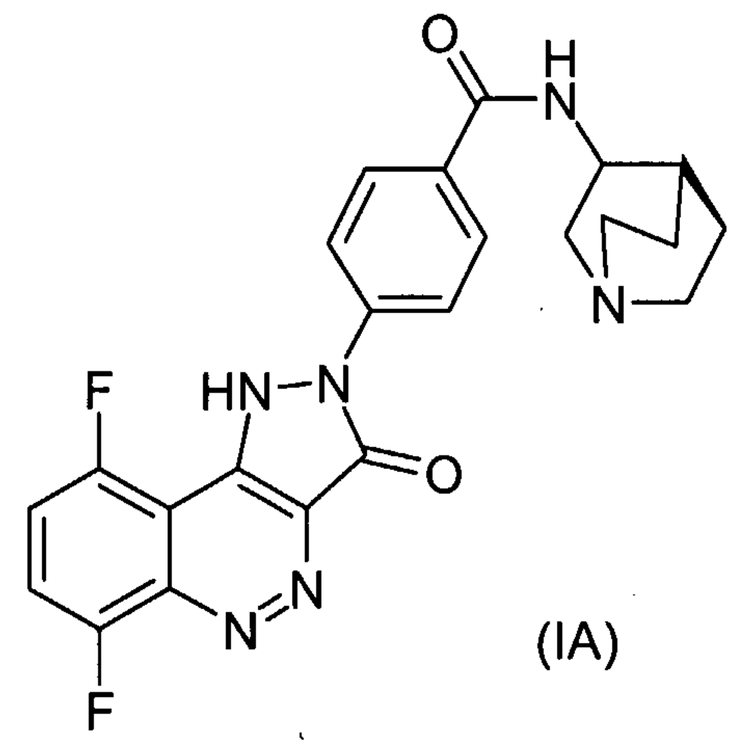
substituted monocyclic heterocyclic ring having 5, 6 or 7 ring atoms; and

X represents a bond or a divalent radical of formula $-(Z)_n-(Alk)-$ or $-(Alk)-(Z)_n-$ wherein Z represents –O-, -S- or –NH-, Alk is as defined in relation to R_6 and n is 0 or 1.

Description of the invention

The present invention relates to a specific compound falling within the general formula (I) of the above-mentioned PCT/GB2004/001008,

The invention provides the compound N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide of formula (IA):

