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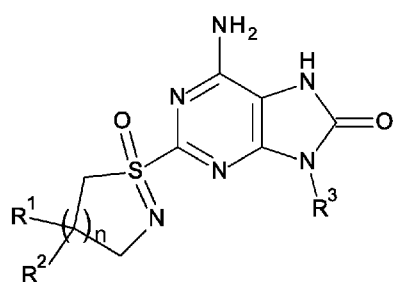
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(54) Title: NOVEL CYCLICSULFONIMIDOYLPURINONE COMPOUNDS AND DERIVATIVES FOR THE TREATMENT AND PROPHYLAXIS OF VIRUS INFECTION



(I)

(57) Abstract: The present invention relates to compounds of formula (I), wherein R¹, R² and R³ and n are as described herein, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof, and compositions including the compounds and methods of using the compounds.



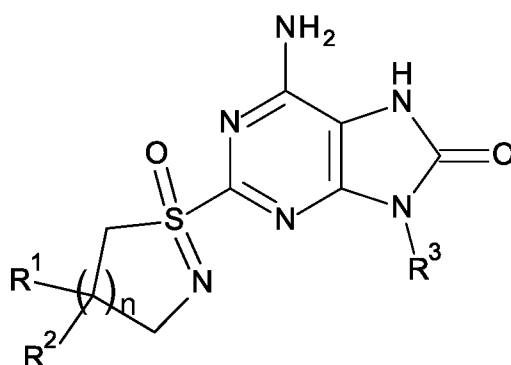
Novel cyclicsulfonimidoylpurinone compounds and derivatives for the treatment and prophylaxis of virus infection

The present invention relates to novel sulfonimidoylpurinones and their derivatives that have Toll-like receptor agonism activity and their prodrugs thereof, as well as their manufacture, pharmaceutical compositions containing them and their potential use as medicaments.

5

FIELD OF THE INVENTION

The present invention relates to compounds of formula (I),



10 wherein R^1 , R^2 , R^3 and n are described below, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Toll-like receptors (TLRs) detect a wide range of conserved pathogen-associated molecular patterns (PAMPs). They play an important role of sensing invading pathogens and subsequent initiation of innate immune responses. There are 10 known members of the TLR family in
15 human, which are type I transmembrane proteins featuring an extracellular leucine-rich domain and a cytoplasmic tail that contains a conserved Toll/ interleukin (IL)-1 receptor (TIR) domain. Within this family, TLR3, TLR7 TLR8, and TLR9 are located within endosomes. TLR7 can be activated by binding to a specific small molecule ligand (i.e., TLR7 agonist) or its native ligand (i.e., single-stranded RNA, ssRNA). Following binding of ssRNA to TLR7, the receptor in its
20 dimerized form is believed to undergo a structural change leading to the subsequent recruitment

of adapter proteins at its cytoplasmic domain, including the myeloid differentiation primary response gene 88 (MyD88). Following the initiation of the receptor signalling cascade via the MyD88 pathway, cytoplasmic transcription factors such as interferon regulatory factor 7 (IRF-7) and nuclear factor kappa B (NF- κ B) are activated. These transcription factors then translocate to the nucleus and initiate the transcription of various genes, e.g., IFN- α and other antiviral cytokine genes. TLR7 is predominately expressed on plasmacytoid cells, and also on B-cells. Altered responsiveness of immune cells might contribute to the reduced innate immune responses during chronic viral infections. Agonist-induced activation of TLR7 might therefore represent a novel approach for the treatment of chronic viral infections. (D. J Connolly and L. AJ O'Neill, *Current Opinion in Pharmacology* 2012, 12:510-518, P. A. Roethle *et al*, *J. Med. Chem.* 2013, 56, 7324-7333).

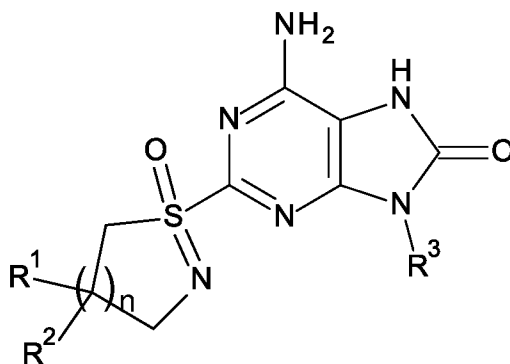
The current therapy of chronic HBV infection is based on two different types of drugs: the traditional antiviral nucleos(t)ide analogues and the more recent Pegylated IFN- α (PEG-IFN- α). The oral nucleos(t)ide analogues act by suppressing the HBV replication. This is a life-long course of treatment during which drug resistance often occurs. As an alternative option, Pegylated IFN- α (PEG-IFN- α) has been used to treat some chronic infected HBV patients within finite therapy duration. Although it has achieved seroconversion in HBeAg at least in a small percentage of HBV patients, the adverse effect makes it poorly tolerable. Notably, functional cure defined as HBsAg seroconversion is very rare with both current therapies. A new generation therapeutic option to treat HBV patients for a functional cure is therefore of urgent need. Treatment with an oral TLR7 agonist represents a promising solution to provide greater efficacy with better tolerability. Pegylated IFN- α (PEG-IFN- α) is currently used to treat chronic HBV and is an alternative to potentially life-long treatment with antiviral nucleos(t)ide analogues. In a subset of chronic HBV patients, PEG-IFN- α therapy can induce sustained immunologic control of the virus following a finite duration of therapy. However, the percentage of HBV patients that achieve seroconversion with interferon therapy is low (up to 27% for HBeAg-positive patients) and the treatment is typically poorly tolerated. Furthermore, functional cure (defined as HBsAg loss and seroconversion) is also very infrequent with both PEG-IFN- α and nucleos(t)ide treatment. Given these limitations, there is an urgent need for improved therapeutic options to treat and induce a functional cure for chronic HBV. Treatment with an oral, small-molecule TLR7 agonist is a promising approach that has the potential to provide greater efficacy and tolerability (T. Asselah *et al*, *Clin Liver Dis* 2007, 11, 839-849).

