(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 June 2012 (21.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/080728 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 17/04* (2006.01)
A61K 31/4188 (2006.01) *A61P 17/12* (2006.01)
A61K 31/4745 (2006.01) *A61P 31/12* (2006.01)
A61P 11/06 (2006.01) *A61P 31/18* (2006.01)
A61P 17/06 (2006.01) *A61P 31/04* (2006.01)
A61P 37/08 (2006.01) *A61P 1/16* (2006.01)

(21) International Application Number:
PCT/GB2011/052474

(22) International Filing Date:
14 December 2011 (14.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/423,644 16 December 2010 (16.12.2010) US

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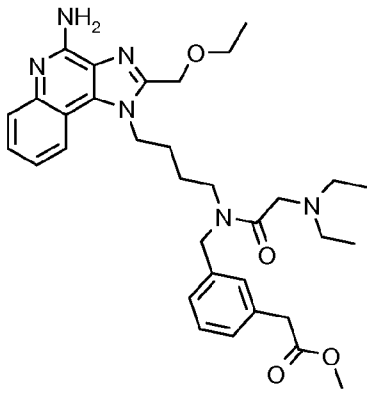
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: IMIDAZO [4, 5 -C] QUINOLIN- 1 -YL DERIVATIVE USEFUL IN THERAPY



(I)

(57) **Abstract**: The invention provides the compound of formula (I) and pharmaceutically acceptable salt thereof, pharmaceutical compositions containing the compound and the use of the compound in therapy.

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IMIDAZO [4, 5 -C] QUINOLIN- 1 -YL DERIVATIVE USEFUL IN THERAPY

The present invention relates to the compound methyl (3-{[{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}(*N*,*N*-diethylglycyl)amino]methyl}phenyl)acetate and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing the compound and its use in therapy.

The immune system is comprised of innate and acquired immunity, both of which work cooperatively to protect the host from microbial infections. It has been shown that innate immunity can recognize conserved pathogen-associated molecular patterns through toll-like receptors (TLRs) expressed on the cell surface of immune cells. Recognition of invading pathogens then triggers cytokine production (including interferon alpha (IFNα)) and upregulation of co-stimulatory molecules on phagocytes, leading to modulation of T cell function. Thus, innate immunity is closely linked to acquired immunity and can influence the development and regulation of an acquired response.

TLRs are a family of type I transmembrane receptors characterized by an NH_2-terminal extracellular leucine-rich repeat domain (LRR) and a COOH-terminal intracellular tail containing a conserved region called the Toll/IL-1 receptor (TIR) homology domain. The extracellular domain contains a varying number of LRR, which are thought to be involved in ligand binding. Eleven TLRs have been described to date in humans and mice. They differ from each other in ligand specificities, expression patterns, and in the target genes they can induce.

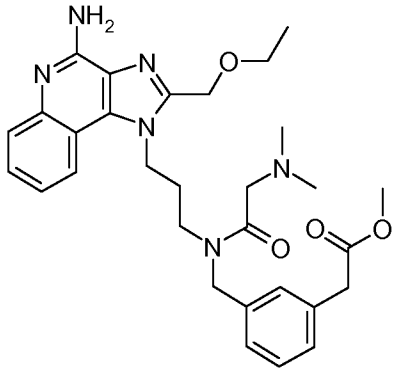
Ligands which act via TLRs (also known as immune response modifiers (IRMS)) have been developed, for example, the imidazoquinoline derivatives described in US Patent No. 4689338 which include the product Imiquimod for treating genital warts, and the adenine derivatives described in WO 98/01448 and WO 99/28321.

TLR7 agonists suppress the Th2 cell dependent immune response through enhancement of the Th1 response. Such agonists are expected to be useful in the treatment of a number of diseases by modulating the Th1/Th2 immune response. However, systemic exposure to a TLR7 agonist may result is undesirable side-effects such as flu-like symptoms caused by induction of cytokines including IL-6, IL-12, and type I IFN.

WO2008/135791 describes a class of imidazoquinoline compounds having immuno-modulating properties which act via TLR7 that are useful in the treatment of, for example, viral or allergic diseases and cancers.

The ester moieties in the compounds described in WO2008/135791 are quickly metabolised in plasma to the less active acid. The compounds are therefore suitable for topical administration and are expected to exert the desired effects at the site of administration, but be quickly converted to the less active acid metabolite upon entry into the systemic circulation, thereby reducing undesirable side effect which may be associated with systemic exposure to a TLR7 agonist.

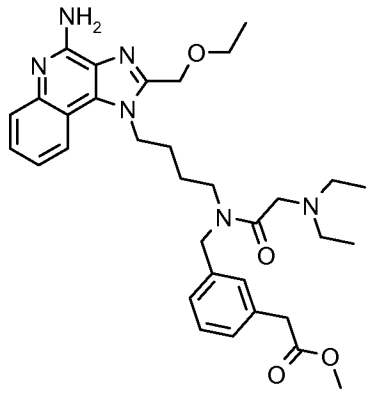
WO2008/135791 discloses 81 specific examples of compounds, salts and crystalline forms. Example 7 of WO2008/135791 is the compound methyl 2-(3-((N-(3-(4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl)propyl)-2-(dimethylamino)acetamido)methyl)phenyl)acetate, of the formula:



WO2008/135791 Example 7

It has now surprisingly been found the compound methyl (3-{[{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}(*N*,*N*-diethylglycyl)amino]methyl}phenyl)acetate is a potent TLR7 agonist. The compound has a number of favourable properties and as such is expected to be particularly suitable in the treatment of a number of conditions discussed hereinafter.

The structure of methyl (3-{[{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}(*N*,*N*-diethylglycyl)amino]methyl}phenyl)acetate (hereafter "Compound (I)") is shown below:



Compound (I)

Thus, in accordance with the present invention, there is provided Compound (I), or a pharmaceutically acceptable salt thereof.

In another aspect of the invention there is provided Compound (I).

In another aspect of the invention there is provided a pharmaceutically acceptable salt of Compound (I).It is to be understood that Compound (I), or a pharmaceutically acceptable salt thereof, may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

It is also to be understood that Compound (I) may exhibit polymorphism, and that the invention encompasses all such forms.

A suitable pharmaceutically acceptable salt of Compound (I) is, for example, an acid-addition salt of Compound (I), for example an acid-addition salt with a suitable inorganic or organic acid. Examples of inorganic acid addition salts include hydrochloride, hydrobromide, sulfate, hydroiodide, nitrate and phosphate. Examples of organic acid salts include oxalate, acetate, formate, propionate, benzoate, trifluoroacetate, fumarate, succinate, saccharin, maleate, citrate, lactate, tartrate, pyruvate, methanesulfonate, benzenesulfonate and p-toluenesulfonate. The salt may be a non-stoichiometric or stoichiometric salt, for example a mono or di-salt, such as a mono-saccharin or di-saccharin salt.