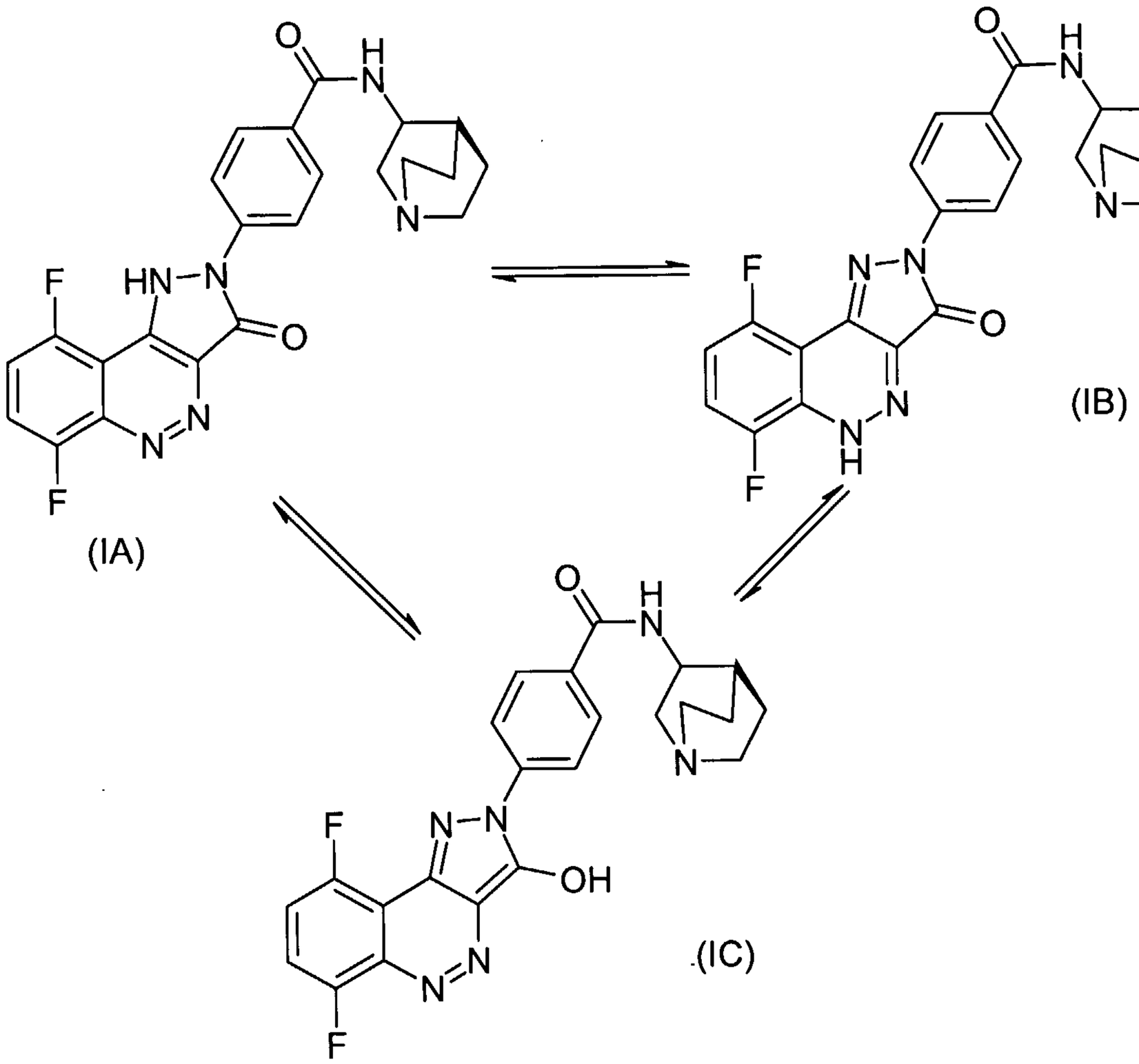


(IA)

and salts, hydrates and solvates thereof.

The carbon atom of the 1-aza-bicyclo[2.2.2]oct-3-yl ring system linked to the benzamido nitrogen is asymmetric, and thus the compound of the invention exists as (R)- or (S)- enantiomers or as an (RS)-enantiomeric mixture. In structure (IA) and elsewhere herein, the bond between that carbon and the benzamido nitrogen is shown in undefined orientation. Both enantiomers (and of course the mixture) have CD80 antagoinist activity, but the (R) enantiomer is currently preferred. The invention therefore includes the compound in the form of the (R)-enantiomer, as well as the (S)- enantiomer, and (RS)-enantiomeric mixtures.

Compound (IA) may exist in the form of tautomers, such as (IB) and (IC):



(IA) (IB) (IC)

The invention includes all tautomeric forms of N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide, including in particular those of formulae (IA), (IB), and (IC).

The compound of the invention is a CD80 antagonist. It inhibits the interaction between CD80 and CD28 and thus the activation of T cells, thereby modulating the immune response.

Accordingly the invention also includes:

(i) N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, for use in the

treatment of conditions which benefit from immunomodulation, and in particular for immuno-inhibition.

(ii) the use of N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation, and in particular for immuno-inhibition.

(iii) a method of immunomodulation, and in particular immuno-inhibition, in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.

(iv) a pharmaceutical or veterinary composition comprising N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, together with a pharmaceutically or veterinarily acceptable excipient or carrier.

Conditions which benefit from immunomodulation include:

Acute disseminated encephalomyelitis
Adrenal insufficiency
Allergic angiitis and granulomatosis
Amylodosis
Ankylosing spondylitis
Asthma
Autoimmune Addison's disease
Autoimmune alopecia
Autoimmune chronic active hepatitis
Autoimmune haemolytic anaemia
Autoimmune Neutrogena

Autoimmune thrombocytopenic purpura

Behçet's disease

Cerebellar degeneration

Chronic active hepatitis

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic neuropathy with monoclonal gammopathy