In fact, several identified TLR7 agonists have been considered for therapeutic purposes. So far Imiquimod (ALDARATM) is a U.S. FDA approved TLR7 agonist drug for topical use to treat skin lesions by human papillomavirus. The TLR7/8 dual agonist resiquimod (R-848) and the TLR7 agonist 852A have been evaluated for treating human genital herpes and chemotherapy-refractory metastatic melanoma, respectively. ANA773 is an oral pro-drug TLR7 agonist, developed for the treatment of patients with chronic hepatitis C virus (HCV) infection and chronic hepatitis B infection. GS-9620 is an orally available TLR7 agonist. A phase Ib study demonstrated that treatment with GS-9620 was safe, well tolerated and resulted in dose-dependent ISG15 mRNA induction in patients with chronic hepatitis B (E. J. Gane *et al*, Annu Meet Am Assoc Study Liver Dis (November 1-5, Washington, D.C.) 2013, Abst 946). Therefore there is high unmet clinical need for developing potent and safe TLR7 agonists as new HBV treatment to offer more therapeutic solutions or replace existing partly effective treatment.

SUMMARY OF THE INVENTION

The present invention provides a series of novel 6-amino-2-sulfonimidoyl-9-substituted-7H-purin-8-one compounds that have Toll-like receptor agonism activity and their prodrugs. The invention also provides the bio-activity of such compounds to induce SEAP level increase by activating Toll-like receptors, such as TLR7 receptor, the metabolic conversion of prodrugs to parent compounds in the presence of human hepatocytes, and the therapeutic or prophylactic use of such compounds and their pharmaceutical compositions comprising these compounds and their prodrugs to treat or prevent infectious disease like HBV or HCV. The present invention also provides compounds with superior activity. In addition, the compounds of formula (I) also show good solubility, selectivity over TLR8, in vitro and in vivo clearance, Ames, hERG, GSH, PK and safety profiles.

The present invention relates to novel compounds of formula (I),



wherein

R¹ and R² are independently selected from H and C₁₋₆alkyl;

R³ is benzyl, said benzyl being unsubstituted or substituted by halogen, cyano, C₁₋₆alkyl or C₁₋₆alkoxy;

5 n is 0, 1, 2, 3, 4, 5 or 6;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

The invention also relates to their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula (I), thereof as TLR7 agonist. Accordingly, the compounds of formula (I) are useful for the
10 treatment or prophylaxis of HBV and/or HCV infection with Toll-like receptors agonism.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention
15 belongs. Furthermore, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention.

DEFINITIONS

The term “C₁₋₆alkyl” denotes a saturated, linear or branched chain alkyl group containing 1
20 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl and *n*-propyl.

The term “C₁₋₆alkoxy” denotes a group of the formula C₁₋₆alkyl-O-. Examples of C₁₋₆alkoxy group include, but not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy and *tert*-butoxy. Particular “C₁₋₆alkoxy” groups are methoxy, ethoxy and isopropoxy.
25 A more particular C₁₋₆alkoxy group is ethoxy.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term “enantiomer” denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term “diastereomer” denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities.

5 The term “pharmaceutically acceptable salts” denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

10 The term “pharmaceutically acceptable acid addition salt” denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, 15 ethanesulfonic acid, *p*-toluenesulfonic acid, and salicylic acid.

The term “pharmaceutically acceptable base addition salt” denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic 20 nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethylamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, 25 methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and polyamine resins.