In the context of the present invention, the term “salt” defines a crystalline material in which the Compound (I) and the acid are ionized or alternatively, where both components utilise prominent intermolecular interactions, such as hydrogen bonding, to

combine and yield a uniform crystalline material (a co-crystal). It will be appreciated that a salt according to the invention may be partially ionic and partially co-crystal.

A further aspect of the invention provides a crystalline form of Compound (I), hereafter Compound (I) Form A. Compound (I) Form A is crystalline and provides an X-ray powder diffraction pattern substantially as shown in Figure 1 when measured at a wavelength of 1.5418Å. The most prominent peaks (2θ values) of the XRPD pattern for Compound (I) Form A are shown in Table 1. The 2θ values in Table 1 are measured to an accuracy of +/- 0.1°.

Table 1

Angle 2-Theta (2θ)°	Angle 2-Theta (2θ)°
5.3	21.3
7.6	21.8
9.3	22.2
10.7	22.8
11.6	23.4
12.4	24.1
13.0	24.8
13.2	25.2
13.8	26.1
14.5	26.6
15.2	27.9
15.6	30.2
15.9	31.0
16.9	31.8
17.8	32.3
18.2	33.0
18.5	33.4
19.7	34.1
20.0	35.6
20.5	37.6
20.8	38.6

Compound (I) Form A may be prepared as described in Example 1 hereinafter.

Accordingly, in one embodiment of the invention there is provided Compound (I) Form A, characterised in that said Form A has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value selected from Table 1 +/- 0.1°, when measured at a wavelength of 1.5418Å.

According to another embodiment of the invention there is provided Compound (I) Form A, characterised in that said Form A has an X-ray powder diffraction pattern with at least two specific peaks (for example at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 peaks) at 2θ values selected from Table 1 +/- 0.1°, when measured at a wavelength of 1.5418Å.

According to another embodiment of the invention there is provided Compound (I) Form A, characterised in that said Form A has an X-ray powder diffraction pattern substantially as shown in Figure 1.

Compound (I) Form A is crystalline. Suitably, Compound (I) Form A is substantially free from other crystalline and non-crystalline forms of Compound (I). For example, Compound (I) Form A suitably includes less than 20%, 15%, 10%, 5%, 3% or particularly, less than 1% by weight of other crystalline and non-crystalline forms of Compound (I).

When herein reference is made to Compound (I) Form A being crystalline, suitably the degree of crystallinity as determined by X-ray powder diffraction data, is for example greater than about 60%, such as greater than about 80%, particularly greater than about 90%, more particularly greater than about 95%. In embodiments of the invention, the degree of crystallinity as determined by X-ray powder diffraction data is greater than about 98%, wherein the % crystallinity refers to the % by weight of the total sample mass which is crystalline.

It is known in the art that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or machine used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, persons skilled in the art of X-ray powder diffraction will realise that the relative intensities of peaks may vary according to the orientation of the sample under test and on the type and setting of the instrument used.

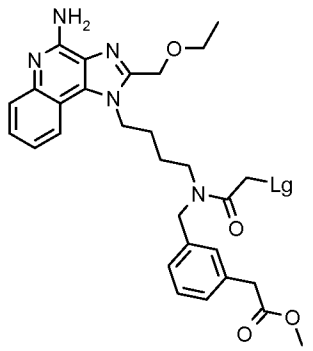
The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute and any crystalline form that provides a power diffraction pattern substantially identical to those disclosed herein fall within the scope of the present disclosure (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996).

Compound (I) may be prepared using analogous methods to those described WO2008/135791 and as illustrated in the Examples herein.

A further aspect of the present invention provides a process for the preparation of a Compound (I), or a pharmaceutically acceptable salt thereof comprising:

Process (a):

the reaction of a compound of the formula (II), or a salt thereof:



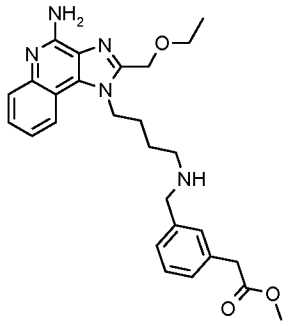
(II)

wherein Lg is a leaving group;

with diethylamine; or

Process (b)

the coupling reaction of a compound of the formula (III), or a salt thereof:



(III)

with 2-(diethylamino)acetic acid or a salt thereof;

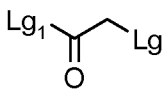
and thereafter optionally forming a pharmaceutically acceptable salt of Compound (I).

Process (a) Conditions

Examples of leaving groups represented by Lg in the compound of formula (II) include halo (for example chloro, bromo or iodo), mesylate (methylsulfonyloxy), triflate (trifluoromethanesulfonyloxy), besylate (benzenesulfonyloxy) or tosylate (toluenesulfonyloxy).

The reaction is suitably carried out in the presence of a solvent for example a polar aprotic solvent such as tetrahydrofuran, dichloromethane, dimethylformamide or dimethylsulfoxide or a non-polar organic solvent such as toluene. The reaction temperature is suitably performed at a temperature in the range of room temperature to the reflux temperature of the reaction mixture, particularly at room temperature.

The compound of formula (II) may be prepared by, for example, reacting a compound of formula (III), or a salt thereof as hereinbefore defined in relation to Process (a), with a compound of the formula (IV):



(IV)

wherein Lg and Lg^1 are leaving groups.

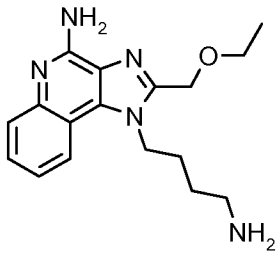
The leaving groups Lg and Lg^1 may be the same or different, provided that Lg^1 is more labile than Lg. Possible leaving groups are as hereinbefore defined in relation to Process (a). Suitably Lg^1 is halo, for example chloro. In one embodiment Lg and Lg^1 are both chloro.

Conveniently the compound of the formula (I) may be prepared directly from the compound of formula (III) by reacting the compound of formulae (III) and (IV) followed by reaction with the diethylamine, without isolating the compound of formula (III).

Process (b) Conditions

The coupling reaction is suitably carried out in the presence of a suitable coupling agent and optionally in the presence of a suitable base. An example of a suitable coupling agent is for example,O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. The base may be for example, an organic amine base such as triethylamine. The 2-(diethylamino)acetic acid is suitably used in the form of a salt, for example the hydrochloride salt. The coupling reaction is suitably carried out in the presence of a suitable solvent, for example, N,N-dimethylformamide or N-methyl pyrrolidine, at a temperature of, for example from 0 to 60 °C, conveniently at room temperature.

