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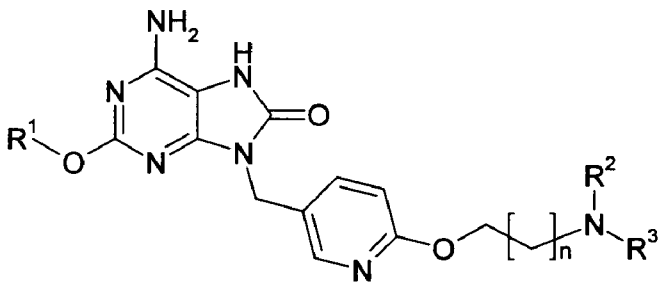
(54) **Title**: PROCESS FOR PREPARING ADENINE COMPOUNDS AND INTERMEDIATES THEREOF



(III)

(57) **Abstract**: The present invention relates to a process for preparing a compound of Formula (III), or a salt thereof; wherein R^1 is C_{1-6} alkyl; R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring; and n is 1, 2 or 3.

DESCRIPTION

PROCESS FOR PREPARING ADENINE COMPOUNDS AND INTERMEDIATES THEREOF

TECHNICAL FIELD

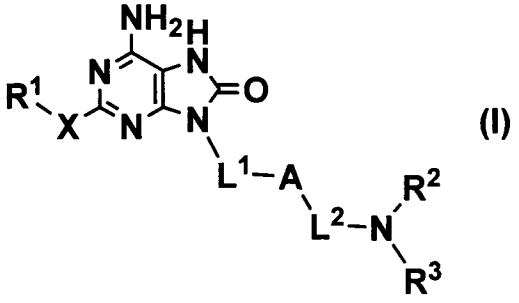
[0001] The present invention relates to a process for preparing certain adenine compounds. Furthermore, the invention relates to intermediates useful in the preparation of said adenine compounds.

BACKGROUND ART

[0002] Various adenine compounds have been reported. For example, a patent document EP2133353 discloses a compound of Formula (I):

[0003]

[Chemical formula 1]



(I)

wherein A represents a substituted or an unsubstituted aromatic hydrocarbon ring, etc., L^1 represents a single bond, etc., L^2 represents a single bond, etc., R^1 represents a substituted or an unsubstituted alkyl group, etc., R^2 and R^3 are independently a hydrogen atom, a substituted or an unsubstituted alkyl group, etc., X represents an oxygen atom, etc. Said compound is reported to be useful as TLR activating agents and may be suitable for use in a pharmaceutical context.

[0004] EP2133353 discloses a general method for preparing adenine compounds of Formula (I). However, a process route disclosed in EP2133353 includes a preparation of an intermediate compound that itself has a potent biological activity which may be responsible for inducing undesirable effects experienced by workers involved with its preparation. Such undesirable effects may include fever and/or headache.

[0005] [Patent document 1] EP2133353

DISCLOSURE OF INVENTION

PROBLEMS TO BE SOLVED BY INVENTION

[0006] There remains a need to provide a better way of making some of the compounds disclosed in EP2133353 for use on a larger scale in a pharmaceutical context by achieving one or more advantages relating to a reduced toxicity for workers (and/or an improved safety in other respects), an improved purity and an improved efficiency in processing, work-up and/or isolations; lower environmental impacts; and improved reproducibility of processing. The advantages of the present invention are important in the context of a large-scale manufacture.

MEANS OF SOLVING PROBLEMS

[0007] The present inventors have undertaken extensive work to tackle the safety concerns as mentioned above and one aspect of the present invention provides a solution to this problem. Surprisingly, the problem has been solved by using certain 8-alkoxy adenine compounds as an intermediate for the synthesis of a compound of Formula (I). The 8-alkoxy adenine compounds used in the present invention do not seem to possess the potent and unwanted biological activity of the prior art intermediates, since safety issues relating to toxicity for chemistry workers are significantly reduced. The 8-alkoxy adenine compounds are represented by Formula (II) as defined below, which are useful as pharmaceutical intermediates in the improved process of the present invention.

BRIEF DESCRIPTION OF DRAWINGS

[0008] FIG. 1 shows a differential scanning calorimetry (DSC) trace for Compound (XII) described in Example 8. The x-axis shows temperature (°C) and the y-axis heat flow (watts/g).

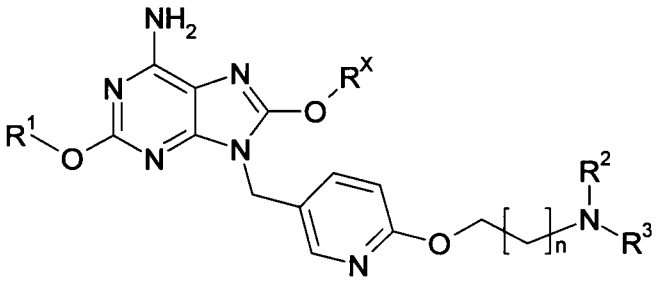
[0009] FIG. 2 shows an X-ray powder diffraction pattern of Compound (XII) shown in Example 9.

BEST MODE FOR CARRYING OUT THE INVENTION

[0010] Therefore, in the first aspect of the invention, a compound of Formula (II):

[0011]

[Chemical formula 2]



(II)

wherein:

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or

R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring;

R^X is C_{1-6} alkyl; and

n is 1, 2 or 3; or a salt thereof is provided.

[0012] It is understood that a salt of a compound defined herein may be an acid addition salt. An acid may be an inorganic acid or an organic acid. Therefore, an acid addition salt may be formed using an inorganic or organic acid. For example, an acid addition salt may be formed using an inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. For example, an acid addition salt may be also formed using an organic acid selected from trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid and *p*-toluenesulfonic acid.

[0013] Herein, the term "alkyl" includes both straight and branched chain alkyl groups.

References to individual alkyl groups such as "propyl" are specific for the straight chain version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only.

Therefore, "C_{1-4} alkyl" means a straight or branched chain saturated hydrocarbon group having 1 to 4 carbon atoms. Examples of "C_{1-4} alkyl" are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

The term "C_{1-6} alkyl" means a straight or branched chain saturated hydrocarbon group having 1 to 6 carbon atoms.

[0014] In one embodiment, R^2 and R^3 are each methyl.

In one embodiment, R^1 is ethyl.

In one embodiment, n is 1.

In one embodiment, in the compounds of the present application that have R^X group, R^X group is C_{1-4} alkyl. In a further embodiment, R^X group may be selected from methyl, ethyl, propyl and butyl.

In one embodiment, R^X is methyl or ethyl.

In one embodiment, R^X is methyl.

[0015] Therefore, in one embodiment, a compound of Formula (II), as depicted above, wherein:

R^1 is ethyl;

R^2 and R^3 are each methyl;

R^X is C_{1-6} alkyl; and

n is 1; or a salt thereof is provided.

[0016] In one embodiment, a compound of Formula (II), wherein the compound is: 9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-2-ethoxy-8-methoxy-9*H*-purin-6-amine; or a salt thereof is provided.

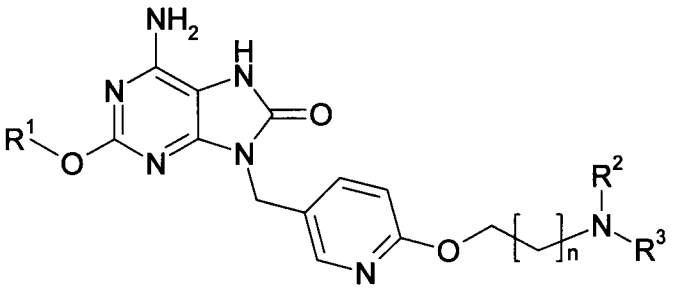
In one embodiment, a salt of a compound of Formula (II), wherein the salt is a hydrochloride salt of 9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-2-ethoxy-8-methoxy-9*H*-purin-6-amine is provided.

[0017] In one embodiment, a compound of Formula (II), wherein the compound is: 9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-2-ethoxy-8-methoxy-9*H*-purin-6-amine is provided.

[0018] In one aspect of the invention, a process for preparing a compound of Formula (III):

[0019]

[Chemical formula 3]



(III)

wherein:

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or

R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring; and

n is 1, 2 or 3; or a salt thereof;

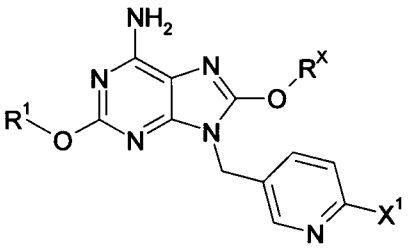
which comprises reacting a compound of Formula (II), as defined herein, or a salt thereof; with an acid to provide a compound of Formula (III), as defined herein; and optionally thereafter, forming a salt thereof, is provided.

[0020] In one embodiment, the above-mentioned process for preparing a compound of Formula (III) or a salt thereof is a process for preparing a compound of Formula (III) wherein R^1 is ethyl; and R^2 and R^3 are each methyl; or a salt thereof. In one embodiment, the above-mentioned process for preparing a compound of Formula (III) or a salt thereof is a process where the acid comprises an inorganic or an organic acid such as hydrochloric acid, etc.

[0021] In a further aspect of the invention, a process for the preparation of a compound of Formula (II) or a salt thereof as defined herein, which comprises reacting a compound of Formula (IV):

[0022]

[Chemical formula 4]



(IV)

wherein:

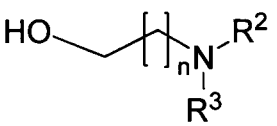
R^1 and R^X are the same as defined above; and

X^1 is a suitable leaving group; or a salt thereof;

with a compound of Formula (V):

[0023]

[Chemical formula 5]



(V)

wherein R^2, R^3 and n are the same as defined above; or a salt thereof;

in the presence of a suitable base;

and optionally thereafter, forming a salt thereof, is provided.

[0024] In one embodiment, the above-mentioned process for the preparation of a compound of Formula (II) or a salt thereof is a process for the preparation of a compound of Formula (II) wherein R^1 is ethyl, R^2 and R^3 are each methyl, and n is 1, or a salt thereof.

[0025] The skilled person would understand that the suitable base used in the above process includes any bases that are capable of deprotonating hydroxyl group in a compound of Formula (V). Therefore, said base may include alkali metal hydride bases, for example sodium hydride, potassium hydride, or lithium hydride; or deprotonated amine bases, for example lithium diisopropylamide; or alkyllithium bases, for example butyllithium or methyllithium; or bulky alkoxide bases such as a metal *tert*-butoxide base, for example sodium *tert*-butoxide, lithium *tert*-butoxide or potassium *tert*-butoxide. In one embodiment, the suitable base is a metal hydride base. In a further embodiment, the suitable base is selected from sodium hydride and potassium hydride.

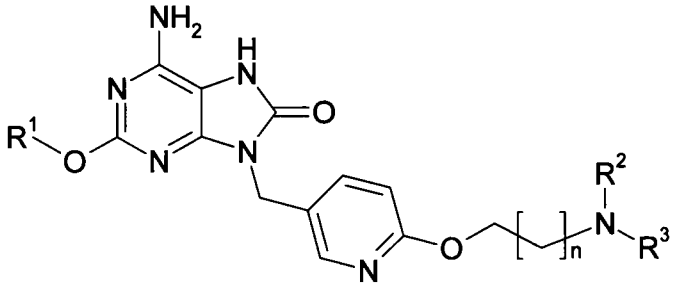
[0026] The skilled person would understand the kinds of leaving groups that will be suitable for X^1 group. For example, X^1 may be bromo or chloro. In one embodiment, X^1 is chloro.

Therefore in one embodiment, the above-mentioned process for the preparation of a compound of Formula (II) or a salt thereof is a process for the preparation of a compound of Formula (II) wherein R^1 is ethyl, R^2 and R^3 are each methyl, n is 1 and X^1 is chloro, or a salt thereof.