Compounds of the general formula (I) and their prodrugs which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the 30 enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-

tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

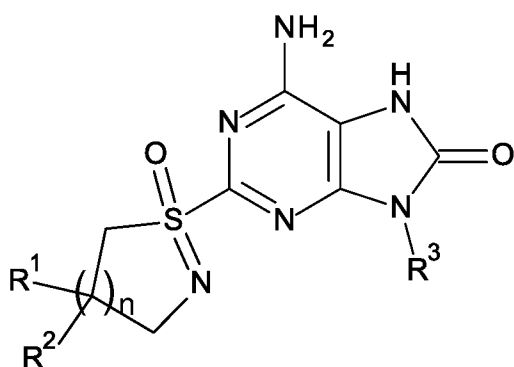
“A pharmaceutically active metabolite” is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. After entry into the body, most drugs are substrates for chemical reactions that may change their physical properties and biologic effects. These metabolic conversions, which usually affect the polarity of the compounds of the invention, alter the way in which drugs are distributed in and excreted from the body. However, in some cases, metabolism of a drug is required for therapeutic effect.

The term “therapeutically effective amount” denotes an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

The term “pharmaceutical composition” denotes a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

TLR7 AGONIST

The present invention relates to (i) a compound of formula (I),



wherein

R¹ and R² are independently selected from H and C₁₋₆alkyl;

R³ is benzyl, said benzyl being unsubstituted or substituted by halogen, cyano, C₁₋₆alkyl or C₁₋₆alkoxy;

5 n is 0, 1, 2, 3, 4, 5 or 6;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (ii) a compound of formula (I), wherein

R¹ and R² are simultaneously H or C₁₋₆alkyl;

R³ is benzyl, said benzyl being unsubstituted or substituted by halogen, C₁₋₆alkyl or C₁₋₆alkoxy;

10 n is 1, 2 or 3;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (iii) a compound of formula (I), wherein R¹ and R² are independently selected from H and methyl.

15

A further embodiment of present invention is (iv) a compound of formula (I), wherein R¹ and R² are simultaneously H or methyl.

A further embodiment of present invention is (v) a compound of formula (I), wherein R³ is

20 benzyl, methylbenzyl, fluorobenzyl, chlorobenzyl or methoxybenzyl.

A further embodiment of present invention is (vi) a compound of formula (I), wherein n is 1 or 2.

25 Another embodiment of present invention is (vii) a compound of formula (I), wherein

R¹ and R² are simultaneously H or methyl;

R³ is benzyl, methylbenzyl, fluorobenzyl, chlorobenzyl or methoxybenzyl;

n is 1 or 2;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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In another embodiment of the present invention, compounds of the present invention are selected from:

6-Amino-9-benzyl-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one;

6-Amino-2-(1-*oxo*-4,5-dihydro-3*H*-isothiazol-1-yl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-*oxo*-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one;
6-Amino-9-[(4-methoxyphenyl)methyl]-2-(1-*oxo*-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one;
5 6-Amino-9-[(4-fluorophenyl)methyl]-2-(1-*oxo*-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-*oxo*- λ^6 -thia-2-azacyclohexen-1-yl)-7*H*-purin-8-one;
and
6-Amino-9-benzyl-2-(4,4-dimethyl-1-*oxo*-3,5-dihydroisothiazol-1-yl)-7*H*-purin-8-one;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

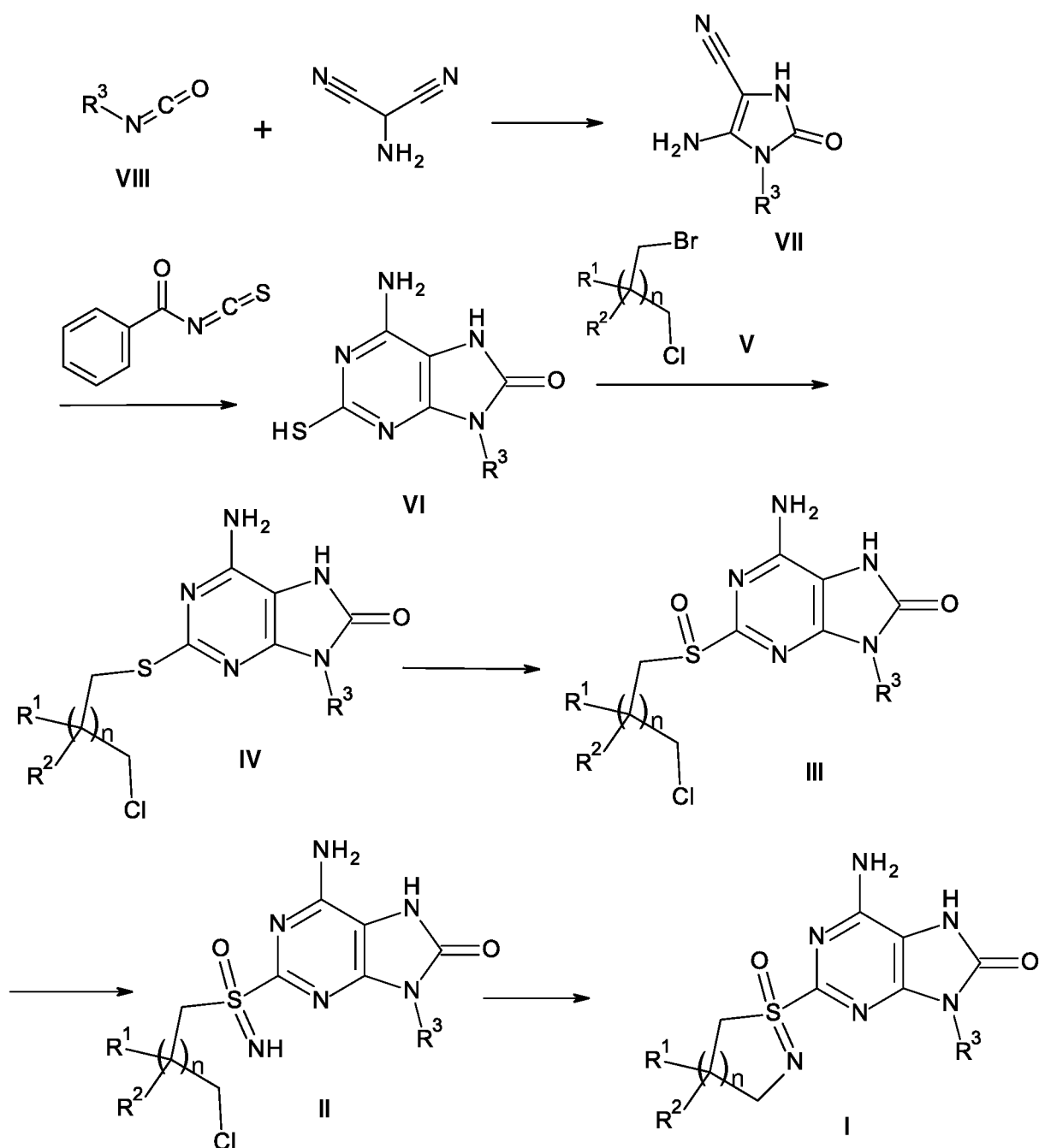
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SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R¹ to R³ and n
15 are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