The compound of formula (III), or a salt thereof, may be prepared by reacting a compound of the formula (V) or a salt thereof:



(V)

with methyl 2-(3-formylphenyl)acetate in the presence of a suitable reducing agent.

Examples of reducing agents, include a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride, or, suitably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran or diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. A particular reducing agent is

sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 0 to 100°C, such as 0 to 40°C or, conveniently, at or near ambient temperature. The reaction may optionally be carried out in the presence of an acid, such as an organic acid, for example acetic acid.

Suitably the compound of formula (V) is used in the form of a salt, for example as the hydrochloride salt.

The compound of formula (V) may be prepared using known methods, such as the method described in the Examples herein.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of Compound (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The removal of any protecting groups and the formation of a pharmaceutically acceptable salt of Compound (I) are within the skill of an ordinary organic chemist using standard techniques. For example salts Compound (I) may be prepared by reacting Compound (I) with a suitable acid. Alternatively, using well-known counter ion exchange methods may be used to convert one salt to another.

Certain intermediates used in the preparation of Compound (I) are novel including compounds of the formulae (II) and (III). Such intermediates form a further aspect of the present invention.

According to another aspect of the invention there is provided a compound of the formula (II), or a salt thereof as hereinbefore defined. For example methyl (3-{[{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}(chloroacetyl)amino]methyl}phenyl)acetate, or a salt thereof.

According to another aspect of the invention there is provided a compound of the formula (III), or a salt thereof as hereinbefore defined. For example, methyl {3-[({4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}amino)methyl]phenyl}acetate.

The intermediates described herein may be used in the form of a salt. The salt may be a pharmaceutically acceptable salt, such as one of the salts mentioned hereinbefore in relation to Compound (I). Alternatively, if required, the intermediates may be used in the form of a salt which is not a pharmaceutically acceptable salt. Such salts may be advantageously used in the synthesis of compounds according to the invention, for example as a result of advantageous physical and/or chemical properties, such as crystallinity.

Compound (I) and pharmaceutically acceptable salts thereof have antedrug properties. An antedrug is defined as an active synthetic derivative that is designed to undergo biotransformations to a readily excretable less active form upon entry into the systemic circulation, therefore minimizing systemic side-effects. Thus, on administration, a compound of the invention is rapidly degraded enzymatically to yield a degradation product having a substantially reduced medical effect. A medical effect as defined herein means a pharmacological activity of the compound of the invention, including specifically interferon inducing activity and/or suppression of IL-4/IL-5 production activity.

The medical effect of the degradation product is preferably 10 times, more preferably 100 times less than that of the compound of the invention (i.e. parent compound).

The pharmacological activity can be measured using methods known in the art, preferably using in vitro evaluation methods such as commercially available ELISA kits or the biological assay described herein.

Diseases and Medical Conditions

Compound (I), or a pharmaceutically acceptable salt thereof, according to the invention is useful as a modulator of TLR7 activity and is expected to provide an immuno-modulator effect and thus be useful as a therapeutic and prophylactic agent for diseases associated with an abnormal immune response (e.g. autoimmune diseases and allergic diseases) and various infections and cancers which are required for activation of an immune response. Compound (I), or a pharmaceutically acceptable salt thereof may also be useful as a vaccine adjuvant. For example, Compound (I), or a pharmaceutically acceptable salt thereof, may be administered to a mammal, including man, for the treatment of the following conditions or diseases:

1. **respiratory tract:** obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. **skin:** psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, actinic keratosis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; hemangioma; pre-cancerous skin lesions; basal cell carcinoma, for example superficial basal cell carcinoma, nodular basal cell carcinoma and bowen's disease; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions; skin scarring, including keloids; cutaneous infections, including viral cutaneous infections; and cosmetic effects including photo-damaged skin;

3. **eyes:** blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative

or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

4. **genitourinary**: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. **allograft rejection:** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. **other auto-immune and allergic disorders** including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. **oncology**: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumours and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. **infectious diseases**: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

Thus, the present invention provides Compound (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

In a further aspect, the present invention provides the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In particular, Compound (I), or a pharmaceutically acceptable salt thereof according to the invention may be used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or a skin condition as listed hereinbefore (for example, atopic dermatitis, actinic keratosis, pre-cancerous skin lesions or cutaneous vial infections). Compound (I), or a pharmaceutically acceptable salt thereof, may also be useful as a vaccine adjuvant.

Accordingly, as a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma, COPD or allergic rhinitis.

As a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma.

As a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of COPD.

As a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of allergic rhinitis.

As a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use as a vaccine adjuvant.

As a further aspect of the invention there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a skin condition as hereinbefore described (for example atopic dermatitis, actinic keratosis, pre-cancerous lesions or cutaneous vial infections).

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of asthma, COPD or allergic rhinitis.

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of asthma.

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of COPD.

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of allergic rhinitis.

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a skin condition as hereinbefore described (for example atopic dermatitis, actinic keratosis, pre-cancerous lesions or cutaneous vial infections).

As a further aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, as a vaccine adjuvant, in the manufacture of a vaccine for the treatment of a disease or condition.

The invention therefore provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating an airways disease, e.g. a reversible obstructive airways disease such as asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable salt thereof.

The invention still further provides a method of treating, or reducing the risk of, a disease or condition comprising or arising from abnormal cell growth (e.g. a cancer), which method comprises administering to a patient in need thereof a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable salt thereof.

The invention still further provides a method of treating, or reducing the risk of, a skin disease or condition as hereinbefore described (for example atopic dermatitis, actinic keratosis, pre-cancerous lesions or cutaneous vial infections), which method comprises administering to a patient in need thereof a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable salt thereof.

The invention still further provides a method of treating, or reducing the risk of, a disease or condition, which method comprises administering to a patient in need thereof a therapeutically effective amount of a vaccine and a salt of Compound (I) defined herein or a solvate of the salt.

The invention still further provides a method of increasing the response to a vaccine in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a vaccine and Compound (I), or a pharmaceutically acceptable salt thereof.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of Compound (I), or a pharmaceutically acceptable salt thereof, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). For example a dose of about 0.1, to 100 μg/kg such as a dose of about 0.1, 0.5, 1, 1.5, 2, 5, 10, 20, 50 or 100 μg/kg. Alternatively, if Compound (I), or a pharmaceutically acceptable salt thereof, is administered orally, then the daily dosage may be in the range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg). For example an oral dose of about 0.1 to 100 μg/kg such as a dose of about 1, 2, 5, 10, 20, 50 or 100 μg/kg.