[0027] Therefore, in a further embodiment of the invention, a process for preparing a compound of Formula (III):

[0028]

[Chemical formula 6]



(III)

wherein:

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or

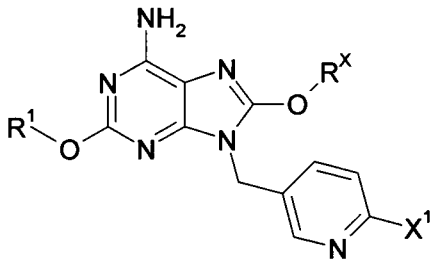
R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring; and

n is 1, 2 or 3; or a salt thereof;

which comprises reacting a compound of Formula (IV):

[0029]

[Chemical formula 7]



(IV)

wherein:

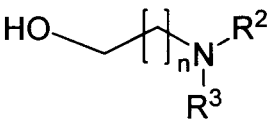
R^1 and R^X are the same as defined above; and

X^1 is a suitable leaving group; or a salt thereof;

with a compound of Formula (V):

[0030]

[Chemical formula 8]



(V)

wherein R^2, R^3 and n are the same as defined above; or a salt thereof;

in the presence of a suitable base;

to form a compound of Formula (II), as defined herein;

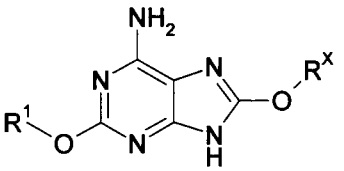
then reacting the compound of Formula (II) with an acid to provide a compound of Formula (III), as defined herein;

and optionally thereafter, forming a salt thereof, is provided.

[0031] In a further embodiment of the invention, a process for preparing a compound of Formula (III), as described above, wherein a compound of Formula (IV) is prepared by a process comprising reacting a compound of Formula (VI):

[0032]

[Chemical formula 9]



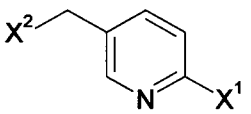
(VI)

wherein R^1 and R^X are the same as defined herein; or a salt thereof;

with a compound of Formula (VII):

[0033]

[Chemical formula 10]



(VII)

wherein X^1 is the same as defined herein, and X^2 is a leaving group selected from halo and (C_{1-8} hydrocarbyl)sulfonyloxy; or a salt thereof;

in the presence of a base to obtain a compound of Formula (IV);

and thereafter, optionally, forming a salt thereof, is provided.

Examples of '(C_{1-8} hydrocarbyl)sulfonyloxy' are methanesulfonyloxy, phenylsulfonyloxy and *para*-toluenesulfonyloxy.

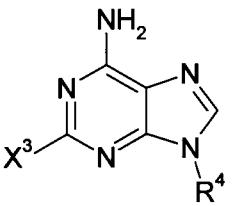
Herein, 'halo' refers to fluoro, chloro, bromo and iodo.

In one embodiment, X^2 is a leaving group selected from chloro, bromo, methanesulfonyloxy, phenylsulfonyloxy and *para*-toluenesulfonyloxy.

In a further embodiment of the invention, a process for preparing a compound of Formula (III), as described above, wherein a compound of Formula (VI) is prepared by a process comprising reacting a compound of Formula (VIII):

[0034]

[Chemical formula 11]



(VIII)

wherein X^3 is a group selected from chloro, bromo and iodo; R^4 is a protecting group selected

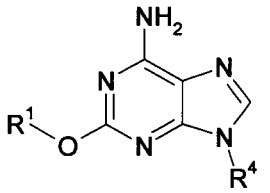
from tetrahydro-2*H*-pyran-2-yl and tetrahydrofuran-2-yl; or a salt thereof;

with a metal alkoxide salt of Formula 'R^1OM^1', where R^1 is the same as defined herein and M^1 is an alkali metal;

to obtain a compound of Formula (IX):

[0035]

[Chemical formula 12]



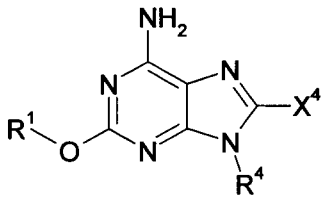
(IX)

wherein R^1 and R^4 are the same as defined herein; or a salt thereof;

and then reacting the compound of Formula (IX) or a salt thereof with a halogenating agent to obtain a compound of Formula (X):

[0036]

[Chemical formula 13]



(X)

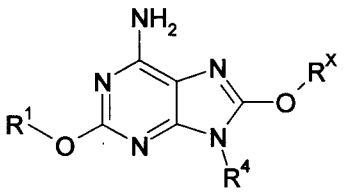
wherein R^1 and R^4 are the same as defined herein and X^4 is a group selected from chloro, bromo and iodo, or a salt thereof;

and then reacting the compound of Formula (X) or a salt thereof with an alcohol of Formula R^XOH, wherein R^X is the same as defined herein, in the presence of a base;

to obtain a compound of Formula (XI):

[0037]

[Chemical formula 14]



(XI)

wherein R^1 and R^4 are the same as defined herein; or a salt thereof;

and then reacting the compound of Formula (XI) or a salt thereof with an acid to obtain a compound of Formula (VI) or a salt thereof is provided.

[0038] In one embodiment, M^1 is selected from lithium, sodium and potassium.

The skilled person would understand that a halogenating agent is capable of delivering a chloro, bromo or iodo group to a chemical substrate, and that said halogenating agent may be formed *in-situ* in some cases, from other components. Examples of the halogenating agent include Cl_2, Br_2, PBr_3, PCl_3, $POCl_3$, $POBr_3$, hydrogentribromide, *N*-bromosuccinimide, *N*-chlorosuccinimide and *N*-iodosuccinimide etc.

[0039] Various embodiments of the invention are mentioned below. It is to be understood that any number of the embodiments may be used in any combination with each other to define further embodiments of the invention.

[0040] In one embodiment, any one of processes, as described herein, wherein R^1 is ethyl is provided.

[0041] In one embodiment, any one of processes, as described herein, wherein R^2 is methyl and R^3 is methyl is provided.

[0042] In one embodiment, any one of processes, as described herein, wherein X^1 is chloro and X^2 is chloro is provided.

[0043] In one embodiment, any one of processes, as described herein, wherein X^3 is chloro is provided.

[0044] In one embodiment, any one of processes, as described herein, wherein R^4 is tetrahydro-2*H*-pyran-2-yl is provided.

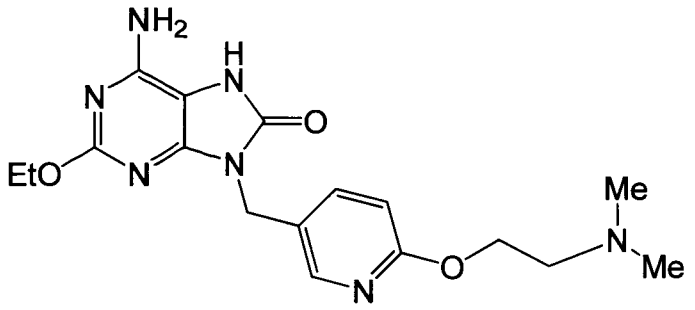
[0045] In one embodiment, any one of processes wherein the halogenating agent is Br_2 is provided.

[0046] In one embodiment, any one of processes, as described herein, wherein X^4 is bromo is provided.

[0047] In one embodiment, any one of processes, as described herein, wherein n is 1 is provided.

[0048] In one aspect of the invention, a new crystal form of a compound of Formula (XII):

[Chemical formula 15]



(XII)

which exhibits the characteristic X-ray powder diffraction peaks (expressed in degrees 2θ) as shown in Table 1 in Example 9 below is provided.

Unless stated otherwise, the X-ray powder diffraction data described herein was obtained using CuKα radiation as described in Example 9.

[0049] The invention also provides solvates (including hydrates) of Compound (XII) according to the invention. In an embodiment of the invention, a crystal form of Compound (XII) or a solvate thereof has crystalline properties and is preferably at least 50% crystalline, more preferably at least 60% crystalline, still more preferably at least 70% crystalline and most preferably at least 80% crystalline of this invention. A crystallinity can be estimated by conventional X-ray diffractometry techniques.

In another embodiment of the invention, a crystal form of Compound (XII) or a solvate thereof is from 50%, 60%, 70%, 80% or 90% to 95%, 96%, 97%, 98%, 99% or 100% crystalline of this invention.

[0050] According to a further aspect of the invention, a crystal form of Compound (XII), characterised in that said crystal form has an X-ray powder diffraction pattern with at least one specific peak, preferably all of the peaks at 2θ about = 4.5°, 9.0° or 17.9°, is provided.

According to a further aspect of the invention, a crystal form of Compound (XII), characterised in that the crystal form has an X-ray powder diffraction pattern with at least one specific peak, preferably all of the peaks at 2θ about = 4.5°, 8.6°, 9.0°, 9.2°, 17.9°, 18.9°, 20.1°, 22.4°, 22.7°, 25.1° or 27.6°, is provided.

[0051] According to a further aspect of the invention, a crystal form of Compound (XII), characterised in that said crystal form has an X-ray powder diffraction pattern with specific peaks at 2θ about =4.5°, 9.0° and 17.9°, is provided.

According to a further aspect of the invention, a crystal form of Compound (XII), characterised in that said crystal form has an X-ray powder diffraction pattern with specific peaks at 2θ about = 4.5°, 8.6°, 9.0°, 9.2°, 17.9°, 18.9°, 20.1°, 22.4°, 22.7°, 25.1° and 27.6°, is

provided.

According to a further aspect of the invention, a crystal form of Compound (XII), characterised in that said crystal form has an X-ray powder diffraction pattern substantially as shown in Figure 2, is provided.

[0052] When heated in a Differential Scanning Calorimeter (DSC) (in conditions as described in the Examples section), the crystal form of Compound (XII) exhibits a melting endotherm with an onset temperature at about 267°C, and a peak temperature at about 270°C, as illustrated in Figure 1.

[0053] In the preceding paragraphs defining the X-ray powder diffraction peaks for the crystalline form of Compound (XII), the term "about = " which is used in the expression "...at 2θ about = ..." means that the precise position of peaks (i.e. the recited 2-theta angle values) should not be construed as being absolute values because, as will be appreciated by those skilled in the art, the precise position of peaks may vary slightly between one measurement apparatus and another, from one sample to another, or as a result of slight variations in measurement conditions utilised. It is also stated in the preceding paragraphs that the crystalline form of Compound (XII) provides X-ray powder diffraction patterns 'substantially' the same as the X-ray powder diffraction patterns shown in Figure 2, and has substantially the most prominent peaks (in 2-theta angle values) shown in Table 1 in Example 9. It is to be understood that the use of the term 'substantially' in this context is also intended to indicate that the 2-theta angle values of the X-ray powder diffraction patterns may vary slightly from one apparatus to another, from one sample to another, or as a result of slight variations in measurement conditions utilised, and so the peak positions shown in the Figure or quoted in the Table are again not to be construed as being absolute values.

[0054] The person skilled in the art of X-ray powder diffraction will realize that the relative intensity of peaks can be affected by, for example, grains above approximately 30 micrometer in size and non-unitary aspect ratios which may affect analysis of samples. Furthermore, it should be understood that intensities may fluctuate depending on experimental conditions and sample preparation such as preferred orientation of particles in the sample. The use of automatic or fixed divergence slits will also influence calculations of the relative intensity. A person skilled in the art can handle such effects in comparing diffraction patterns.

[0055] The person skilled in the art of X-ray powder diffraction will also realize that differences in sample heights and errors in a calibration of a detector position could cause a small shift in the 2θ positions. Generally, a value with a difference of ± 0.1° from the given value is to be considered a correct value.

[0056] The person skilled in the art will also appreciate that slight variations in a melting point measured by DSC may occur as a result of variations in sample purities, sample preparations and the measurement conditions (e.g. heating rate). It will be appreciated that alternative measurement of a melting point may be given by other types of equipment or by using conditions different to those described hereinafter. Hence, the melting point and endotherm figures quoted herein are not to be taken as absolute values and such measurement errors are to be taken into account in analyzing DSC data. Typically, melting points may vary by ± 5°C, preferably ± 3°C or less.

[0057] A crystal form of Compound (XII) in the present invention is chemically and physically stable and useful for a material for manufacturing a pharmaceutical composition comprising Compound (XII).

[0058] In the context of the present specification, the term "therapy" includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

As used herein, the term "treatment" is intended to have its normal everyday meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology.

As used herein, the term "prophylaxis" is intended to have its normal everyday meaning and includes primary prophylaxis to prevent the development of a disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

[0059] A crystal form of Compound (XII) according to the invention and a pharmaceutical composition comprising the crystal form are useful as modulators of TLR7 activity and thus may be administered to a mammal, including a human being, 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;

[0060] 2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, 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; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

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;

[0061] 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 bladder, head and neck,

prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, uterus, liver, renal, skin, and brain tumors 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.