Scheme 1

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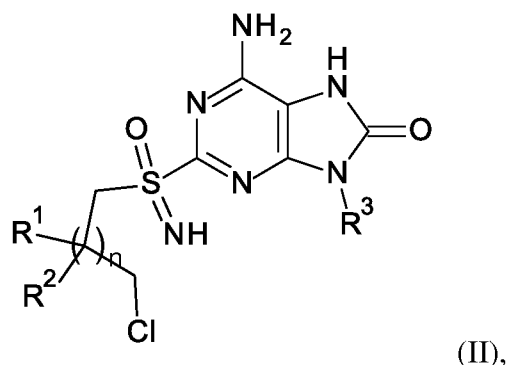


A compound of formula **VII** is prepared by cyclization of isocyanate **VIII** with aminomalononitrile *p*-toluenesulfonate. The bicycle compound of formula **VI** is synthesized by reaction of compound of formula **VII** with benzoyl isothiocyanate in the presence of inorganic base, such as sodium hydroxide or potassium hydroxide. Alkylation of bicycle compound of formula **VI** with alkylhalide **V** in the presence of base, such as K₂CO₃, NaH or Cs₂CO₃, gives compound of formula **IV**. Compound of formula **III** is prepared by oxidation of compound of formula **IV** with an oxidant, such as *meta*-chloroperoxybenzoic acid, urea-hydrogen peroxide adduct or HIO₄. Compound of formula **II** is obtained by imination of compound of formula **III**

with imination reagent, such as sodium azide in acid, said acid is, for example, Eaton's reagent or PPA. Compound of formula **I** is obtained by cyclization of compound of formula **II** in the presence of a base, such as sodium hydride.

This invention also relates to a process for the preparation of a compound of formula (I) comprising the following reaction:

(a) the reaction of a compound of formula (II),



with a base;

wherein R¹, R², R³ and n are defined above.

In step (a), the base can be for example sodium hydride.

A compound of formula (I) when manufactured according to the above process is also an object of the invention.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) are formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (I) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to activate TLR7 receptor and lead to produce INF- α and other cytokines, which can be used, but not limited, for the treatment or prevention of hepatitis B and/or C viral infected patients.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.1 to 50 mg/kg, alternatively about 0.1 to 30 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 20 to about 1000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients.

Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant
5 presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 20 to 1000 mg of the compound of the invention compounded with about 30 to 90 mg anhydrous lactose, about 5
10 to 40 mg sodium croscarmellose, about 5 to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 20 to 1000
15 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salts or enantiomers or diastereomers thereof.

20 In a further embodiment includes a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salts or enantiomers or diastereomers thereof, together with a pharmaceutically acceptable carrier or excipient.

Another embodiment includes a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salts or enantiomers or diastereomers thereof for use
25 in the treatment of hepatitis B virus infection.

INDICATIONS AND METHODS OF TREATMENT

The present invention provides methods for treating or preventing a hepatitis B viral infection and/or hepatitis C viral infection in a patient in need thereof.