The dosages mentioned herein refer to the dose of Compound (I) as the free base. Accordingly, the equivalent dose of a particular salt will be higher because of the increased molecular weight of the salt compared to the free base.

The compounds according to the invention may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the Compound (I), or a pharmaceutically acceptable salt thereof, is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for

example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of Compound (I), all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing Compound (I), or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways (by oral or nasal inhalation) administration) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned

excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

Pharmaceutical Compositions for Administration by Inhalation

In one embodiment of the invention, the pharmaceutical composition is administered by inhalation (oral or nasal).

The Compound (I), or a pharmaceutically acceptable salt thereof, may be administered using a suitable delivery device, for example from a dry powder inhaler, a metered dose inhaler, a nebuliser or a nasal delivery device. Such devices are well known.

In a further embodiment, the pharmaceutical composition is administered by means of a dry powder inhaler (DPI).

The DPI may be "passive" or breath-actuated, or "active" where the powder is dispersed by some mechanism other than the patient's inhalation, for instance, an internal supply of compressed air. At present, three types of passive dry powder inhalers are available: single-dose, multiple unit dose or multidose (reservoir) inhalers. In single-dose devices, individual doses are provided, usually in gelatine capsules, and have to be loaded into the inhaler before use, examples of which include Spinhaler® (Aventis), Rotahaler® (GlaxoSmithKline), Aeroliser™ (Novartis), Inhalator® (Boehringer) and Eclipse (Aventis) devices. Multiple unit dose inhalers contain a number of individually packaged doses, either as multiple gelatine capsules or in blisters, examples of which include Diskhaler® (GlaxoSmithKline), Diskus® (GlaxoSmithKline) and Aerohaler® (Boehringer) devices. In multidose devices, drug is stored in a bulk powder reservoir from which individual doses are metered, examples of which include Turbuhaler® (AstraZeneca),

Easyhaler® (Orion), Novolizer® (ASTA Medica), Clickhaler® (Innovata Biomed) and Pulvinal® (Chiesi) devices.

An inhalable pharmaceutical composition or dry powder formulation for use in a DPI can be prepared by mixing finely divided active ingredient (having a mass median diameter generally equal to or less than 10 μm, preferably equal to or less than 5 μm) with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars or sugar alcohols, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. The carrier particles may have a mass median diameter of from 20 to 1000 μm, more usually from 50 to 500 μm. The powder mixture may then, as required, be dispensed into hard gelatine capsules, each containing the desired dose of the active ingredient.

Alternatively, an inhalable pharmaceutical composition may be prepared by processing a finely divided powder (e.g. consisting of finely divided active ingredient and finely divided carrier particles) into spheres that break up during the inhalation procedure. This spheronized powder is filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient.

Accordingly, the present invention also provides a dry powder inhaler, in particular a multiple unit dose dry powder inhaler, containing an inhalable pharmaceutical composition of the invention.

In a further embodiment, Compound (I), or a pharmaceutically acceptable salt thereof, is administered by means of a metered dose inhaler (MDI), particularly a pressurised metered dose inhaler (pMDI). The pMDI contains the active as a suitable solution or suspension in a pressurised container. The active is delivered by actuating a valve on the pMDI device. Actuation may be manual or breath actuated. In manually actuated pMDIs the device is actuated by the user as they inhale, for example by pressing a suitable release mechanism on the pMDI device. Breath actuated pMDIs are actuated when the patient inhales through the mouthpiece of the pMDI. This can be advantageous as the actuation of the device is timed with the patients' inhalation and can result in a more consistent dosing of the active. An example of a pMDI device includes Rapihaler® (AstraZeneca).

An inhalable pharmaceutical composition for use in a pMDIcan be prepared by dissolving or dispersing Compound (I), or a pharmaceutically acceptable salt thereof, in a suitable propellant and with or without additional excipients such as solvents (for example ethanol), surfactants, lubricants, preservatives or stabilising agents. Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Suitable propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactant and/or other excipients. When Compound (I), or a pharmaceutically acceptable salt thereof, is used as a suspension, the compound is suitably present in finely divided form (having a mass median diameter generally equal to or less than 10 μm, preferably equal to or less than 5 μm).

In a further embodiment, Compound (I), or a pharmaceutically acceptable salt thereof, is administered by means of a metered dose inhaler in combination with a spacer. Suitable spacers are well known and include Nebuchamber® (AstraZeneca) or Volumatic® (GSK).

In a further embodiment, Compound (I), or a pharmaceutically acceptable salt thereof, is administered by means of a nebuliser. Suitable nebulisers are well known.

An inhalable pharmaceutical composition for use in a nebuliser can be prepared by dispersing or preferably dissolving the Compound (I), or a pharmaceutically acceptable salt thereof, in a suitable aqueous medium. The composition may also include for example suitable pH and/or tonicity adjustment, surfactants and preservatives. In a further embodiment, Compound (I), or a pharmaceutically acceptable salt thereof, is administered nasally as a spray from a suitable nasal delivery device, for example a spray pump or an MDI adapted for nasal delivery. Alternatively, the salt could be administered nasally as a powder using a suitable DPI device e.g. Rhinocort® Turbuhaler® (AstraZeneca).

A nasally inhalable pharmaceutical composition for use in a spray pump or MDI nasal delivery device can be prepared by dispersing or dissolving the Compound (I), or a pharmaceutically acceptable salt thereof, in a suitable aqueous medium similar to those described above for inhalation via an MDI device. Suitable dry powder compositions for nasal delivery are as hereinbefore described in relation to DPI delivery. However, where it is desirable to limit the penetration of the compound into the lung and keep the compound in the nasal cavity, it may be necessary to use the compound as larger particle sizes, for

example with an average particle diameter greater than about 10 μm, for example from 10 μm to 50 μm.

Accordingly, the present invention also provides an inhaler device suitable for nasal administration (for example a dry powder inhaler, in particular a multiple unit dose dry powder inhaler, or a pMDI inhaler) containing an inhalable pharmaceutical composition of the invention.

Pharmaceutical Compositions for External Topical Administration

When Compound (I), or a pharmaceutically acceptable salt thereof, is administered as an external topical pharmaceutical composition, suitable compositions include, for example, ointments, lotions, creams, gels, tapes, transdermal patches, cataplasms, or powders for external administration.

Ointments, creams and gels suitably contain Compound (I) in an amount of about 0.01-10 w/w %, and further comprise for example, one or more additional excipients including thickening agents, an aqueous or oily base, a gelling agent or a solvent. Suitable aqueous/oily bases include water and/or oil such as liquid paraffin, a vegetable oil such as arachis oil or castor oil. Examples of suitable solvents include polyethylene glycol. Examples of suitable thickening and gelling agents include soft paraffin, aluminium stearate, cetostearic alcohol, polyethylene glycol, sheep fat, beeswax, carboxypolymethylene and cellulose derivatives, glyceryl monostearate and/or nonionic emulsifiers.