[0062] It is envisaged that for the methods of treatment mentioned herein, a crystal form of Compound (XII) will be administered to a mammal, more particularly a human being. Similarly, for the uses of a crystal form of Compound (XII) for the treatment of diseases or medical conditions mentioned herein, it is envisaged that a crystal form of Compound (XII) according to the invention or a pharmaceutical composition comprising the crystal form will be administered to a mammal, more particularly a human being.

[0063] According to another aspect of the invention, therefore, a crystal form of Compound (XII) as defined hereinbefore is provided for use as a medicament.

According to a further aspect of the invention, a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form as defined herein is provided for use in the treatment of a disease mediated through TLR7. In one embodiment of the invention, said disease mediated through TLR7 is cancer. In a further embodiment of the invention, said cancer is selected from bladder cancer, head and neck cancer, prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors. In one embodiment of the invention, said disease mediated through TLR7 is asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

[0064] In one aspect of the invention, a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form is provided for use in the treatment of the disease or conditions described above.

In one aspect of the invention, a use of a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form for the treatment of the diseases or conditions described above is provided.

In one aspect of the invention, a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form may be useful as a vaccine adjuvant.

As a further aspect of the invention, a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form is provided for use as a vaccine adjuvant.

As a further aspect of the invention, a use of a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form, as defined herein, as a vaccine adjuvant, in the manufacture of a vaccine for the treatment of a disease or condition is provided.

[0065] 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 crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form, as defined herein, in combination with a vaccine.

The invention still further provides a method of increasing a response to a vaccine in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form, as defined herein, in combination with a vaccine.

[0066] For the above-mentioned therapeutic uses, the dosage administered will, of course, vary with the crystal form employed, the mode of administration, the treatment desired and the disorder indicated.

For example, dosage ranges are from about 0.1 ng/kg to about 10 mg/kg of an active ingredient.

[0067] The invention further relates to combination therapies wherein a salt according to the invention, or a pharmaceutical composition comprising a crystal form of Compound (XII) according to the invention 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 herein.

[0068] According to a further aspect of the invention, a pharmaceutical composition which comprises a crystal form of Compound (XII) as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier is provided. The pharmaceutical composition may be used in the treatment of cancer. The composition may be in a form suitable for oral

administration, for example as a tablet or capsule; for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository.

[0069] A crystal form of Compound (XII), or a pharmaceutically acceptable salt thereof, could also be administered as an air spray for inhalation. The air spray (e.g., spray, aerosol, dry powder preparation, etc.) could be optionally formulated as an aqueous solution or suspension, or as an aerosol delivered by a pressurized pack such as a pressurised metered dose inhaler by using, for example, a liquefied propellant. A dry powder preparation may also be used. An aerosol appropriate for inhalation may be either a suspension or solution, and would typically contain a crystal form of Compound (XII), and any appropriate propellants such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or a mixture thereof. Specifically, it may contain hydrofluoroalkane, particularly 1,1,1,2-tetrafluoroethane, heptafluoroalkane (HFA) such as 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof. An aerosol may optionally contain an additional preparation excipient well-known to those skilled in the art such as surfactant (e.g., oleic acid or lecithin) and cosolvent (e.g., ethanol), etc. Specifically, an aerosol preparation could be delivered using the inhaler known as "Turbuhaler™".

[0070] For an oral administration, a crystal form of Compound (XII) 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 a tablet. If a coated tablet is required, the core, 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 core may be coated with a suitable polymer dissolved in a readily volatile organic solvent to give a tablet.

[0071] For the preparation of soft gelatine capsules, a crystal form of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of a crystal form of the invention using any of the above-mentioned excipients for tablets. Also liquid or semisolid formulations of a crystal form of the invention may be filled into hard gelatine capsules.

[0072] Liquid preparations for an oral application may be in the form of syrups or suspensions, for example, solutions containing a crystal form of the invention wherein the

balance is comprised of 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.

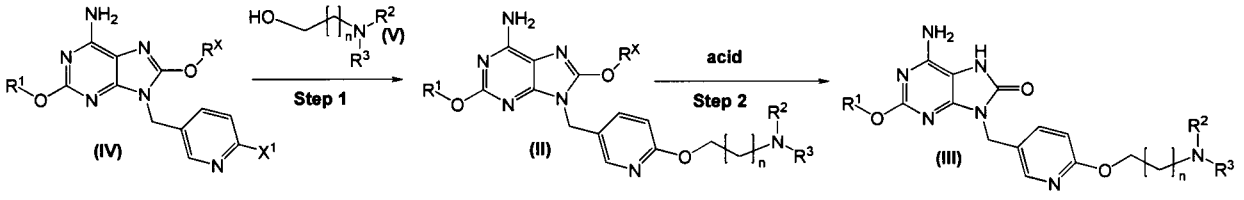
[0073] A crystal form of Compound (XII) or a pharmaceutical composition comprising the crystal form will normally be administered to a warm-blooded animal at a unit dose within the range of 5-5000 mg/m^2 body area of the animal, i.e. approximately 0.1-100 mg/kg, which normally provides a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually contain, for example 1-250 mg of the active ingredient. Preferably, a daily dose in the range of 1-50 mg/kg is employed. However, the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patients.

[0074] For further information on Routes of Administration and Dosage Regimes, the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990).

[0075] One aspect of the invention relates to the following process:

[0076]

[Chemical formula 16]



[wherein R^1, R^2, R^3, R^X, X^1 and n are the same as defined herein]

[0077]

Step 1:

A compound of Formula (IV) may be reacted with compound (V) in the presence of a base such as sodium hydride (NaH) or potassium hydride (KH) in a suitable solvent for about 1 to 20 hrs, preferably for about 2 to 10 hrs, to give compound (II). The suitable solvent includes solvents that are inert to the base used in the reaction and which dissolve the reactants, at least partially. Such solvents may include ethers such as tetrahydrofuran (THF), diethyl ether or 1,4-dioxane, etc., or dipolar aprotic solvents such as acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA) or dimethylsulfoxide

(DMSO), etc. The reaction temperature may be selected from the range of about 0°C up to around the boiling temperature of the solvent being used. The reaction temperature is preferably the range of about 60°C to about 110°C, preferably about 60°C to about 100°C. A compound of Formula (V) is usually used in an amount of 1 to 20 molar equivalents for 1 molar equivalent of a compound of Formula (IV). The base (for example, NaH or KH) is usually used in an amount of 1 to 15 molar equivalents for 1 molar equivalent of a compound of Formula (IV).

[0078]

Step 2:

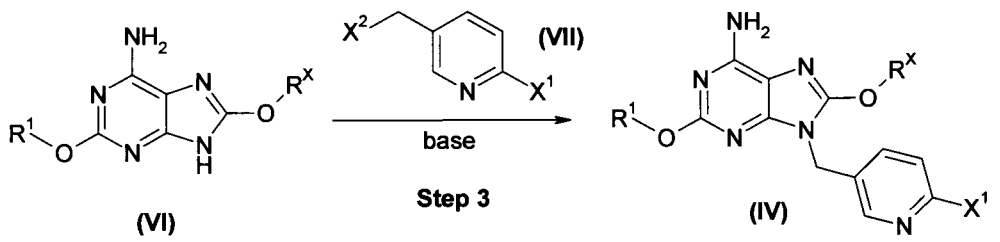
A compound of Formula (II) may be reacted with an acid in a suitable solvent to give a compound of Formula (III). The suitable solvent may include alcohol solvents such as methanol or ethanol, etc.; ethers such as tetrahydrofuran, diethyl ether or 1,4-dioxane, etc.; or dipolar aprotic solvents such as MeCN, DMF, DMA, etc. The solvent is preferably methanol. The reaction temperature may be selected from the range of about room temperature (r.t.) to about the boiling temperature of the solvent being used. The reaction temperature is preferably the range of about 20°C to 80°C, preferably about 20°C to about 30°C. The acid may be an inorganic acid, such as hydrochloric acid, hydrobromic acid, or sulfuric acid, or it may be an organic acid such as trifluoroacetic acid (TFA), etc. The acid is preferably hydrochloric acid. The concentration of hydrochloric acid is preferably from about 0.01 M to about 2 M in the reaction mixture. As the acid, for example, from 1N to 4N HCl/Dioxane, from 1M to 10M HCl in water, or 5-15%, preferably about 10%, HCl/methanol may be used. The reaction may be performed for about 1 to 20 hrs. The acid is usually used in an amount of 1 to 20 molar equivalents for 1 molar equivalent of a compound of Formula (IV).

[0079] In the above process, R^1 is preferably ethyl, both R^2 and R^3 are preferably methyl, X^1 is preferably bromo, R^X is preferably methyl, and n is 1.

[0080] In another embodiment, the invention includes the following process:

[0081]

[Chemical formula 17]



[wherein R^1, R^X, X^1 and X^2 are the same as defined herein].

[0082]

Step 3:

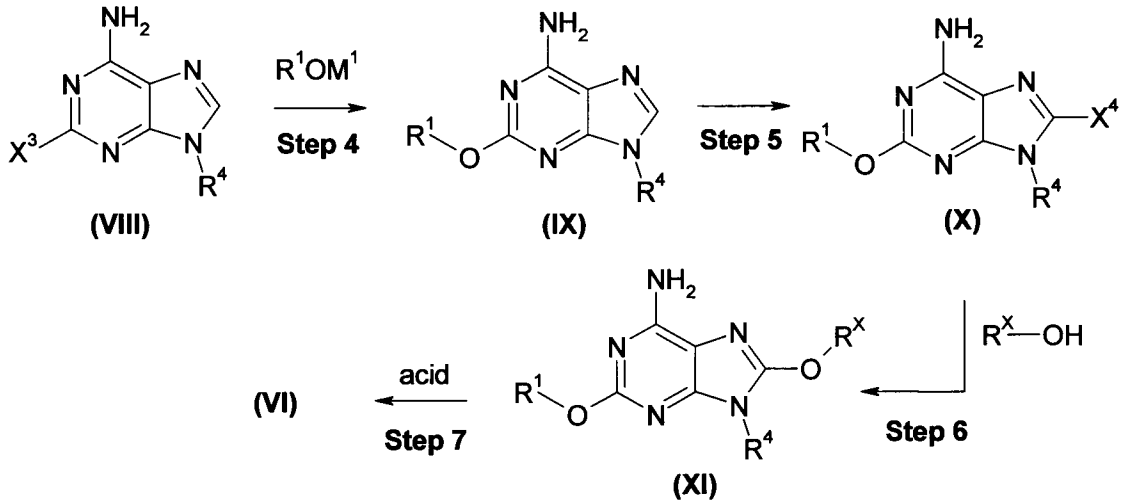
A compound of Formula (VI) may be reacted with a compound of Formula (VII) in the presence of a base in a suitable solvent for about 1 to 20 hrs to give a compound of Formula (IV). The base may be any conventional base used as a base in conventional organic reactions. Said base includes for example, alkaline-earth metal carbonates such as calcium carbonate, etc., alkali metal carbonates such as sodium carbonate, or potassium carbonate, etc., alkali alkoxides such as potassium *tert*-butoxide, etc., or metallic hydroxides such as sodium hydroxide or potassium hydroxide, etc. The base is preferably sodium carbonate, or potassium carbonate, more preferably potassium carbonate. The solvent may be an ether such as tetrahydrofuran, diethyl ether or 1,4-dioxane, etc., or a dipolar aprotic solvent such as acetonitrile, *N*,*N*-dimethylformamide or dimethylsulfoxide, etc, or a halogenated hydrocarbon such as chloroform, dichloromethane or carbon tetrachloride, etc. The solvent is preferably *N*,*N*-dimethylformamide. The reaction temperature may be selected from the range of about room temperature to about 100°C. The reaction temperature is preferably the range of about 40°C to about 80°C. A compound of Formula (VII) is usually used in an amount of 1 to 5 molar equivalents for 1 molar equivalent of a compound of Formula (VI). The base is usually used in an amount of 2 to 5 molar equivalents for 1 molar equivalent of a compound of Formula (VI).

[0083] In the above process, R^1 is preferably ethyl, and both X^1 and X^2 are preferably chloro. In one embodiment, R^X is methyl.

[0084] In one embodiment, the process of the present invention includes the following steps:

[0085]

[Chemical formula 18]



wherein R^1, M^1, R^4, R^X, X^3 and X^4 are the same as defined herein.