Classic polyarteritis nodosa

Congenital adrenal hyperplasia

Cryopathies

Dermatitis herpetiformis

Diabetes

Eaton-Lambert myasthenic syndrome

Encephalomyelitis

Epidermolysis bullosa acquisita

Erythema nodosa

Gluten-sensitive enteropathy

Goodpasture's syndrome

Guillain-Barre syndrome

Hashimoto's thyroiditis

Hyperthyroidism

Idiopathic hemachromatosis

Idiopathic membranous glomerulonephritis

Isolated vasculitis of the central nervous system

Kawasaki's disease

Minimal change renal disease

Miscellaneous vasculitides

Mixed connective tissue disease

Multifocal motor neuropathy with conduction block

Multiple sclerosis

Myasthenia gravis

Opsoclonus-myoclonus syndrome

Pemphigoid

Pemphigus

pernicious anaemia

Polymyositis/dermatomyositis
Post-infective arthritides
Primary biliary sclerosis
Psoriasis
Reactive arthritides
Reiter's disease
Retinopathy
Rheumatoid arthritis
Sclerosing cholangitis
Sjögren's syndrome
Stiff-man syndrome
Subacute thyroiditis
Systemic lupus erythematosis
Systemic necrotizing vasculitides
Systemic sclerosis (scleroderma)
Takayasu's arteritis
Temporal arteritis
Thromboangiitis obliterans
Type I and type II autoimmune polyglandular syndrome
Ulcerative colitis
Uveitis
Wegener's granulomatosis

Salts of N-(1-aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide include include physiologically acceptable acid addition salts and base salts. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate,

stearate, succinate, tartrate, tosylate and trifluoroacetate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

As mentioned above, the invention includes pharmaceutical or veterinary composition comprising the compound of the invention together with a pharmaceutically or veterinarily acceptable excipient or carrier. In such compositions, it will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the cause and severity of the particular disease undergoing therapy. Typical single dose ranges are from 10mg to 1000mg. Optimum dose levels and frequency of dosing will be determined by clinical trial.

The compound may be prepared for administration by any route consistent with its pharmacokinetic properties. Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, 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, glucose syrup, gelatin 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 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.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The drug may also be formulated for administration as a nasal or inhalation spray, or for inhalation as a powder.

The following Example describes the preparation of the compound of the invention by one convenient route. Other routes to the compound are available, using standard literature chemistry, and via routes described in PCT/GB2004/001008.

Example

Preparation of (R)-N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide

A round bottom flask fitted with a reflux condenser, magnetic stirrer and gas bubbler was charged with 4-(6,9-Difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzoic acid (300 mg). Thionyl chloride (5 ml) was added and the obtained red suspension was heated to reflux under nitrogen atmosphere. Upon heating gas evolution was observed. After 2 h reflux the clear red solution was cooled to room temperature and excess thionyl chloride removed under vacuum. The mixture was evaporated to dryness to give a red powder.

The powder was suspended in diethylether (20 ml). The (R)-(+)-3-aminoquinuclidine dihydrochloride (174 mg) was mixed with diethylether (10 ml) and ethyl-diisopropyl-amine (0.566 g, 0.762 ml) and added to the acid chloride suspension. *[Note: Use of the (S) form of 3-aminoquinuclidine dihydrochloride results in the preparation of the (S)-enantiomer of the desired compound].* The resulting mixture was stirred at room temperature under nitrogen atmosphere. After 4 days stirring product peak [M+H]+ 451 detectable, as well as carboxylic acid starting material.

The reaction mixture was quenched with water (50 ml) and the solids were collected by filtration and washed with water. The solids were triturated with saturated sodium bicarbonate solution, filtered and washed with water. The product was then purified by HPLC to give the amide.

MS: MH+ = 451.2

NMR

(d6 DMSO, 500 MHz) 1.74 (m, 1H); 1.92 (m, 2H); 2.14 (m, 1H); 2.22 (m, 1H); 2.54 (s, 1H); 3.24 (m, 4H); 3.70 (t, 1H); 4.32 (m, 1H); 7.42 (dt, 1H); 7.60 (m, 1H); 7.99 (d, 2H); 8.36 (d, 2H); 8.58 (d, 1H); 9.58 (brs, 1H).

The compound was tested in the BIAcore and homogeneous time resolved fluorescence (TR-Fret) Assays described below. The results were as follows:

BIAcore: K_D = 0.35 nM

TR-Fret: EC_{50} = 0.82 nM

BIAcore biomolecular interaction assay

Biotinylated human CD80 (hCD80-BT) is a recombinant soluble form of a membrane bound receptor molecule (CD80) which binds to CD28 to initiate T cell activation. The interaction between CD80 and CD28 has been extensively investigated (Collins et al, 2002). Biotinlyated human HLA-A2-tax is the recombinant soluble form of a membrane bound receptor molecule used as a control protein, and is not expected to interact with the compound.