Lotions suitably contain Compound (I) in an amount of about 0.01-10 w/w % and further comprise for example, one or more additional excipients including an aqueous or oily base, emulsifiers, stabilizers, dispersing agents, precipitation inhibitors or thickening agents.

Powders for external use suitably contain the Compound (I) in an amount of 0.01-10 w/w %, and it may be formulated using a suitable powdery base such as talc, lactose and starch.

The pharmaceutical compositions for external topical Administration may be particularly suitable for the treatment of skin conditions mentioned herein (for example, atopic dermatitis, actinic keratosis, pre-cancerous lesions or cutaneous vial infections).

Compound (I), or a pharmaceutically acceptable salt thereof, may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein Compound (I), or a pharmaceutically acceptable salt thereof, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed above. For example Compound (I), or a pharmaceutically acceptable salt thereof, may be combined with one or more of the agents listed below:

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 23, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig (abatacept), HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family.

The present invention further relates to the combination of a compound of the invention, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including

theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, telenzepine, tolterodine or aclidinium bromide.

The present invention still further relates to the combination of a compound of the invention, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof, indacaterol, milveterol, carmoterol, olodaterol, (previously known as BI 1744 CL), for example as the hydrochloride salt, vilanterol (previously known as GW642444), for example as the trifenatate (triphenylacetete) salt.

The present invention further relates to the combination of a compound of the invention, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, fluticasone furoate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptiline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example gefitinib or imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cylin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-

CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:
(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-reductase such as finasteride;
(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);
(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab

[C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or

(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a further aspect the present invention provides a combination product (for example for use as a medicament for the treatment of one of the conditions listed herein such as COPD, asthma or allergic rhinitis) comprising Compound (I), or a pharmaceutically

acceptable salt thereof as hereinbefore defined, and one or more agents independently selected from:

a) a PDE4 inhibitor including an inhibitor of the isoform PDE4D;

b) a β-adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, indacaterol or carmoterol;

c) a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, telenzepine or tolterodine;

d) a modulator of chemokine receptor function (such as a CCR1 or CCR8 receptor antagonist);

e) an inhibitor of kinase function;

f) a non-steroidal glucocorticoid receptor agonist;

g) a steroidal glucocorticoid receptor agonist;

h) a protease inhibitor (such as a MMP12 or MMP9 inhibitor); and

i) an antiproliferative agent.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is Compound (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, and a preparation of one or more second active ingredient(s0 selected from:

a) a PDE4 inhibitor including an inhibitor of the isoform PDE4D;

b) a β-adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, indacaterol or carmoterol;

c) a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine, telenzepine or tolterodine;

d) a modulator of chemokine receptor function (such as a CCR1 or CCR8 receptor antagonist);

e) an inhibitor of kinase function;

f) a non-steroidal glucocorticoid receptor agonist;

g) a steroidal glucocorticoid receptor agonist;

h) a protease inhibitor (such as a MMP12 or MMP9 inhibitor); and

i) an antiproliferative agent;

and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

Brief Description of the Drawings

Figure 1 is an X-ray powder diffraction pattern of Compound (I) Form A measured at a wavelength of 1.5418Å. The x-axis shows the 2-theta value and the y-axis the intensity.

Figure 2 is a differential scanning calorimetry (DSC) trace for Compound (I) Form A. The x-axis shows temperature (°C) and the y-axis heat flow (watts/g).

Examples

The present invention will now be further illustrated by reference to the following examples in which, unless stated otherwise:

(i) Temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C.

(ii) In general, the course of reactions was followed by HPLC and reaction times are given for illustration only.

(iii) Yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required.

(iv) Chemical symbols have their usual meanings; SI units and symbols are used.

(v) Solvent ratios are given in volume: volume (v/v) terms.

(vi) Unless stated otherwise, starting materials were commercially available.

(vii) Unless stated otherwise, example names have been generated using the IUPAC naming function of ACD Labs Version 10 (Advanced Chemistry Development, Inc.).

General Methods

^{1}H NMR spectra were recorded at 298K on a Bruker Avance-III 500 spectrometer, operating at 500 MHz.

"RPHPLC" means reversed phase preparative HPLC using Waters Symmetry C8, Xterra, XBridge or Phenomenex Gemini columns using acetonitrile and either aqueous

ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel. The term "passed through an SCX" means the mixture was absorbed on SCX and eluted with an appropriate solvent such as methanol or acetonitrile then the free base product eluted with aqueous ammonia/methanol.

Mass spectra were run on an Agilent 100 HPLCMS equipped with a multimode source.

X-Ray Powder Diffraction (XRPD) patterns were measured using a PANalytical X'Pert machine in 2Ø - Ø configuration or a PANalytical Cubix machine in Ø – Ø configuration over the scan range 2° to 40° 2Ø with 100-second exposure per 0.02° increment. The X-rays were generated by a copper long-fine focus tube operated at 45kV and 40mA. The wavelength of the copper X-rays was 1.5418 Å. The Data was collected on zero background holders on which ~ 2mg of the compound was placed. The holder was made from a single crystal of silicon, which had been cut along a non-diffracting plane and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction.

Differential Scanning Calorimetry (DSC) thermograms were measured using a TA Q2000 Differential Scanning Calorimeter, with aluminium pans. The sample weights varied between 0.5 to 5mg. The procedure was carried out under a flow of nitrogen gas (50ml/min) and the temperature studied from 0 to 300°C at a constant rate of temperature increase of 10°C per minute.

Thermogravimetric Vapour Sorption (TGA) thermograms were measured using a TA Q500 Thermogravimetric Analyser, with platinum pans. The sample weights varied between 1 and 5mg. The procedure was carried out under a flow of nitrogen gas (60ml/min) and the temperature studied from Room Temperature to 300°C at a constant rate of temperature increase of 10°C per minute.

Gravimetric Vapour Sorption (GVS) profiles were measured using a TA Instruments Q5000SA instrument. The solid sample approximately 1-5mg was placed into a metal vessel and the weight of the sample was recorded during a dual cycle step method (40 to 90 to 0 to 90 to 0% relative humidity (RH), in steps of 10% RH).