The present invention further provides methods for introducing a therapeutically effective amount of a compound of formula (I) or other compounds of the invention into the blood stream of a patient for the treatment and/or prevention of hepatitis B and/or C viral infection.

The methods of the present invention are particularly well suited for human patients. In particular, the methods and doses of the present invention can be useful for, but not limited to, HBV and/or HCV infected patients. The methods and doses of the present invention are also useful for patients undergoing other antiviral treatments. The prevention methods of the present invention are particularly useful for patients at risk of viral infection. These patients include, but are not limited to health care workers, *e.g.*, doctors, nurses, hospice care givers; military personnel; teachers; childcare workers; patients traveling to, or living in, foreign locales, in particular third world locales including social aid workers, missionaries, and foreign diplomats. Finally, the methods and compositions include the treatment of refractory patients or patients resistant to treatment such as resistance to reverse transcriptase inhibitors, protease inhibitors, *etc.*

Another embodiment includes a method of treating or preventing hepatitis B viral infection and/or hepatitis C viral infection in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or enantiomers, diastereomers, prodrugs or pharmaceutically acceptable salts thereof.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

ABBREVIATIONS

	aq.	aqueous
25	CDCl ₃ :	deuterated chloroform
	CD ₃ OD:	deuterated methanol
	CDI:	<i>N,N'</i> -carbonyl diimidazole
	DIEPA:	<i>N, N</i> -diethylpropylamine
	DMF:	dimethyl formamide
30	DMSO:	dimethyl sulfoxide
	EC ₅₀ :	the molar concentration of an agonist, which produces 50% of the maximum possible response for that agonist.

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	EtOAc or EA:	ethyl acetate
	hr(s):	hour(s)
	HPLC:	high performance liquid chromatography
	MS (ESI):	mass spectroscopy (electron spray ionization)
5	m-CPBA:	3-chloroperbenzoic acid
	min(s)	minute(s)
	MTEB:	methyl <i>tert</i> -butyl ether
	NMR:	nuclear magnetic resonance
	obsd.	observed
10	PE:	petroleum ether
	PMB:	<i>p</i> -methoxybenzyl
	PPA:	polyphosphoric acid
	RT or rt:	room temperature
	sat.	saturated
15	TFA:	trifluoroacetic acid
	THF:	tetrahydrofuran
	TEA:	triethylamine
	V/V	volume ratio

GENERAL EXPERIMENTAL CONDITIONS

20 Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 µm; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

25 Intermediates and final compounds were purified by preparative HPLC on reversed phase column using X Bridge™ Perp C₁₈ (5 µm, OBD™ 30 × 100 mm) column or SunFire™ Perp C₁₈ (5 µm, OBD™ 30 × 100 mm) column.

LC/MS spectra were obtained using a Waters UPLC-SQD Mass. Standard LC/MS conditions were as follows (running time 3 minutes):

30 Acidic condition: A: 0.1% formic acid and 1% acetonitrile in H₂O; B: 0.1% formic acid in acetonitrile;
Basic condition: A: 0.05% NH₃·H₂O in H₂O; B: acetonitrile.

-15-

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion (M+H)⁺.

NMR Spectra were obtained using Bruker Avance 400MHz.

All reactions involving air-sensitive reagents were performed under an argon atmosphere.

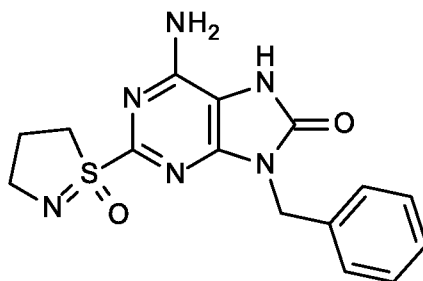
- 5 Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

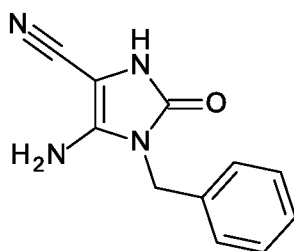
10

Example 1

6-Amino-9-benzyl-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one

**1**

Step 1: Preparation of 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile

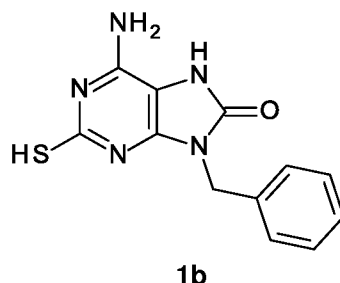
**1a**

- 15 To a solution of aminomalononitrile *p*-toluenesulfonate (200 g, 790 mmol) in dry THF (2.5 L) was added isocyanatomethylbenzene (110 g, 830 mmol) and DIPEA (75 g, 577 mmol) at 20 °C. After stirred at RT for 16 hrs, the reaction was concentrated *in vacuo* and the residue was suspended in water (2.0 L) to form grey precipitate which was collected by filtration. The filtrate was extracted with DCM/*i*-PrOH (v/v = 4/1, 1 L) three times. The organic layer was dried over
- 20 Na₂SO₄ and concentrated *in vacuo*. The residue and the filter cake were dissolved in a mixture of THF (800 mL) and sodium hydroxide solution (1N, 1600 mL) and stirred at 50 °C for 1 hr. The separated aq. layer was neutralized with 10 wt.% sodium hydrogen sulfate solution and extracted