The BIAcore S51™ system was used for screening the compounds of Examples 1-4 above. A series S sensor chip CM5 was docked onto the BIAcore S51™. Streptavidin was coupled to the carboxymethyl surface using standard amine coupling. The chip surface was activated with 0.2M EDC / 0.05M NHS, followed by binding of streptavidin (0.25 mg/ml in 10 mM sodium acetate pH 5.0) and saturation of unoccupied sites with 1 M ethylenediamine.

The BIAcore S51 sensor chip has two separate sensor spots for immobilisation of proteins. hCD80-BT was immobilised on the streptavidin-coated surface of one sensor spot until a response of approximately 3000 RU was observed. A protein to control for non-specific binding of the compound was immobilised on a second sensor spot. The control protein used for these experiments was a biotinylated, soluble form of the human HLA protein.

Dilution series of the compound (1000nM – 0.05nM) were prepared in running buffer (10 mM, pH 7.4, 150 mM NaCl, 0.005% P20; 5% DMSO).

BIAcore S51™ was run at a flow rate of 30 µl/min using running buffer. Compounds and DMSO standard solutions for correction of data for solvent effects were injected. Data were recorded automatically and were analysed using BIAcore S51 Evaluation software.

References

Collins AV *et al.* (2002) Immunity 17, 201-210 "The interaction properties of costimulatory molecules revisited"

Homogenous time resolved fluorescence assay

The compound was tested in a cell free homogenous time resolved fluorescence (HT-Fret) assay to determine their activity as an inhibitor of the CD80-CD28 interaction.

In the assay, europium and allophycocyanin (APC) are associated with CD28 and CD80 indirectly (through antibody linkers) to form a complex, which brings the europium and APC into close proximity to generate a signal. The complex comprises the following six proteins: fluorescent label 1, linker antibody 1, CD28 fusion protein, CD80 fusion protein, linker antibody 2, and fluorescent label 2. The table below describes these reagents in greater detail.

Fluorescent label 1	Anti-Rabbit IgG labelled with Europium (1μg/ml)
Linker antibody 1	Rabbit IgG specific for mouse Fc fragment (3μg/ml)
CD28 fusion protein	CD28 - mouse Fc fragment fusion protein (0.48μg/ml)
CD80 fusion protein	CD80 mouse Fab fragment (C215) fusion protein (1.9μg/ml)
Linker antibody 2	GαMκ-biotin: biotinylated goat IgG specific for mouse kappa chain (2μg/ml)
Fluorescent label 2	SA-APC: streptavidin labelled allophycocyanin (8μg/ml)

On formation of the complex, europium and APC are brought into proximity and a signal is generated.

Non-specific interaction was measured by substituting a mouse Fab fragment (C215) for the CD80 mouse Fab fragment fusion protein (1.9μg/ml). The assay was carried out in black 384 well plates in a final volume of 30μl. Assay

buffer: 50mM Tris-HCl, 150mM NaCl pH7.8, containing 0.1% BSA (w/v) added just prior to use.

Compounds were added to the above reagents in a concentration series ranging between 100μM – 1.7nM. The reaction was incubated for 4 hours at room temperature. Dual measurements were made using a Wallac Victor 1420 Multilabel Counter. First measurement: excitation 340nm, emission 665nm, delay 50μs, window time 200μs. second measurement: excitation 340nm, emission 615nm, delay 50μs, window time 200μs. Counts were automatically corrected for fluorescence crossover, quenching and background.

Claims:

1. N-(1-Aza-bicyclo[2.2.2]oct-3-yl)-4-(6,9-difluoro-3-oxo-1,3-dihydro-pyrazolo[4,3-c]cinnolin-2-yl)-benzamide, or a salt, hydrate or solvate thereof.

2. A compound as claimed in claim 1 in the form of the (R)-enantiomer.

3. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 or claim 2 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

4. A compound as claimed in claim 1 or claim 2 for use in the treatment of conditions which benefit from immunomodulation.

5. The use of a compound as claimed in claim 1 or claim 2 in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation,

6. A method of immunomodulation in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of a compound as claimed in claim 1 or claim 2.

7. A compound for use as claimed in claim 4, the use as claimed in claim 5 or a method as claimed in claim 6 wherein the immunomodulation is immuno-inhibition.

8. A compound for use as claimed in claim 4, the use as claimed in claim 5 or a method as claimed in claim 6 wherein the condition is autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis or psoriasis.