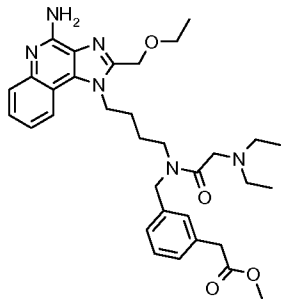
Abbreviations

The following abbreviations have been used.

aq.	aqueous
DCM:	dichloromethane
DMF:	*N,N*-dimethylformamide
EtOAc:	ethyl acetate
hrs:	hours
MeCN:	acetonitrile
MeOH:	methanol
MS:	mass spectrometry
mins:	minutes
rt:	room temperature

Example 1

Methyl (3-{[{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}(*N*,*N*-diethylglycyl)amino]methyl}phenyl)acetate



A suspension of methyl {3-[({4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}amino)methyl]phenyl}acetate (507 mg) in MeCN (8mL) was treated dropwise with chloroacetyl chloride (94µL) and the mixture stirred at rt for 1 hour. DMF (3mL) was added and the solvent evaporated under reduced pressure to remove the MeCN. The mixture was cooled in an ice bath and diethylamine (390mg) was added then stirred for 18 hours at rt. The solution was then partitioned between EtOAc and brine, the organics were combined, dried and solvent removed. The crude product was purified by RPHPLC and the pure fractions were partially evaporated down to remove the MeCN and the remaining water mixture cooled and neutralised by addition of solid sodium bicarbonate and sodium chloride, the mixture then extracted with DCM . The combined organics were dried, filtered and the solvent removed under reduced pressure to yield the

title compound as a solid (350mg); MS multimode (+) 589; ^{1}H NMR (500 MHz, DMSO, 91°C) δ 7.98 (d, 1H), 7.63 (d, 1H), 7.43 (t, 1H), 7.25 (d, 2H), 7.15 - 7.06 (m, 3H), 6.19 (s, 2H), 4.73 (s, 2H), 4.63 - 4.47 (m, 4H), 3.62 - 3.54 (m, 7H), 3.34 (s, 2H), 3.21 (s, 2H), 2.50 - 2.45 (m, 4H), 1.83 (s, 2H), 1.67 (s, 2H), 1.15 (t 3H), 0.87 (t, 6H).

The methyl {3-[({4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}amino)methyl]phenyl}acetate used as the starting material was prepared as follows.

(i) *tert*-butyl {4-[(3-nitroquinolin-4-yl)amino]butyl}carbamate

To a suspension of 3-nitroquinolin-4-ol (60g) in DCM (600mL) and DMF (18mL), thionyl chloride (29.9mL) was added drop wise over 10 mins and then heated at 40 °C for 2 hours. The mixture was evaporated to dryness and the solid residue was added to a stirred solution of *tert*-butyl 4-aminobutylcarbamate (65.3g) and triethylamine (176mL) in DCM (1000mL) at 0°C. The mixture was stirred at rt for 2 hours, then evaporated to dryness and the residue triturated with water . Drying in an oven gave the subtitle compound as a solid (110g); MS multimode (+) 361;

(ii) *tert*-butyl {4-[(3-aminoquinolin-4-yl)amino]butyl}carbamate

Nickel(II) chloride hexahydrate (18.4g) was dissolved in MeOH (360mL) and cooled to 5°C. Sodium borohydride (2.9g) was added followed by the product from step (i) (28g,). More sodium borohydride (11.7g) was added slowly keeping the temperature below 23°C then stirred for 1h. The reaction mixture was filtered through celite and the filtrate was poured into sodium bicarbonate solution (300mL). The solvent was reduced by half and then extracted with chloroform, combined organics were dried, and solvent removed to give the subtitle compound as a solid (22g); MS multimode (+) 331

(iii) 2-ethoxyacetyl chloride

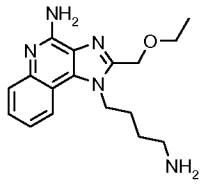
To a solution of 2-ethoxyacetic acid (25g) in DCM (300mL) dicyclohexylamine (47.4mL) was added dropwise, and stirred for one hour. Thionyl chloride (19.2mL) was then added dropwise and the mixture stirred for 3 hours. The reaction was diluted with ether (600mL) and filtered, the filtrate was evaporated to dryness to give the subtitle compound as a pale brown oil (30g).

(iv) *tert*-butyl {4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate

The product from step (iii) (10.38g) was added dropwise to a solution of the product from step (ii) (28g) at 0 °C in DCM (400mL) and triethylamine (11.81mL) over 1

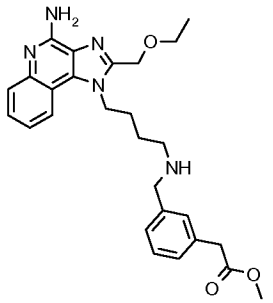
hour then heated under reflux overnight. The reaction was cooled to rt and the solution washed with saturated sodium hydrogen carbonate, dried and solvent removed. The crude product was purified on silica to give the subtitle compound as a solid (26g); MS multimode (+) 399.

(v) 1-(4-aminobutyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



A solution of the product from step (iv) (3g) in MeOH (100mL) was treated with HCl in dioxane (14.51mL, 4M) and the reaction mixture allowed to stand at 20°C for 3 hours. The solvent was evaporated under reduced pressure and the residue was azeotroped with MeCN to give the solid hydrochloride salt. This was dissolved in MeOH (100mL) and passed through a SCX cartridge eluting with 10% NH_3/ MeOH. The solvent was evaporated under reduced pressure and the residue azeotroped with MeCN to give the subtitle compound as a solid (2.3g); MS multimode (+) 314.

(vi) methyl {3-[({4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}amino)methyl]phenyl}acetate



A solution of the product from step (v) (1.1g) in MeOH (30mL) was treated with acetic acid (0.37mL) followed by methyl 2-(3-formylphenyl)acetate (0.61g) and was stirred at rt for 20 mins and then cooled in an ice bath. Sodium cyanoborohydride (0.41g) was added and the reaction mixture was stirred at rt for 3 hours. The solvent was evaporated under reduced pressure and the residue partitioned between EtOAc and sodium

bicarbonate solution. The organic layer was evaporated under reduced pressure and the crude product was purified by silica chromatography to give the subtitle compound as a solid (1.16g); MS multimode (+) 476; ^{1}H NMR (500 MHz, DMSO) δ 9.41 (s, 2H), 8.95 (s, 2H), 8.74 (dd, 1H), 8.17 (dd, 1H), 7.75 (dd, 1H), 7.46 - 7.28 (m, 4H), 4.94 - 4.74 (m, 4H), 4.14 (s, 2H), 3.68 (s, 2H), 3.65 - 3.35 (m, 5H), 3.00 (s, 2H), 2.04 - 1.87 (m, 2H), 1.81 - 1.67 (m, 2H), 1.18 (t, 3H).

The compound prepared in Example 1 was crystalline (Compound (I) Form A) and provided the XRPD pattern shown in Figure 1 when measured at a wavelength of 1.5418 Å. The most prominent peaks of the XRPD pattern for Compound (I) Form A are shown in Table 1 in the description.