-16-

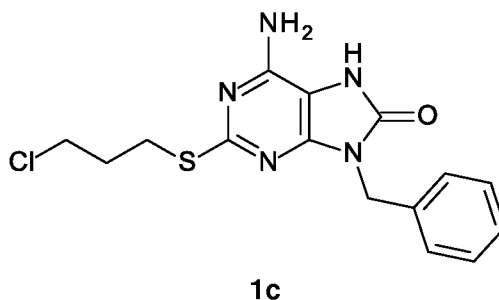
with EtOAc (1 L) four times. The separated organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile (164.0 g, compound **1a**) as a grey solid, which was used in the next step without further purification. MS obsd. (ESI⁺) [(M+H)⁺]: 215.

5 Step 2: Preparation of 6-amino-9-benzyl-2-sulfanyl-7H-purin-8-one



To a solution of 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile (82.0 g, compound **1a**) in THF (2 L) was added benzoylisothiocyanate (155 g) dropwise. After being stirred at RT for 16 hrs, the reaction mixture was concentrated *in vacuo*. The residue was triturated in THF (1 L) and the resulting precipitate was collected by filtration. To a solution of the obtained precipitate in THF (500 mL) was added sodium hydroxide (2 N, 500 mL). The mixture was stirred at 80 °C for 20 hrs and then cooled to RT. The reaction mixture was acidified with 15 wt.% aq. potassium hydrogen sulfate solution to bring the pH to 5. The resulting precipitate was collected by filtration and dried *in vacuo* to give a crude product of 6-amino-9-benzyl-2-sulfanyl-7H-purin-8-one (60.0 g, compound **1b**) as a yellow solid, which was used in the next step without further purification. MS obsd. (ESI⁺) [(M+H)⁺]: 274.

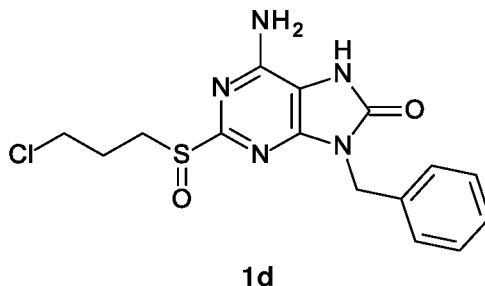
Step 3: Preparation of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7H-purin-8-one



To a mixture of 6-amino-9-benzyl-2-sulfanyl-7H-purin-8-one (80 mg, compound **1b**) and potassium carbonate (80.8 g, 586 mmol) in DMF (1 L) was added 1-bromo-3-chloropropane (50.5 g). The mixture was stirred at 20 °C for 16 hrs. The solvent was removed *in vacuo* and the residue was suspended in water (1.5 L). The reaction mixture was filtered and the filter cake was washed with MTBE (400 mL) and dried *in vacuo*. 6-Amino-9-benzyl-2-(3-

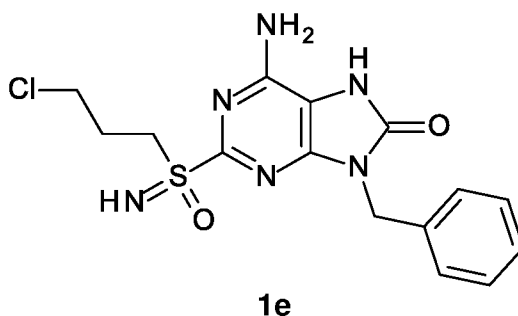
chloropropylsulfanyl)-7*H*-purin-8-one (85 g, compound **1c**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 350.

Step 4: Preparation of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one



- 5 To a solution of *m*-CPBA (47.5 g, 274 mmol) in THF (100 mL) was added dropwise a mixture of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (80 g, 229 mmol, compound **1c**) in THF (900 mL) at 0 °C. The mixture was stirred at this temperature for 2 hrs. The precipitate was collected by filtration and dried *in vacuo*. 6-Amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (60 g, compound **1d**) was obtained as a yellow solid, which was used in the next step without further purification. MS obsd. (ESI⁺) [(M+H)⁺]: 366.
- 10

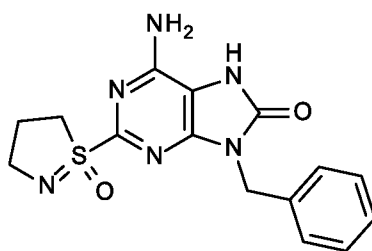
Step 5: Preparation of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one