[0086]

Step 4:

A compound of Formula (VIII) may be reacted with a compound of Formula R^1OM^1 in the presence of an organic solvent for about 1 to about 8 hours, preferably from about 2 to about 6 hours to give a compound of Formula (IX). When R^1OM^1 is used, the organic solvent R^1OH is usually used. The reaction temperature may be selected from the range of about 50°C to about 200°C. A compound of Formula R^1OM^1 may be used in an amount of 1 to 15 molar equivalents for 1 molar equivalent of a compound of Formula (VIII).

[0087]

Step 5:

A compound of Formula (IX) may be reacted with a halogenating agent in the presence of a solvent for about 1 to about 5 hours, preferably about 1 to about 3 hours to give a compound of Formula (X). Examples of the halogenating agent are described hereinbefore. The halogenated agent is preferably Cl_2 or Br_2, more preferably Br_2. Auxiliary agents such as sodium acetate may be used when the halogenating agent is bromine. The suitable solvent may include ethers such as tetrahydrofuran, diethyl ether, or 1,4-dioxane, etc., halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, or carbon tetrachloride, etc., esters such as ethyl acetate etc., acids such as acetic acid; or carbon disulfide etc. The reaction temperature may be selected from the range of about 0°C to about the boiling temperature of the solvent being used. The reaction temperature is preferably the range of about 0°C to about room temperature (i.e. around 20°C).

[0088]

Step 6:

A compound of Formula (X) may be reacted with an alcohol (R^XOH) in the presence of a base for about 0.5 hours to about 3 hours to provide a compound of Formula (XI). The base may be an aqueous solution of an alkali metal hydroxide, for example NaOH. The use of aqueous NaOH has been seen to cause the formation of an unwanted by-product in the reaction mixture. Surprisingly, it has been found that the use of solid sodium hydroxide (20-40 mesh) in an alcohol solvent, such as methanol results in negligible unwanted by-product, and more of a compound of Formula (XI). When aqueous alkali is used as the base, for example, an aqueous solution of sodium hydroxide, or an aqueous solution of potassium hydroxide, the aqueous alkali solution is usually used in a concentration of 0.5 to 5 mol/L. The reaction temperature may be selected from the range of about room temperature to about the boiling temperature of the solvent being used. When aqueous alkali solution is used, it is

usually used in an amount of 1 to 20 molar equivalents of alkali for 1 molar equivalent of a compound of Formula (X).

A compound of Formula (X) may be reacted with a metal methoxide such as sodium methoxide in the presence of anhydrous methanol to give a compound of Formula (XI).

[0089]

Step 7:

A compound of Formula (XI) may be reacted with an acid in the presence of an organic solvent for about 1 to about 48 hours to give a compound of Formula (VI). The acid may be, for example, an inorganic acid, such as hydrochloric acid, hydrobromic acid, or sulfuric acid; or an organic acid such as trifluoroacetic acid, etc. The acid is preferably trifluoroacetic acid. The organic solvent may be, for example, water; alcoholic solvents such as methanol or ethanol; ethers such as tetrahydrofuran, diethyl ether, or 1,4-dioxane, etc.; dipolar aprotic solvents such as acetonitrile, *N*,*N*-dimethylformamide, or dimethylsulfoxide, etc., or a mixture of these solvents. The organic solvent is preferably methanol or ethanol. The reaction temperature may be selected from the range of about room temperature to about the boiling temperature of the solvent being used. The reaction temperature is preferably room temperature. The acid is usually used in an amount of 1 to 5 molar equivalents for 1 molar equivalent of a compound of Formula (XI).

[0090] In the above process, R^1 is preferably ethyl; R^X is preferably methyl; R^4 is preferably tetrahydro-2*H*-pyran-2-yl group; X^3 is preferably chloro; and X^4 is preferably bromo.

EXAMPLES

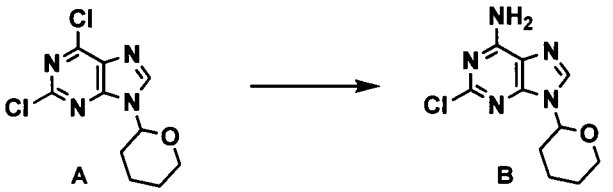
[0091] The present invention is illustrated in more detail by Reference Example and Examples shown below, but the present invention should not be construed to be limited thereto. Additional abbreviations used are: THF = tetrahydrofuran; MeOH = methanol; EtOH = ethanol; EtOAc = ethyl acetate; r.t. = room temperature; MeCN = acetonitrile; DCM = dichloromethane. All relative equivalents and relative volumes were calculated from an assay of 100% w/w of the relevant starting materials. Proton NMR spectra (^{1}H NMR) were determined at 400MHz in deuterated DMSO, unless otherwise stated. NMR abbreviations used include: s = singlet; m = multiplet; d = doublet; t = triplet, q = quartet; br = broad; dd = doublet of doublets, etc.

[0092]

Reference Example: Preparation of 2-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Compound B)

[0093]

[Chemical formula 19]



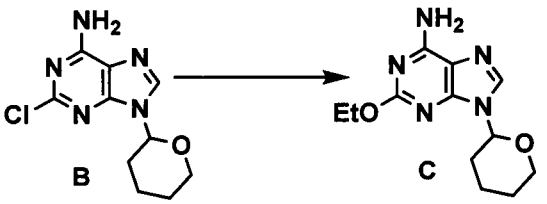
An aqueous ammonia solution (28%, 1500 mL) was added to a solution of Compound A (146 g, 534 mmol) in tetrahydrofuran and the mixture was stirred at r.t. for 24 hours. After a half volume of the solvent was removed under reduced pressure, the resulting solid was collected by filtration, washed with water (2000 mL) and dried under reduced pressure to give the title compound as a colorless solid (135 g, 534 mmol, >99%).

[0094]

Example 1: Preparation of 2-ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Compound C)

[0095]

[Chemical formula 20]



Sodium ethoxide (20% solution in EtOH, 185 mL, ca. 473 mmol) was added to an EtOH (185 mL) solution of Compound B (30 g, 118.3 mmol) and the mixture was stirred under reflux for 5.5 hours. Water (150 mL) was then added and the mixture was neutralized with acetic acid (24 mL, 420 mmol) at 0°C and then extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was stirred in a mixture of hexane and EtOAc (2:1, 360 mL) under reflux for 30 min, and then cooled to r.t. The solid was collected by filtration and dried *in vacuo* to give the title compound as an orange solid (23.10 g, 87.7 mmol). After the filtrate was concentrated, the resulting residue was stirred in the mixture of hexane and EtOAc (2:1, 360 mL) under reflux for 30 min, and then cooled to r.t. The resulting solid was collected by filtration and dried *in vacuo* to provide more of the title compound as an orange solid (5.80 g, 22.0 mmol). Total amount Compound C from this procedure was 28.90 g (109.8 mmol, 93% yield).

[0096]

Alternative preparation of Compound C:

To a nitrogen-inerted 5L reactor was added Compound B (264 g; 1.00 eq: 1.04 mol) and sodium ethoxide (1.42 kg of 25% wt/wt solution in EtOH; 5.0 eq). The slurry was heated at 90°C while stirring for 130 min giving a conversion > 98.5%, as analyzed by HPLC (210 nm). The reaction mixture was cooled (18.6°C) and acetic acid (300 g; 5.0 eq) was charged over a period of 30 minutes. A thick slurry with precipitated sodium acetate was produced. Water was then added (792 mL; 3.0 vol) followed by the addition of 2-methyltetrahydrofuran (Me-THF, 1.58 L; 6.0 vol) and the mixture was stirred at 40°C. The clear aqueous phase (670 mL) was separated off and NaCl (0.8 kg in 1.32 L water) was added, while stirring, to the red-coloured organic phase at 40°C. The resulting aqueous phase (1475 mL) was separated off and organic layer was cooled and left overnight. The organic layer was concentrated *in vacuo* (60°C) to approximately 4 relative volumes (1.1 L) to give a red-coloured slurry. The mixture was co-evaporated with EtOAc (790 mL; 3.0 vol) to approximately 3.5-4 volumes (1 L) solution. This procedure was repeated once more to give a mixture of crystalline material in EtOAc. The mixture was then heated to 60°C and thereafter the solution was cooled slowly to 35°C. A cooling ramp was set to reach 0°C during a period of 4 hours and cyclohexane (1.06 L; 4.0 vol) was added slowly during the cooling procedure. The resulting slurry was left overnight. The solid was isolated on a T-1000 filter disk using a Teflon™ filter (180 mm) to give a 25 mm high filter cake which was displacement washed with a cold mixture of EtOAc/cyclohexane (300 mL/400 mL). The wet solid was dried *in vacuo* at 40°C to afford 275 g of material containing Compound C. Analysis suggested a HPLC purity >99 area% at 210nm and the NMR assay was 76.0 % w/w. Yield calculated from the NMR assay was 76%.

[0097]

Alternative preparation of Compound C

Sodium ethoxide (21% w/w in EtOH, 311 mL, 834.09 mmol) was added to Compound B (21.16 g, 83.41 mmol) and the resulting suspension was stirred at 110°C for 3 hours. The mixture was then diluted with EtOH (300 mL) and cooled to 0°C. Acetic acid (44 mL, 768.60 mmol) was added drop-wise until the mixture reached ~pH7. The resulting suspension was then filtered through diatomaceous earth (Celite™) and the liquors were concentrated to dryness to give crude product. This was purified by recrystallisation from EtOAc to afford Compound C (20.90 g, 95 %) as a pale yellow crystalline solid.

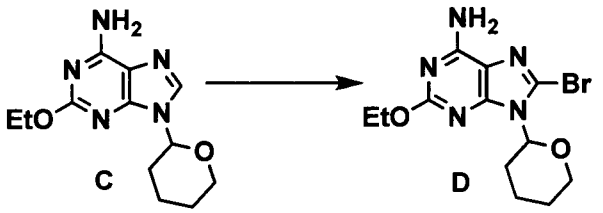
m/z (ES+) MH^+ 264.48; ^1H NMR: 1.28 (3H, t), 1.49-1.63 (2H, m), 1.64-1.78 (1H, m), 1.85-2.01 (2H, m), 2.15-2.30 (1H, m), 3.64 (1H, ddd), 3.99 (1H, dd), 4.26 (2H, q), 5.48 (1H, dd), 7.17 (2H, br s), 8.09 (1H, s).

[0098]

Example 2: Preparation of 8-bromo-2-ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Compound D)

[0099]

[Chemical formula 21]



A solution of Br_2 (35.1 g, 219.6 mmol) in $CHCl_3$ (100 mL) was slowly added to a mixture of Compound C (28.9 g, 109.8 mmol) and sodium acetate (45.0 g, 549 mmol) in $CHCl_3$ (400 mL) at 0°C. After stirring at 0°C for 2 hours, the mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$, extracted with $CHCl_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was triturated with $CHCl_3$ (70 mL) and hexane (350 mL). The resulting solid was collected by filtration and dried *in vacuo* to give the title compound as a pale yellow solid (33.4 g, 97.6 mmol, 89% yield).

[0100]

Alternative preparation of Compound D:

Compound C (246.5 g; 936 mmol; 1.00 eq), CH_2Cl_2 (2.7 L; 11 vol) and sodium ethanoate (251.7 g; 3.30 eq) was added to a 5L reactor at 0°C. A solution of Br_2 (299 g; 2.00 eq) in DCM (976 mL; 3.96 vol) slowly added over a period of 2.5 hours, while keeping the temperature of the reaction mixture below 5°C. Analysis of the resulting red slurry by HPLC (210 nm) suggested full conversion to desired product. The jacket of the vessel was set to a temperature of -10°C and a solution of sodium thiosulfate (296 g; 2.00 eq;) in water (2.50 l; 10.2 vol) was added to the mixture, while maintaining the reaction temperature below 7°C. The jacket temperature was then set to 20°C and the organic phase was separated off. The aqueous phase (pH 3) was discarded. The organic phase was washed with a solution of $NaHCO_3$ (76.5 g; 1.0 eq) in water (2 L; 8.1 vol) and left for separation overnight. The aqueous phase was separated off (and discarded) and the organic phase was concentrated, using a jacket temperature of 50°C to give approximately 0.7 L (2.8 vol) of a red-coloured slurry which was co-evaporated with EtOAc (2.5 L; 10 vol) to a volume of 0.6 L (2.4 vol). EtOAc (1.23 L; 5.0 vol) was added to the slurry and the mixture was heated to form a clear solution (jacket temperature 90°C). The almost clear solution was cooled to -5°C during approximately 2 hours and isooctane (2.50 L; 10 vol) was charged during approximately 1

hour to the fine crystalline slurry. The resulting solid was isolated on a T-1000 filter disk using a Teflon™ filter (180 mm) and the filter cake was displacement washed with a cold mixture of EtOAc/isooctane (250 mL / 740 mL). The wet solid was dried *in vacuo* at 40°C giving 298.2 g. Analyses gave a HPLC purity of >98.3 area% at 230 nm and the NMR assay was 94.6 % w/w. Yield calculated from the NMR assay was 88%.