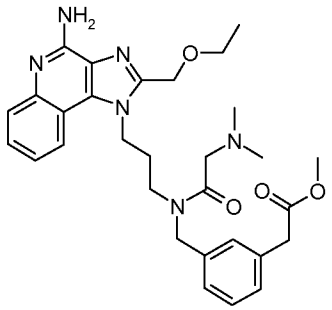
When heated in a Differential Scanning Calorimeter (DSC) (conditions as described in the Examples section) Compound (I) Form A exhibits a melting endotherm with an onset temperature at about 108°C, as illustrated in Figure 2.

Thermogravimetric Vapour Sorption (TGA) thermograms on Compound (I) Form A showed no mass loss prior to the melting of the compound.

Gravimetric Vapour Sorption (GVS) profiles on Compound (I) Form A showed a mass increase at 80% relative humidity of 0.5% in cycle 1 and 0.64% in cycle 2.

Comparative Example 1

Methyl 2-(3-((N-(3-(4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl)propyl)-2-(dimethylamino)acetamido)methyl)phenyl)acetate



The compound may be prepared using the method described in Example 7 of WO2008/135791.

Biological Activity

Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (pEC50).

Compound (I) (Example 1) gave a mean pEC50 of 7.4 (n=7).

Comparative Example 1 gave a mean pEC50 of 6.4 (n=4).

Cynomolgous monkey plasma stability

To determine the half life of the test compound in cynomolgous monkey plasma, incubations were performed at 37°C in a shaking water bath. The test compound (5µL of 100µM stock in MeCN) was spiked into 0.495mL plasma to give final incubation concentration of 1µM. Aliquots (50µL) were withdrawn at various time points (typically 0, 20 & 40 sec, 1, 2, 3, 5 & 10 mins) and quenched into MeCN (300µL) followed by analysis for parent compound by LC-MS-MS (MRM mode). The half life was calculated from the decline of test compound peak area over time

Compound (I) (Example 1) gave a mean half life of 1.2 minutes (n=6)

Comparative Example 1 gave a half life of 11 minutes (n=1)

Human plasma stability

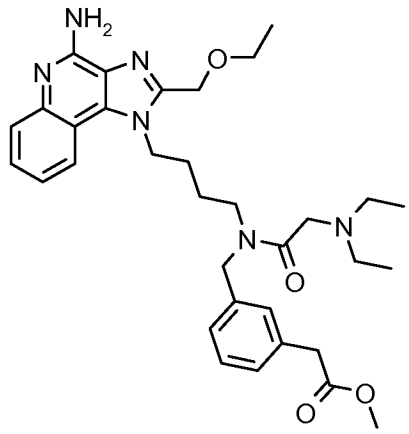
To determine the half life of the test compound in human plasma, incubations were performed at 37°C in a shaking water bath. Compound (5 µL of 100 µM stock in MeCN) was spiked into 0.495mL plasma to give final incubation concentration of 1 µM. Aliquots (50µL) were withdrawn at various time points (typically 0, 20 & 40 sec, 1, 2, 3, 5 & 10 mins) and quenched into MeCN (300µL) followed by analysis for parent compound by LC-MS-MS (MRM mode). The half life was calculated from the decline of test compound peak area over time.

Example 1 (Compound (I)) gave a mean half life of 0.3 minutes (n=8)

Comparative Example 1 gave a half life of 0.7 minutes (n=1)

CLAIMS

1. The compound, which is of the formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

2. The compound, which is of the formula (I) as defined in Claim 1.

3. The compound, which is a pharmaceutically acceptable salt of the compound of formula (I) as defined in claim 1.

4. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 3 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

5. A compound according to any one of Claims 1 to 3 for use in therapy.

6. A compound according to any one of Claims 1 to 3 for use in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, actinic keratosis or pre-cancerous skin lesions.

7. A compound according to any one of Claims 1 to 3 for use in the treatment of COPD.

8. A compound according to any one of Claims 1 to 3 for use in the treatment of asthma.

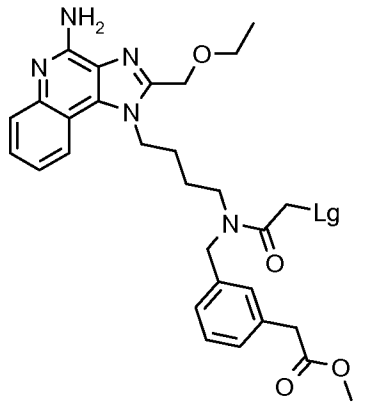
9. A compound according to any one of Claims 1 to 3 for use as a vaccine adjuvant.

10. A method of treating asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections, actinic keratosis or pre-cancerous skin lesions, which comprises administering to the patient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 3.

11. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof as defined in claim 1 comprising

Process (a):

the reaction of a compound of the formula (II), or a salt thereof:



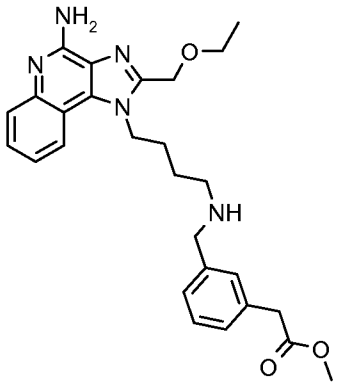
(II)

wherein Lg is a leaving group;

with diethylamine; or

Process (b):

the coupling reaction of a compound of the formula (III), or a salt thereof:

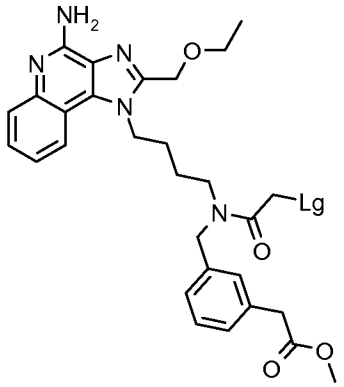


(III)

with 2-(diethylamino)acetic acid or a salt thereof;

and thereafter optionally forming a pharmaceutically acceptable salt of a compound of formula (I).

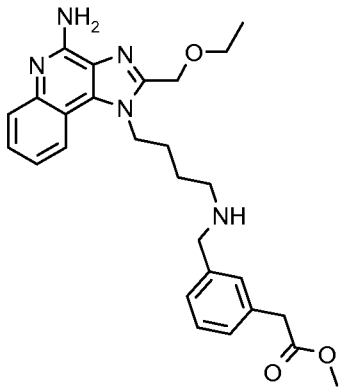
12. A compound of the formula (II), or a salt thereof:



(II)

wherein Lg is a leaving group.