- To a solution of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (10 g, 27.4 mmol, compound **1d**) in Eaton's reagent (80 mL, phosphorus pentoxide, 7.5 wt.% in methanesulphonic acid) was added sodium azide (4.5 g, 68.5 mmol) at 50 °C. After being stirred at this temperature for 30 min and cooled to RT. Three parallel reactions were performed using the same reaction conditions and three batches of the resulting mixture were combined. Then the reaction mixture was carefully poured into ammonium hydroxide solution (1.5 L, 1M) at 0 °C. Yellow precipitate was formed and filtered, the filter cake was washed with THF (200 mL) and dried *in vacuo*. 6-Amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one (17.6 g, compound **1e**) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 381.
- 15
- 20

Step 6: Preparation of 6-amino-9-benzyl-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one

-18-

**1**

To a solution of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (17.6 g, 46.3 mmol, compound **1e**) in DMF (170 mL) was added NaH (4.6 g, 60 wt.%, 116 mmol).at 0 °C. After being stirred at 20 °C for 10 hrs, the reaction mixture was poured into sat. NH₄Cl

5 solution (1 L) and the resulting precipitate was collected by filtration. The filtrate was extracted with DCM/*i*-PrOH (v/v = 4/1, 500 mL) three times and the organic layer was dried over Na₂SO₄ and concentrated. The residue and filter cake were combined, washed with MeOH (200 mL) and THF (200 mL), and purified by HPLC 6-Amino-9-benzyl-2-(1-*oxo*-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one (20 mg, **Example 1**) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.80 (br s, 1H), 7.23-7.35 (m, 5H), 7.07 (br s, 2H), 4.94 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.81 (m, 1H), 3.31-3.42 (m, 1H), 3.12-3.16 (m, 1H), 2.23-2.34 (m, 1H), 2.12-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 345.

Separation of compound of **Example 1** (3.0 g) by chiral HPLC affords **Example 1-A** (1.0 g, faster eluting) and **Example 1-B** (1.05 g, slower eluting) as white solids with methanol 5%-
15 40% (0.05%DEA)/CO₂ on ChiralPak OD-3 column.

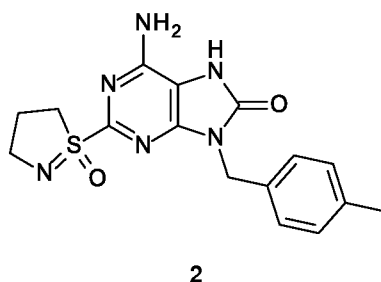
Example 1-A: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.57 (br s, 1H), 7.23-7.35 (m, 5H), 6.99 (br s, 2H), 4.94 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.81 (m, 1H), 3.31-3.42 (m, 1H), 3.09-3.19 (m, 1H), 2.23-2.35 (m, 1H), 2.12-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 345.

Example 1-B: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.57 (br s, 1H), 7.23-7.35 (m, 5H), 7.00 (br s, 2H), 4.95 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.81 (m, 1H), 3.31-3.42 (m, 1H), 3.10-3.19 (m, 1H), 2.22-2.34 (m, 1H), 2.12-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 345.

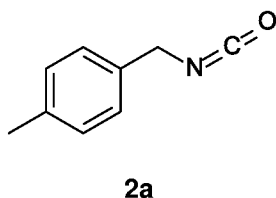
Example 2

6-Amino-2-(1-*oxo*-4,5-dihydro-3H-isothiazol-1-yl)-9-(*p*-tolylmethyl)-7H-purin-8-one

-19-

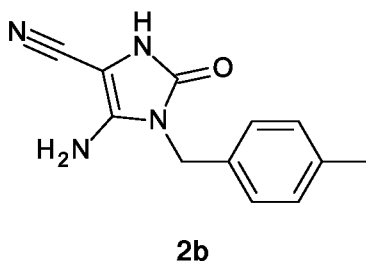


Step 1: Preparation of 1-(isocyanatomethyl)-4-methyl-benzene



A solution of *p*-tolylmethanamine (50.0 g, 413.2 mmol) and Et₃N (83.4 g, 826.4 mmol) in DCM (0.8 L) was added dropwise into a solution of triphosgene (40.5 g, 136.3 mmol) in DCM (1.2 L) at -78 °C under nitrogen. The reaction mixture was stirred at this temperature for 1 h and then warmed to 20 °C and stirred for another 12 hrs. Then the mixture was diluted with DCM (2 L) and the resulting solid was removed by filtration. The filtrate was concentrated *in vacuo* to give the crude product as a yellow oil, which was purified by vacuum distillation (b.p. 150 °C, 10 mmHg) to give 1-(isocyanatomethyl)-4-methyl-benzene (30.0 g, compound **2a**) as a colorless oil.