[0101]

Alternative preparation of Compound D:

A solution of Br_2 (4.47 mL, 87.32 mmol) in $CHCl_3$ (40 mL) was added drop-wise to a mixture of Compound C (20.90 g, 79.38 mmol) and sodium acetate (32.6 g, 396.89 mmol) in $CHCl_3$ (500 mL) and the mixture was cooled to 0°C over a period of 30 minutes. The resulting suspension was stirred at 0°C for a further 20 minutes. The mixture was then washed sequentially with saturated $NaHCO_3$ (300 mL), 20% aqueous sodium thiosulfate (300 mL), and saturated brine (300 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide Compound D (17.62 g, 64.9 %) as a red-brown solid, which was used in subsequent procedures without further purification.

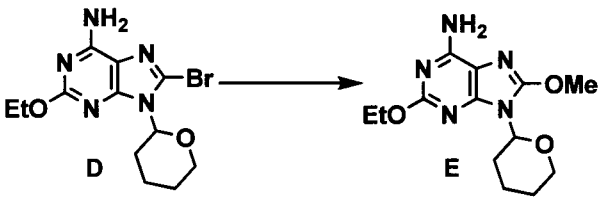
m/z (ES+) MH^+ 344.40; ^1H NMR: 1.29 (3H, t), 1.55 (3H, t), 1.67 (1H, dd), 1.78-1.88 (1H, m), 1.98 (1H, d), 2.96 (1H, ddd), 3.57-3.69 (1H, m), 4.03 (1H, d), 4.25 (2H, q), 5.49 (1H, dd), 7.34 (2H, s).

[0102]

Example 3: Preparation of 2-ethoxy-8-methoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Compound E)

[0103]

[Chemical formula 22]



An aqueous solution of NaOH (2.5N, 300 mL) was added to a suspension of Compound D (33.4 g, 97.6 mmol) in MeOH (600 mL) and the mixture was stirred under reflux for 3 hours. The mixture was then neutralized with acetic acid (42.9 mL, 750 mmol) at 0°C and then concentrated *in vacuo*. The resulting solid was collected by filtration and dried *in vacuo* to afford the title compound as a beige solid (26.03 g, 88.7 mmol, 91% yield).

[0104]

Alternative preparation of Compound E:

Compound D (298.2 g; 824.4 mmol; 1.00 eq), MeOH (4.40 L; 14.7 vol) and NaOH (solid, 20-40 Mesh, 268.4 g; 7.90 eq) were charged to 5L reactor at 20°C while stirring. The jacket temperature was then set to 70°C and the conversion was monitored by HPLC. After 80 minutes the reaction was at reflux temperature (62°C) and HPLC analysis (230 nm) suggested >99.5% conversion. The reaction was cooled to 0°C. Acetic acid (379 mL; 8.00 eq) was added during a period of 70 minutes, giving a fine beige-coloured slurry. The solid was isolated on a T-1000 filter disk using a Teflon™ filter (180 mm) and the filter cake was slurry washed twice with cold water (2 × 745 mL; 5.00 vol), dried *in vacuo* (40°C) to provide 175.8 g of pale beige solid. Analysis suggested a HPLC purity >99.2 area% at 230 nm. NMR assay indicated a strength of 98.7 % w/w. A second crop (40 g) was isolated from mother liquor with a HPLC purity of 98.9 area% at 230 nm and the NMR assay was 91.5 % w/w. Total yield of Compound E: (215.8 g, 86.9% calculated from NMR assay).

[0105]

Alternative preparation of Compound E:

2.5M NaOH solution (185 mL, 463.42 mmol) was added portionwise to Compound D (17.62 g, 51.49 mmol) in MeOH (370 mL). The resulting mixture was stirred at 90°C for 2 hours. The mixture was then concentrated and diluted with EtOAc (500 mL), and washed sequentially with saturated $NaHCO_3$ (300 mL) and saturated brine (300 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash silica chromatography, eluting with 0-3% MeOH in DCM provided Compound E (6.64 g, 44.0 %) as an off-white solid.

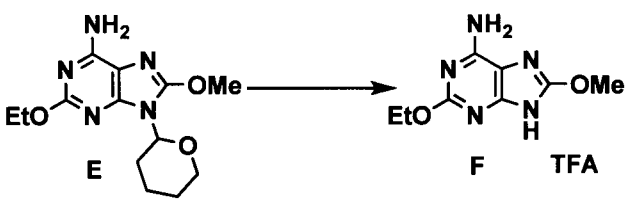
m/z: (ES+) MH^+ 294.51; ^1H NMR: 1.27 (3H, t), 1.49-1.54 (2H, m), 1.62 (1H, ddd), 1.73 (1H, dd), 1.94 (1H, br d), 2.65-2.79 (1H, m), 3.57 (1H, ddd), 3.97 (1H, br d), 4.05 (3H, s), 4.22 (2H, q), 5.34 (1H, dd), 6.77 (2H, br s).

[0106]

Example 4: Preparation of 2-ethoxy-8-methoxy-9*H*-purin-6-amine trifluoroacetate salt (Compound F)

[0107]

[Chemical formula 23]



Compound E (26.03 g, 88.7 mmol) was suspended in MeOH (325 mL), and TFA (65

mL) was added. The mixture was stirred at r.t. for 48 hours and then concentrated *in vacuo*. EtOAc (260 mL) was added to the residue and the resulting solid was collected by filtration. It was then dried *in vacuo* to give Compound F as a white solid (25.94 g, 80.3 mmol, 90% yield).

[0108]

Alternative preparation of Compound F:

Compound E (210 g; 715.9 mmol; 1.00 eq) and MeOH (2.10 L; 10.00 vol) were added to a 5L reactor at 20°C. The resulting solution was cooled to 0°C and trifluoroacetic acid (771 g; 9.44 eq) was added, while maintaining the temperature of the mixture <10°C. The mixture was then left overnight with a jacket temperature of 25°C. Solid precipitated out during this reaction. HPLC analysis (230 nm) and suggested approximately 97.5% conversion. The mixture was then concentrated *in vacuo* using a jacket temperature of 70°C to achieve a volume of approximately 0.6 L (3 vol). The resulting slurry was filtered off and isolated on a T-1000 filter disk using a Teflon™ filter (180 mm diameter). The solid was displacement washed with cold MeOH (420 mL; 2.0 vol) and dried *in vacuo* at 40°C affording 236g off white solid. HPLC purity appeared to be >99area% (230 nm). NMR assay indicated a strength of 98.0 % w/w. Yield of Compound F calculated from the NMR assay was 93.6%.

[0109]

Alternative preparation of Compound F:

Trifluoroacetic acid (16.82 mL, 226.37 mmol) was added slowly to Compound E (6.64 g, 22.64 mmol) in MeOH (150 mL). The resulting mixture was stirred at 60°C for 3 hours and then concentrated to dryness. The crude residue was triturated with EtOAc (150 mL) to give a solid which was collected by filtration and dried *in vacuo* to give Compound F (6.69 g, 91 %) (which is a trifluoroacetate salt), as a white solid.

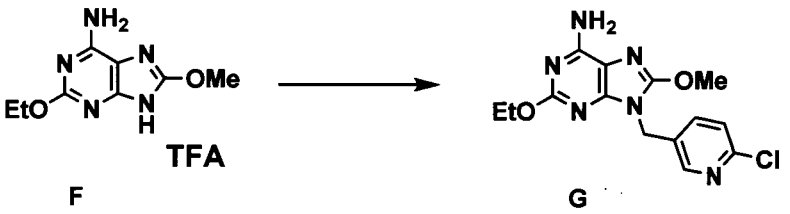
m/z: (ES+) MH^+ 210.39; ^1H NMR: 1.31 (3H, t), 4.04 (3H, s), 4.33 (2H, q), 7.46 (1H, br s).

[0110]

Example 5: Preparation of 9-[(6-chloropyridin-3-yl)methyl]-2-ethoxy-8-methoxy-9*H*-purin-6-amine (Compound G)

[0111]

[Chemical formula 24]



K_2CO_3 (6.41 g, 46.4 mmol) and 2-chloro-5-(chloromethyl)pyridine (3.76 g, 23.2 mmol) were added to the solution of Compound F (5.00 g, 15.5 mmol)) in DMF (20 mL) and the mixture was stirred while heating at 50°C for 2 hours. Water (80 mL) was then added slowly to the mixture at r.t. over 30 minute period. The resulting solid was collected by filtration and purified by silica-gel column chromatography (eluent $CHCl_3$/MeOH) to afford the title compound as a yellow solid (2.85 g, 8.51 mmol). The filtrate was extracted with EtOAc (twice), washed with brine (twice), dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was purified by silica-gel column chromatography to provide more of the title compound as a yellow solid (0.82 g, 2.46 mmol). Total amount of Compound G from this procedure was 3.67 g (10.97 mmol, 71% yield).

[0112]

Alternative preparation of Compound G:

Compound F (125 g; 379 mmol; 1.00 eq), K_2CO_3 (129.8 g; 2.40 eq), 2-chloro-5-(chloromethyl)pyridine (73.5 g; 1.15 eq) and DMF (500 mL; 4.0 vol) were added to a nitrogen-inerted 2L reactor with a jacket temperature of 20°C. The mixture was then heated to 49°C. The reaction was monitored by HPLC until the >96% of the Compound F appeared to be consumed. The mixture was then cooled to 22°C. Water (2.00 L; 16 vol) was added over a period of 2 hours while the mixture was cooled to 0°C. A slurry was produced which was left overnight. Solid was isolated on a T-1000 filter disk (glass filter 120 mm diameter), washed with cold water (2 × 350 mL; 6 vol), dried *in vacuo* at 40°C, to give 125.0 g of cream-coloured material. Analysis suggested a HPLC purity of approx 60 area% (230 nm). This material was combined with a second batch (described below) and purified (see purification step below).

[0113]

Alternative preparation of Compound G:

A second batch of Compound G was prepared from Compound F (125 g; 379 mmol) using the same reaction conditions mentioned above to afford 102 g of product with a HPLC purity of approx 60 area% (230 nm). This material was combined with material from the procedure described immediately above, and the combined material was purified (see

purification step below).

[0114]

Purification of Compound G to remove the undesired isomers:

Compound G produced from the two reactions described above (277 g; 827.4 mmol; 1.00 eq) and MeOH (1.50 L; 5.35 vol) were added to a 5L reactor. The resulting slurry was heated to reflux temperature (jacket temperature 80°C) for 30 minutes and thereafter cooled to 20°C. Solid was isolated on a T-1000 filter disk (Teflon™ filter 180 mm), displacement washed with MeOH (500 mL; 1.80 vol), dried *in vacuo* at 40°C giving 179.6 g of material. Analysis suggested a HPLC purity of approx 85 area% (230 nm) with the main 7-isomer by-product (approx. 15 area%). This mixture was purified by normal phase chromatography on silica to afford Compound G.

[0115]

Alternative preparation of Compound G:

2-Chloro-5-(chloromethyl)pyridine (5.03 g, 31.05 mmol) was added in one portion to Compound F (4.0 g, 12.38 mmol) and K_2CO_3 (5.13 g, 37.13 mmol) in anhydrous DMF (50 mL) at -20°C under nitrogen. The resulting mixture was allowed to warm to r.t. and stir for 18 hours. The mixture was diluted with DCM (500 mL) and washed sequentially with water (3 × 200 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), adsorbed onto silica. Purifiation by flash silica chromatography, eluting with 0-5% MeOH in DCM afforded a yellow solid. This was triturated with MeOH to give a solid which was collected by filtration and dried *in vacuo* to afford Compound G (4.02 g, 58.0%) as a white solid.