13. A compound of the formula (III), or a salt thereof:



(III)

14. A combination product comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in claim 1 and another therapeutic agent.

Figure 1

X-ray powder pattern of Compound (I) Form A

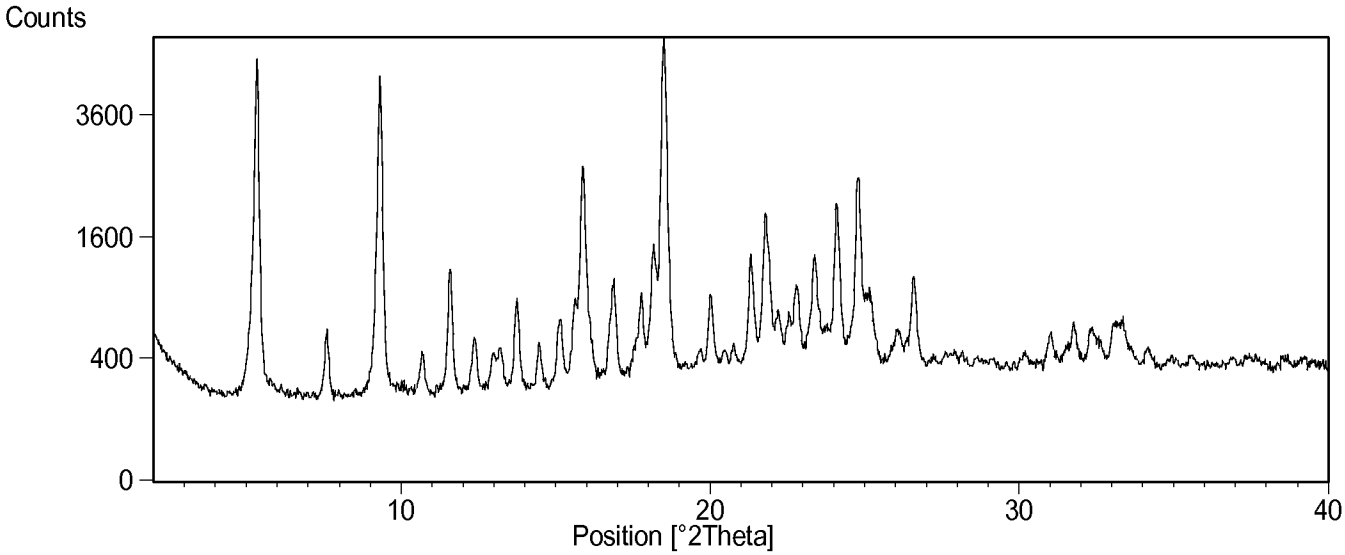
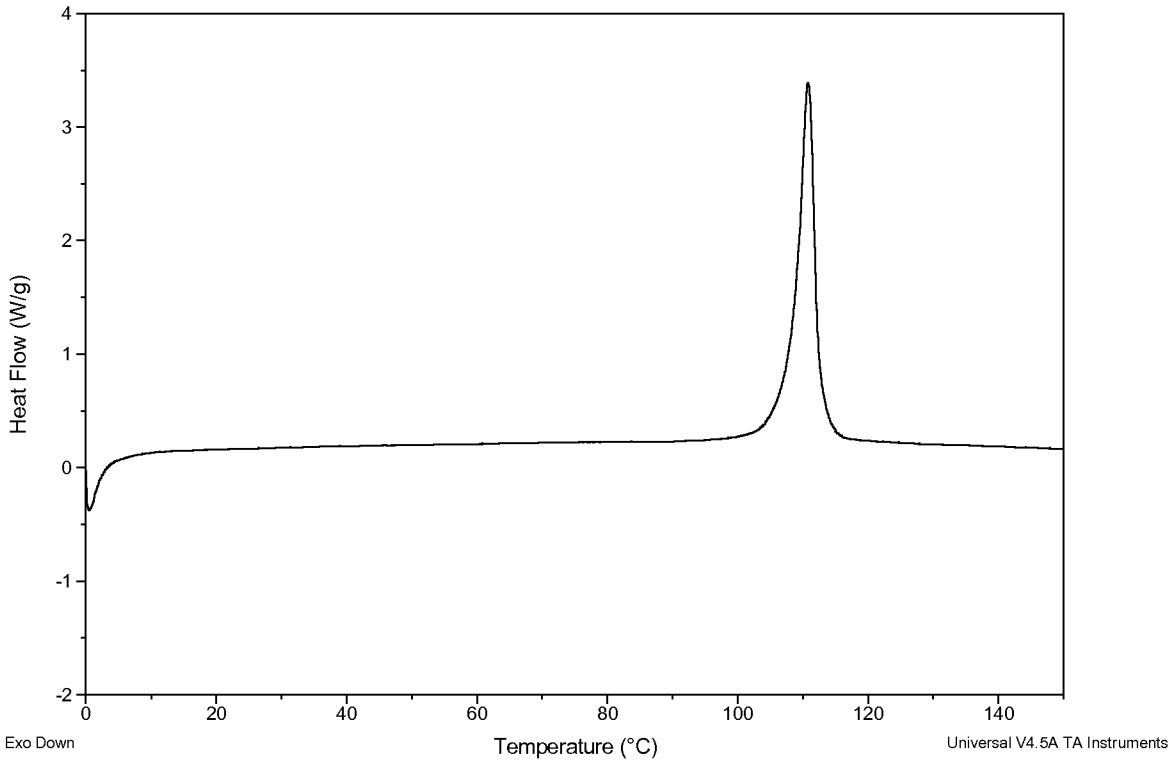


Figure 2

Differential scanning calorimetry (DSC) trace for Compound (I) Form A



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/052474

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4188 A61K31/4745 A61P11/06 A61P11/16
A61P17/06 A61P37/08 A61P17/04 A61P17/12 A61P35/00
A61P31/12 A61P31/18 A61P31/04 A61P1/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/135791 A1 (ASTRAZENECA AB [SE]; DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA UK) 13 November 2008 (2008-11-13) the whole document -----	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2012	21/02/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/052474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008135791 A1	13-11-2008	AR 066492 A1	26-08-2009
		AU 2008247165 A1	13-11-2008
		CA 2686163 A1	13-11-2008
		CN 101687867 A	31-03-2010
		CO 6251247 A2	21-02-2011
		EC SP099750 A	26-02-2010
		EP 2155743 A1	24-02-2010
		JP 2010526129 A	29-07-2010
		KR 20100016289 A	12-02-2010
		PE 02762009 A1	21-04-2009
		RU 2009140465 A	20-06-2011
		TW 200902529 A	16-01-2009
		US 2010280001 A1	04-11-2010
		UY 31069 A1	05-01-2009
		WO 2008135791 A1	13-11-2008