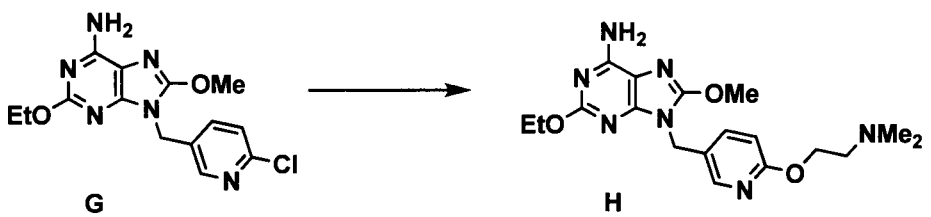
m/z: (ES+) MH^+ 335.44; ^1H NMR: 1.26 (3H, t), 4.05 (3H, s), 4.22 (2H, q), 5.08 (2H, s), 6.82 (2H, br s), 7.49 (1H, dd), 7.72 (1H, dd), 8.39 (1H, d).

[0116]

Example 6: Preparation of 9-{6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl-2-ethoxy-8-methoxy-9*H*-purin-6-amine (Compound H)

[0117]

[Chemical formula 25]



Dimethylaminoethanol (8.56 mL, 85.1 mmol) was added dropwise to a suspension of NaH (55% in mineral oil, 1.86 g, 42.6 mmol) in 1,4-dioxane (30 mL) at 0°C over 15 minute

period. After stirring at r.t. for 30 minutes, Compound G (2.85 g, 8.51 mmol) was added to the mixture and the mixture was stirred at 80°C for 3.5 hours. Water (50 mL) and conc. aq. HCl (6.5 mL) were then added, and the mixture was extracted 3 times with $CHCl_3$, and the combined organic solutions were dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was purified by silica-gel column chromatography to provided Compound H as a white solid (2.12 g, 5.46 mmol, 64% yield).

[0118]

Alternative preparation of Compound H:

2-(Dimethylamino)ethanol (7.22 mL, 72.09 mmol) was added drop-wise to NaH (2.88 g, 72.09 mmol) in 1,4-dioxane (230 mL) over a period of 20 minutes. The resulting mixture was stirred for 30 minutes and then Compound G (4.022 g, 12.01 mmol) was added as a single portion. The reaction was then stirred at 110°C for 3 hours. The mixture was then concentrated *in vacuo* and the resulting residue was dissolved in DCM (500 mL). This solution was washed sequentially with saturated NH_4Cl (3 × 500 mL), water (2 × 200 mL) and saturated brine (200 mL). The combined aqueous washings were then acidified to ~pH 7 and then extracted with DCM (2 × 500 mL). The combined organics were dried ($MgSO_4$) and concentrated to give a yellow solid. This was pre-adsorbed onto silica and purified by flash silica chromatography, (elution gradient 0 to 5% 7M NH_3/MeOH in DCM) to provide Compound H (2.461 g, 52.9%) as a white solid;

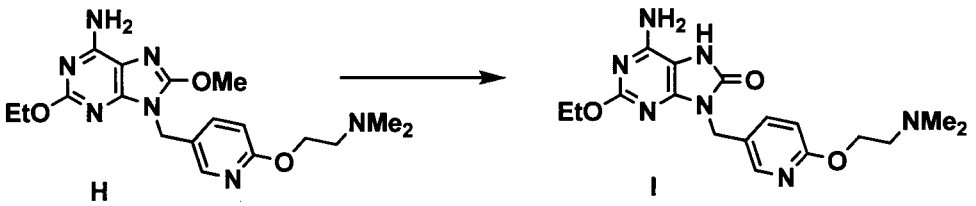
m/z: (ES+) MH^+ 388.54; ^1H NMR: 1.27 (3H, t), 2.17 (6H, s), 2.57 (2H, t), 4.06 (3H, s), 4.24 (2H, q), 4.29 (2H, t), 4.97 (2H, s), 6.76 (1H, dd), 6.78 (2H, br s), 7.61 (1H, dd), 8.13 (1H, d).

[0119]

Example 7: Preparation of 6-amino-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-2-ethoxy-7*H*-purin-8(9*H*)-one (Compound I)

[0120]

[Chemical formula 26]



HCl/1,4-dioxane (4N, 10 mL) was added to a suspension of Compound H (2.11 g, 5.46 mmol) in MeOH (10 mL) at 0°C and the mixture was stirred at r.t. for 2 hours. After cooling to 0°C, water (5 mL) and 4% aq. NH_3 (25 mL) were added to the mixture. It was then extracted 4 times with $CHCl_3$/EtOH (3/1). The combined organic solutions were washed with

brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was recrystallized from MeCN/MeOH (1/3, 100 mL) to provide the title compound as a white solid (1.35 g, 3.61 mmol). The filtrate was concentrated and the resulting residue was purified by silica-gel column chromatography to provide more of the title compound as a white solid (0.23 g, 0.61 mmol). Total amount of Compound I from this procedure was 1.57 g (4.22 mmol, 77% yield).

[0121]

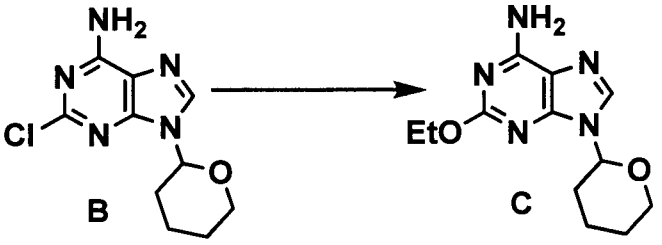
Alternative preparation of Compound I:

10M HCl (9.52 mL, 95.24 mmol) was added dropwise to Compound H (2.46 g, 6.35 mmol) in water (30 mL). The resulting solution was stirred at 70°C for 2 hours and then left to stir at r.t. for 18 hours. The mixture was then diluted with water and neutralised by the drop-wise addition of saturated $NaHCO_3$ whilst stirring rapidly at 0°C. The solid precipitate was collected by filtration and washed with water to give the crude product. Purification by recrystallisation from MeCN/EtOH provided Compound I (1.190 g, 50.2 %) as a white solid. *m/z*: (ES+) MH^+ 374.49; ^1H NMR: 1.26 (3H, t), 2.17 (6H, s), 2.57 (2H, t), 4.21 (2H, q), 4.29 (2H, t), 4.79 (2H, s), 6.41 (2H, br s), 6.76 (1H, d), 7.65 (1H, dd), 8.14 (1H, d), 9.93 (1H, s).

[0122]

Example 1-2: Preparation of 2-ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Alternative preparation of Compound C)

[Chemical formula 27]



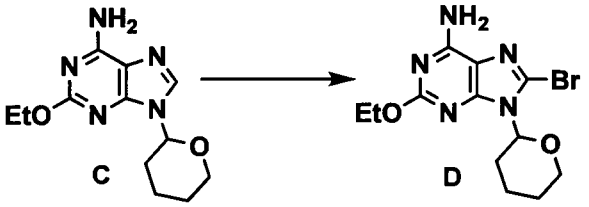
Compound B (4.45 kg, 16.38 mol) was added to sodium ethoxide (20% solution in EtOH, 16.72 g, 49.14 mol) and the mixture was stirred at 80°C for 3 hours. After the reaction mixture was cooled to 12°C, EtOH (16.74 kg, 3.76 w/w) and water (22.26 kg, 5.00 w/w) were added. The mixture was neutralized with acetic acid (2.52 kg, 41.93 mol) at 16°C and extracted with $CHCl_3$ (53.4 kg, 12.0 w/w). The organic layer was concentrated under reduced pressure at 45°C. EtOAc (13.36 kg, 3.00 w/w) was added to the residue and the mixture was concentrated under reduced pressure at 45°C to give a crude solid. EtOAc (13.34 kg, 3.00 w/w) was added to the solid and the mixture was heated to 80°C. Heptane (26.70 kg, 6.00 w/w) was added to the mixture and the mixture was cooled to 14°C over a period of 1 hour. After stirred for 15 hours, the suspension was cooled to 5°C and stirred for 1 hour at the

temperature. The resulting solid was collected by filtration, washed with filtrate liquid and dried under reduced pressure at 45°C to afford the title compound as a pale yellow crystal (4.56 kg, quantitative yield).

[0123]

Example 2-2: Preparation of 8-bromo-2-ethoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Alternative preparation of Compound D)

[Chemical formula 28]

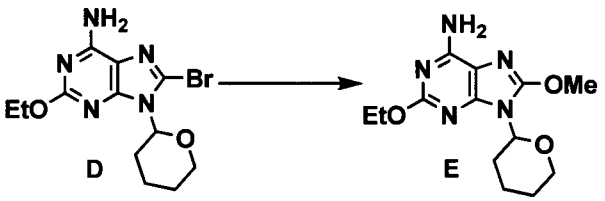


Sodium acetate (3.30 kg, 40.07 mol) was added to a suspension of Compound C (4.22 kg, 16.03 mol) in $CHCl_3$ (105.5 kg, 25.00 w/w) and the mixture was cooled to 2°C. Br_2 (5.12 kg, 32.05 mol) was added to the suspension at 5°C over a 1 hour period and the mixture was stirred for 1 hour at 5°C. Aqueous $NaHCO_3$ (21.10 kg, 6%, 5.00 w/w) was added to the suspension over a period of 5 minutes and was added aqueous $Na_2S_2O_3$ (21.10 kg, 15%, 5.00 w/w) over 10 minutes period and the mixture was stirred for 30 minutes. The organic layer was separated and washed with aqueous $NaHCO_3$ (42.20 kg, 6%, 10.00 w/w) and the aqueous layer was extracted with $CHCl_3$ (21.10 kg, 5.00 w/w). The combined organic layers were concentrated under reduced pressure at 45°C and the resulting solid was dissolved in $CHCl_3$ (12.66 kg, 3.00 w/w) at 25°C. After the solution was stirred for 40 min, heptane (33.76 kg, 8.00 w/w) was added to the solution and the resulting suspension was stirred at 25°C for 16.5 hours. The resulting solid was collected by filtration, washed with filtrate liquid and dried under reduced pressure at 45°C to afford the title compound (4.78 kg, 87.2% yield).

[0124]

Example 3-2: Preparation of 2-ethoxy-8-methoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (Alternative preparation of Compound E)

[Chemical formula 29]



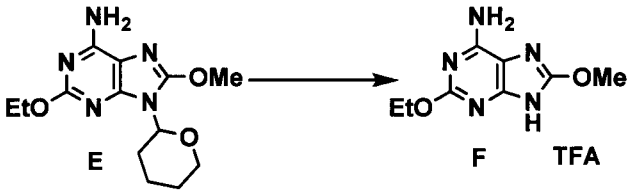
A mixture of Compound D (4.56 kg, 13.33 mol) and MeOH (45.6 kg, 10.00 w/w) was stirred at 28°C for 30 minutes. NaOH (4.56 kg, 1.00 w/w) was added to the solution in a six

portions at interval of 7 minutes. The reaction mixture was heated to 70°C and stirred for 30 minutes. The solution was cooled to 8°C and diluted with water (41.04 kg, 9.00 w/w) over a 20 minutes period. Acetic acid (6.32 kg, 105.17 mol) was added to the mixture over 15 minutes period and the mixture was stirred for 30 minutes. MeOH was removed from the mixture under reduced pressure. The resulting solid was collected by filtration, washed with filtrate liquid and water (22.80 kg, 5.00 w/w) and dried under reduced pressure at 45°C to afford the title compound (3.64 kg, 93.1% yield).

[0125]

Example 4-2: Preparation of 2-ethoxy-8-methoxy-9*H*-purin-6-amine trifluoroacetate salt (Compound F)

[Chemical formula 30]

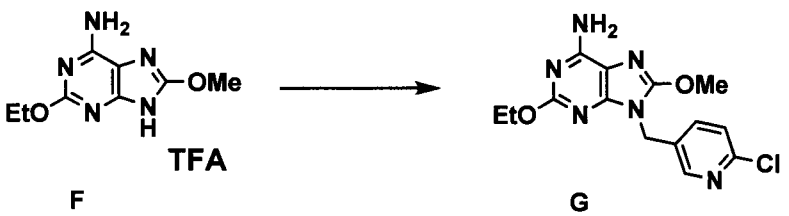


A mixture of Compound E (3.59 kg, 12.24 mol) and MeOH (14.36 kg, 4.00 w/w) was stirred at 27°C for 20 minutes and cooled to 5°C over 15 minutes period. TFA (14.36 kg, 4.00 w/w) was added to the mixture over 40 min period and the mixture was warmed to 30°C and was stirred for 3 hours. After the reaction mixture was concentrated under reduced pressure at 45°C, the mixture was diluted with EtOAc (10.78 kg, 3.00 w/w) and concentrated again under the same conditions to give a crude solid. The solid was suspended in EtOAc (10.77kg, 3.00 w/w) and the mixture was stirred at 27°C for 17 hours. The precipitates were collected by filtration, washed with EtOAc (5.40 kg, 1.50 w/w) and dried under reduced pressure at 45°C to afford the title compound (3.60 kg, 90.9% yield).

[0126]

Example 5-2: Preparation of 9-[(6-chloropyridin-3-yl)methyl]-2-ethoxy-8-methoxy-9*H*-purin-6-amine (Alternative preparation of Compound G)

[Chemical formula 31]



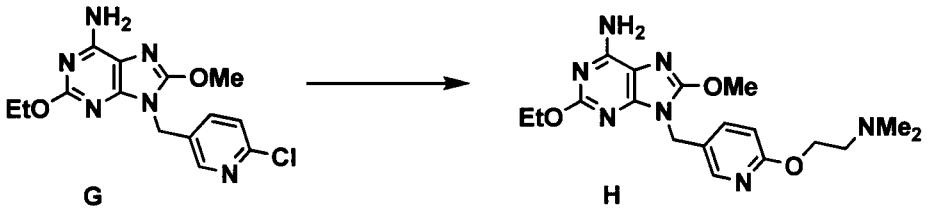
K_2CO_3 (106 g, 767 mmol) was slowly added to a solution of Compound F (82.5 g, 255 mmol) in DMF (291 g) at 50°C under nitrogen atmosphere and the mixture was stirred for 1

hour. 2-Chloro-5-(chloromethyl)pyridine (62.1 g, 383 mmol) was slowly added to the reaction mixture and the mixture was stirred for 2 hours. The mixture was cooled to ambient temperature, diluted with water and stirred for 1 hour. The resulting precipitate was collected by filtration. The wet precipitate was washed by trituration in isopropyl alcohol at 50°C and the suspension was cooled to ambient temperature. The precipitate was collected by filtration and dried in *vacuo*. This product was purified by silica chromatography (eluting with 1% MeOH in $CHCl_3$) and then washed by trituration in toluene. The precipitate was collected by filtration and dried in *vacuo* to afford Compound G (54.4 g, 63.7%) as a white solid.

[0127]

Example 6-2: Preparation of 9-{6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl-2-ethoxy-8-methoxy-9*H*-purin-6-amine (Alternative preparation of Compound H)

[Chemical formula 32]

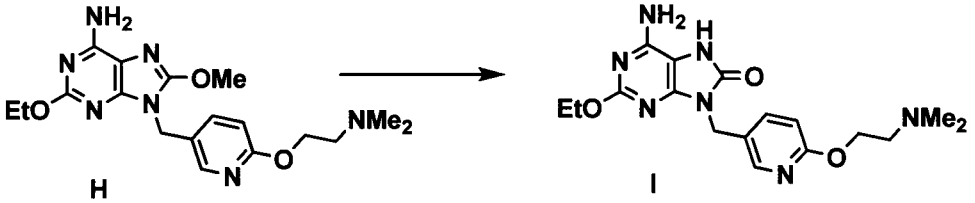


2-(Dimethylamino)ethanol (86.3 g, 968 mmol) was added dropwise to a suspension of NaH (35.2 g, 865 mmol) in 1,4-dioxane (1297 g) over 20 minutes period. The mixture was stirred for 1 hour and then Compound G (54.0 g, 161 mmol) was added to the mixture as a single portion. The reaction mixture was heated to 75°C and stirred for 8.5 hours. After cooling the mixture, 2N aqueous HCl (540 g) and water were added to the mixture in the order. The mixture was extracted with $CHCl_3$ twice. The organic layers were combined together, washed with brine and concentrated *in vacuo*. The resulting residue was dried by azeotropic distillation with ethyl acetate and dissolved in ethyl acetate at 75°C. Hexane was added slowly in the stirred mixture and the mixture was then cooled to 15°C. The precipitate was collected by filtration to provide Compound H (54.2 g, 86.6%) as a white solid.

[0128]

Example 7-2: Preparation of 6-amino-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-2-ethoxy-7*H*-purin-8(9*H*)-one (Alternative preparation of Compound I)

[Chemical formula 33]



10% HCl/MeOH (429 g) was added dropwise to a mixture of Compound H (53.0 g, 137 mmol) in MeOH (79.1 g) and stirred at 50°C for 2 hours. The mixture was cooled to ambient temperature, diluted with water and washed with chloroform. The aqueous layer was separated and neutralized with diluted aqueous ammonia. The mixture was extracted with a mixture of $CHCl_3$ and EtOH. The separated organic phase was washed with brine and concentrated *in vacuo*. Purification of the product by recrystallization from EtOH provided Compound I (40.5 g, 79.3 %) as a white solid.

[0129]

Example 8: Differential Scanning Calorimetry (DSC) of the compound obtained in Example 7.

The calorimetric response of the test sample to increasing temperatures was investigated using a TA Instruments Q1000 Differential Scanning Calorimeter (DSC). Measurements were performed from 10 to 300°C with a ramp rate of 10°C per minute. Approximately 0.5 to 5 mg of the test sample was placed in an aluminum pan with lid (crimped and pinholed) under a flow of nitrogen gas (50 mL/min).

The result is shown in Figure 1. An endothermic peak and an exothermic peak appeared from 260°C.

[0130]

Example 9: X-Ray Powder Diffraction Analyses of the compound obtained in Example 7.

A Panalytical X'pert Alpha1 system with monochromatic CuKα radiation (45 kV and 40 mA) was used for the analysis. The primary optics contained metal mask and an automatic divergence slit. Flat samples were prepared on the zero background plates that were rotated during the measurements. The secondary optics contained soller slits, an automatic anti scatter slit and a monochromator. The diffracted signal was detected with a detector (X'Celerator). Diffraction patterns were collected at $4° \leq 2\theta$ (theta) $\leq 40°$ in a continuous scan mode with 100-second exposure per 0.017°. Raw data were stored electronically. Evaluation was performed on raw or smoothed diffraction patterns.

The results are shown in Figure 2 and Table 1.

[0131]

Table 1 XRD data of the test sample.

[Table 1]

2θ	d-spacing	Relative Intensity (%)
4.5	19.61	100
8.6	10.25	4.3
9.0	9.87	93.4
9.2	9.57	4.3
13.4	6.59	1.2
17.9	4.95	34.0
18.2	4.86	1.4
18.7	4.75	2.7
18.9	4.68	3.4
20.1	4.42	3.6
20.6	4.31	2.7
22.2	4.01	1.1
22.4	3.96	3.5
22.7	3.92	3.2
23.2	3.83	1.8
24.3	3.66	2.0
25.1	3.55	4.2
27.6	3.23	4.2
30.6	2.92	1.5
31.6	2.83	1.1

[0132]

Example 10: Human TLR7 assay

TLR7/NF-kB/SEAPorter™ HEK 293 Cell Line (Imgenex Corporation) is a stably co-transfected cell line which expresses full-length human TLR7 and the secreted alkaline phosphatase (SEAP) reporter gene under the transcriptional control of an NF-kB response element. TLR7 expression in this cell line has been tested by flow cytometry. Transfectants with stable expression were selected using the antibiotic blasticidin and geneticin. TLR signaling leads to the translocation of NF-kB and activation of the promoter results in expression of the SEAP gene.

[0133] TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C according to the following protocol.

Frozen TLR7/NF-kB/SEAP/293 cells were thawed in a water bath incubator set at 37°C and suspended in cell culture medium. The cells were centrifuged at 1,000 rpm for 5 min at 4°C. The supernatant was removed and the cells were resuspended in cell culture medium. The cells were transferred into a 75-cm^2 cell culture flask and cultured in a CO_2 incubator. On the next day, the cell culture medium was replaced with cell culture medium for passage and the cells were continuously cultured in a CO_2 incubator.

[0134] Cells cultured in a 75-cm^2 cell culture flask were washed with PBS (Invitrogen

CORPORATION, Lot No. 814350). Then, thereto was added 0.5 g/L-Trypsin/0.53 mmol/L-EDTA Solution, with Phenol Red (Trypsin/EDTA, Nacalai Tesque, Inc., Lot No. L0N4155) and the cells were incubated at room temperature for 3 min. A cell suspension was prepared by addition of cell culture medium for passage. A portion of the cell suspension was mixed with 3 times the volume of trypan blue staining solution, and live and dead cells were counted, respectively. After confirming that cell viability was greater than 90%, the cell suspension was diluted with cell culture medium for passage to adjust the live cell density to 1-5 × 10^4 cells/mL, seeded in a 75-cm^2 cell culture flask at a volume of 20 mL and cultured in a CO_2 incubator.

[0135] TLR7/NF-kB/SEAP/293 cells cultured in a 75-cm^2 cell culture flask were washed and detached. Assay medium was added and the cells were centrifuged at 1,000 rpm for 5 min at 4°C. The supernatant was removed and the cells were resuspended in assay medium to prepare a cell suspension. A portion of the cell suspension was mixed with 3 times the volume of trypan blue staining solution, and live and dead cells were counted, respectively. After confirming that cell viability was greater than 90%, the cell suspension was diluted with assay medium to adjust the live cell density to 56 × 10^4 cells/mL. This diluted cell suspension was seeded into a 96-well plate at 90 μL/well (5 × 10^4 cells/well) and the cells were cultured in a CO_2 incubator for 16 hours.

[0136] After incubation for 16 hours, 10 μL of Example 7 compound-containing media or vehicle-containing media was added in duplicate to each well of a 96-well plate containing TLR7/NF-kB/SEAP/293 cells for a measurement of several concentrations. The 96-well plate was then placed in a CO_2 incubator and the cells were incubated for 24 hours.

[0137] After incubation for 24 hours, the cell culture supernatant of each well was collected and 2- to 30-fold diluted with assay medium. 20 μL of the diluted cell culture supernatant (sample), each concentration of the Cell-Based Alkaline Phosphatase Standard solutions, or assay medium (standard) was added in duplicate to 180 μL of QUANTI-Blue solution dispensed into a 96-well plate. The 96-well plate was placed in a thermostatic bath set at 37°C and incubated for 1 hour, after which the absorbance was measured by using a microplate reader at a wavelength of 620 nm.

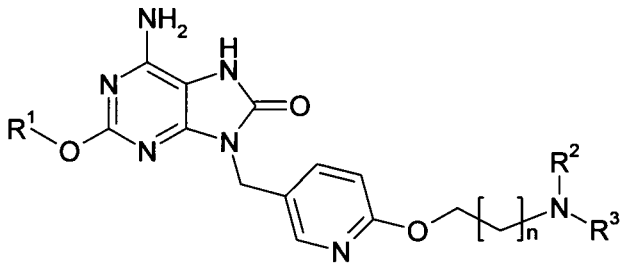
[0138] Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (EC_{50}).

The pEC_{50} values of Example 7 compound in 3 experiments were 7.2, 7.2 and 6.9, respectively. The mean and SD of pEC_{50} of Example 7 compound was 7.1 ± 0.17.

CLAIMS

1. A process for preparing a compound of Formula (III):

[Chemical formula 1]



(III)

wherein:

R^1 is C_{1-6} alkyl;

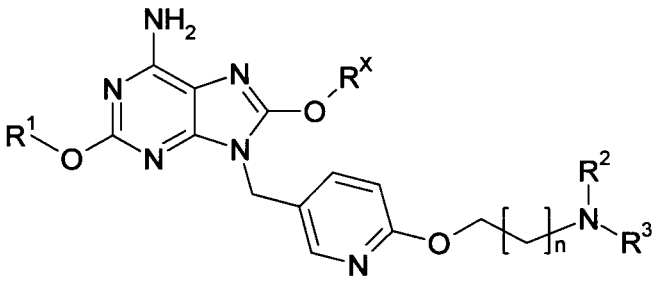
R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or

R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring; and

n is 1, 2 or 3; or a salt thereof;

which comprises a reaction of a compound of Formula (II):

[Chemical formula 2]



(II)

wherein:

R^1, R^2, R^3 and n are the same as defined above; and

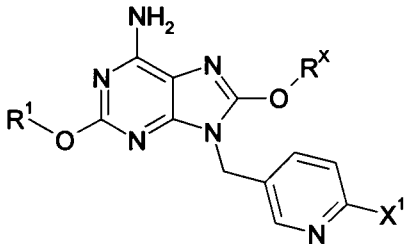
R^X is C_{1-6} alkyl; or a salt thereof;

with an acid.

2. The process according to claim 1, further comprising a step for preparing a compound of Formula (II), or a salt thereof,

which comprises a reaction of a compound of Formula (IV):

[Chemical formula 3]



(IV)

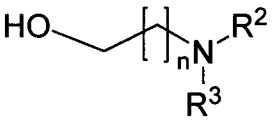
wherein:

R^1 and R^X are the same as defined in claim 1; and

X^1 is a leaving group; or a salt thereof;

with a compound of Formula (V):

[Chemical formula 4]



(V)

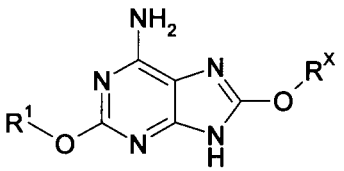
wherein R^2, R^3 and n are the same as defined in claim 1; or a salt thereof;

in the presence of a base.

3. The process according to claim 2, further comprising a step for preparing a compound of Formula (IV), or a salt thereof,

which comprises a reaction of a compound of Formula (VI):

[Chemical formula 5]

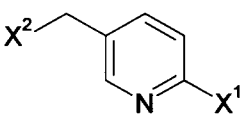


(VI)

wherein R^1 and R^X are the same as defined in claim 1; or a salt thereof;

with a compound of Formula (VII):

[Chemical formula 6]



(VII)

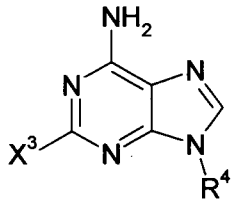
wherein X^1 is the same as defined in claim 2, and X^2 is a leaving group selected from halo and (C_{1-8} hydrocarbyl)sulfonyloxy; or a salt thereof;

in the presence of a base.

4. The process according to claim 3, further comprising a step for preparing a compound of Formula (VI), or a salt thereof,

which comprises reacting a compound of Formula (VIII):

[Chemical formula 7]



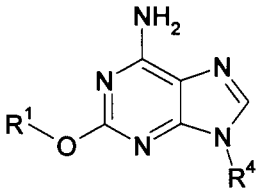
(VIII)

wherein X^3 is a group selected from chloro, bromo and iodo; R^4 is a protecting group selected from tetrahydro-2*H*-pyran-2-yl and tetrahydrofuran-2-yl; or a salt thereof;

with a metal alkoxide salt of Formula 'R^1OM^1', where R^1 is the same as defined in claim 1 and M^1 is an alkali metal;

to obtain a compound of Formula (IX):

[Chemical formula 8]

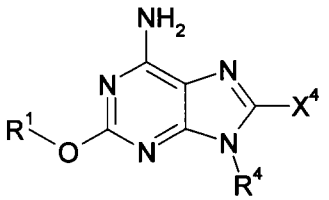


(IX)

wherein R^1 is the same as defined in claim 1 and R^4 is the same as defined above; or a salt thereof;

followed by reacting a compound of Formula (IX) or a salt thereof with a halogenating agent to obtain a compound of Formula (X):

[Chemical formula 9]



(X)

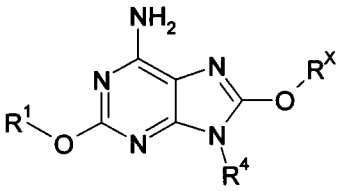
wherein R^1 is the same as defined in claim 1, R^4 are the same as defined above and X^4 is a group selected from chloro, bromo and iodo, or a salt thereof;

followed by reacting a compound of Formula (X) or a salt thereof with an alcohol of Formula

R^XOH, wherein R^X is the same as defined in claim 1, in the presence of a base;

to obtain a compound of Formula (XI):

[Chemical formula 10]



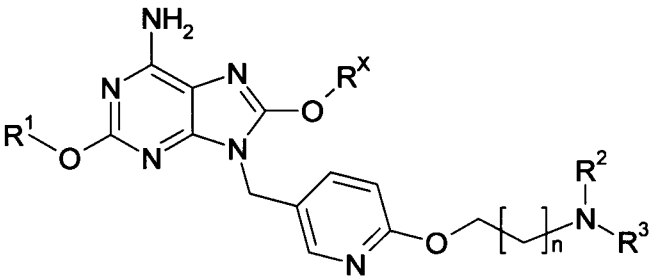
(XI)

wherein R^1 is the same as defined in claim 1 and R^4 is the same as defined above; or a salt thereof;

followed by reacting a compound of Formula (XI) or a salt thereof with an acid.

5. A compound of Formula (II):

[Chemical formula 11]



(II)

wherein:

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl, or

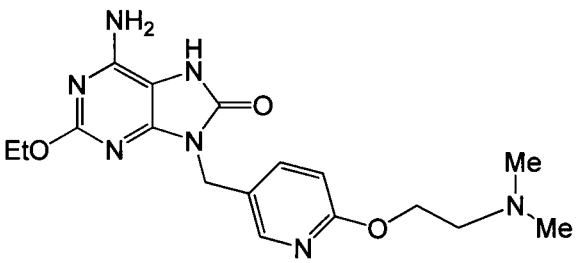
R^2 and R^3 combine together with the nitrogen atom to which they are attached to form a pyrrolidine ring, a morpholine ring, a piperidine ring, or a piperazine ring;

R^X is C_{1-6} alkyl; and

n is 1, 2 or 3; or a salt thereof.

6. A compound of Formula (XII):

[Chemical formula 12]



(XII)

having a crystal form characterised in that the crystal form has an X-ray powder diffraction pattern with specific peaks at 2θ about = 4.5°, 9.0° and 17.9° when measured using CuKα radiation.

Figure 1

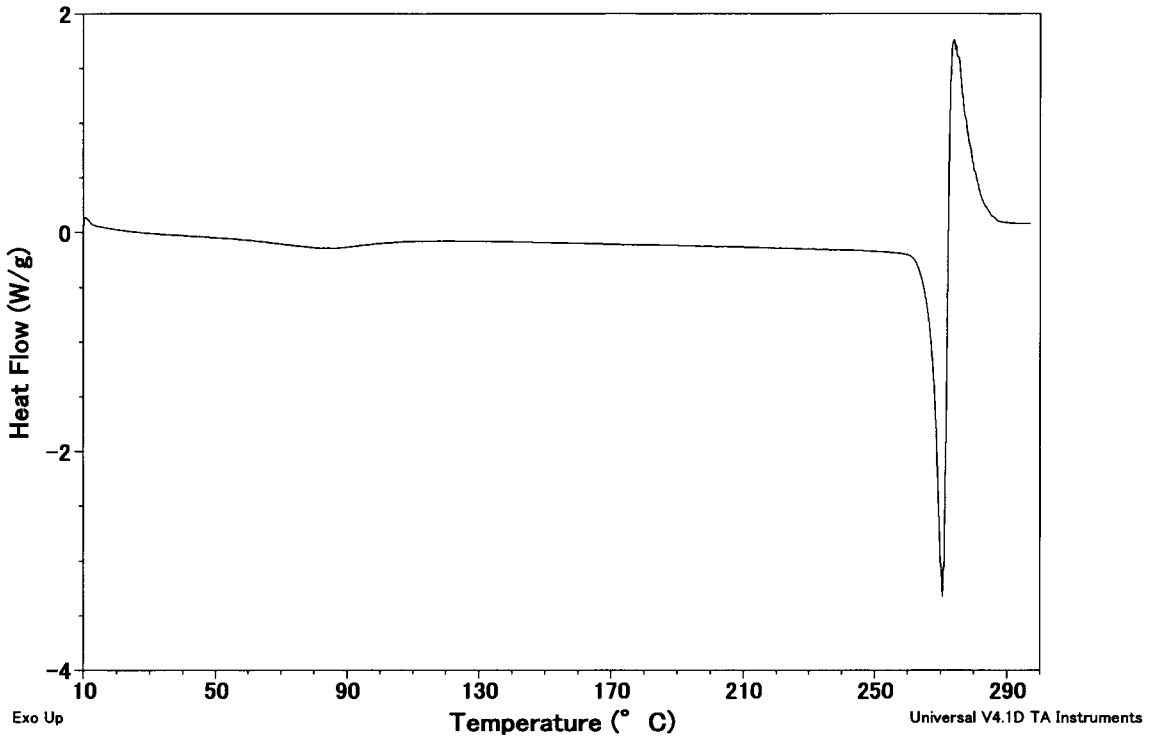


Figure 1 DSC thermogram of the sample.

Figure 2

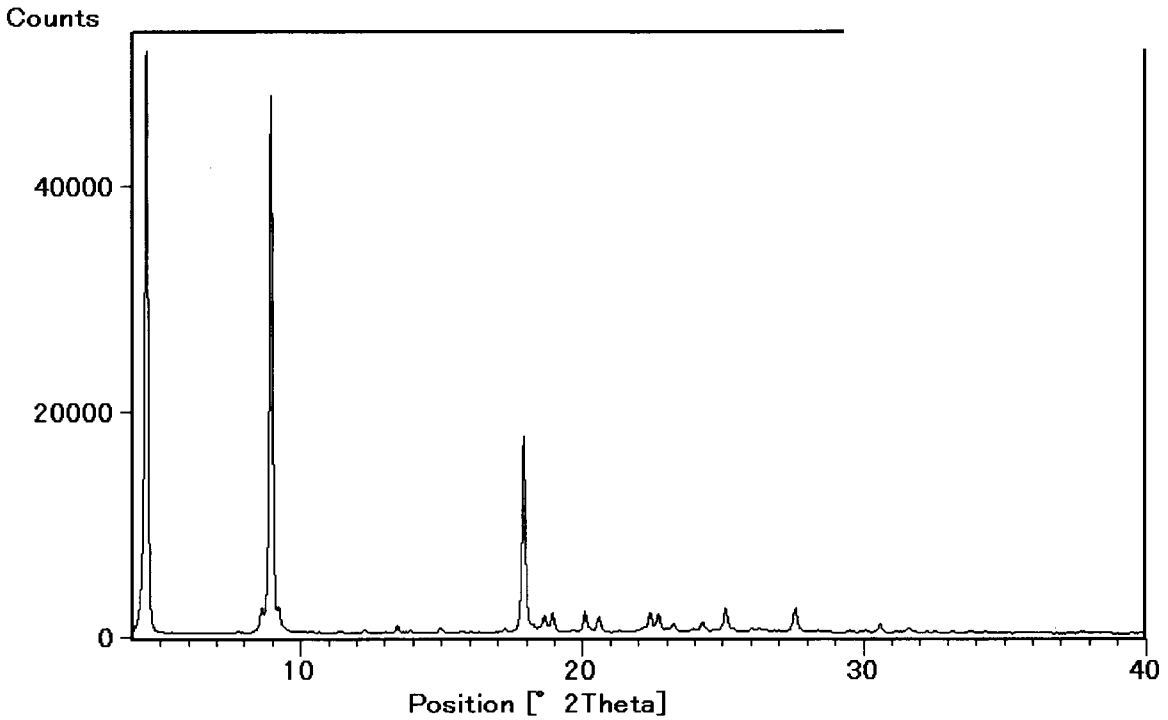


Figure 2 XRD pattern of the test sample.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2011/067018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

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

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, 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.
X	EP 2 133 353 A1 (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 16 December 2009 (2009-12-16) cited in the application	6
A	page 11, last compound	1-5
X	EP 1 939 201 A1 (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 2 July 2008 (2008-07-02) compounds in paragraphs [0295], [0302], [317], [0337]	1-5

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

☒ See patent family annex.

* Special categories of cited documents :

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"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
6 October 2011	17/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2011/067018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2133353 A1	16-12-2009	AR 065784 A1	01-07-2009
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		EC SP099638 A	30-10-2009
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		US 2011028715 A1	03-02-2011
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		US 2009105212 A1	23-04-2009