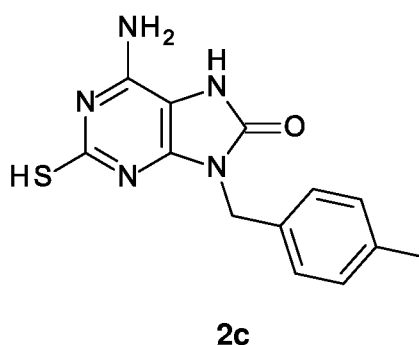
Step 2: Preparation of 4-amino-2-oxo-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile



Compound **2b** was prepared in analogy to **Step 1** of **Example 1** by using 1-(isocyanatomethyl)-4-methyl-benzene (compound **2a**) instead of isocyanatomethylbenzene. 4-amino-2-oxo-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile (40.0 g, compound **2b**) was obtained as a grey solid. MS obsd. (ESI⁺) [(M+H)⁺]: 229.

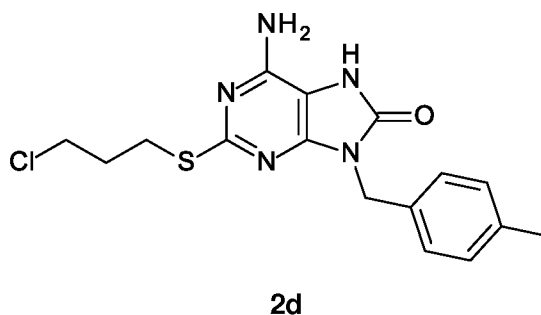
Step 3: Preparation of 6-amino-9-(*p*-tolylmethyl)-2-sulfanylmethyl-7*H*-purin-8-one

-20-



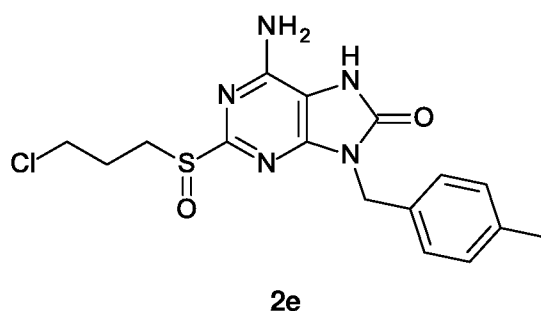
Compound **2c** was prepared in analogy to **Step 2** of **Example 1** by using 4-amino-2-oxo-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile (compound **2b**) instead of 4-amino-3-benzyl-2-oxo-1*H*-imidazole-5-carbonitrile (compound **1a**). 6-Amino-9-(*p*-tolylmethyl)-2-sulfany-7*H*-purin-8-one (30.0 g, compound **2c**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 288.

Step 4: Preparation of 6-amino-2-(3-chloropropylsulfanyl)-9-(p-tolylmethyl)-7*H*-purin-8-one



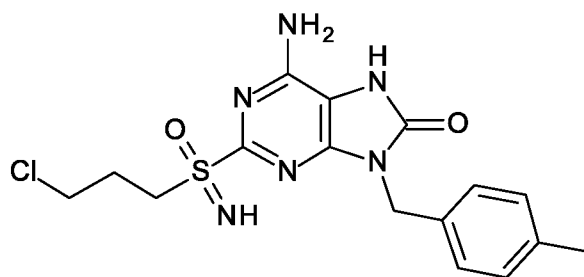
Compound **2d** was prepared in analogy to **Step 3** of **Example 1** by using 6-amino-9-(*p*-tolylmethyl)-2-sulfany-7*H*-purin-8-one (compound **2c**) instead of 6-amino-9-benzyl-2-sulfany-7*H*-purin-8-one (compound **1b**). 6-Amino-2-(3-chloropropylsulfanyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (20.0 g, compound **2d**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 364.

Step 5: Preparation of 6-amino-2-(3-chloropropylsulfinyl)-9-(p-tolylmethyl)-7*H*-purin-8-one



Compound **2e** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-2-(3-chloropropylsulfanyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (compound **2d**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **1c**). 6-Amino-2-(3-chloropropylsulfanyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (15.0 g, compound **2e**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 380.

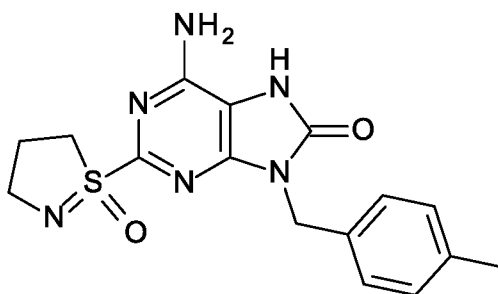
Step 6: Preparation of 6-amino-2-(3-chloropropylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one



2f

Compound **2f** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-2-(3-chloropropylsulfanyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (compound **2e**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(3-chloropropylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (11.0 g, compound **2f**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 395.

Step 7: Preparation of 6-amino-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one



2

Example 2 was prepared in analogy to **Step 6** of **Example 1** by using 6-amino-2-(3-chloropropylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (compound **2f**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one (compound **1e**). 6-Amino-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (6.0 g, **Example 2**) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.58 (br s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.98 (br s, 2H), 4.89 (s, 2H), 4.02-4.08 (m, 1H), 3.74-

3.80 (m, 1H), 3.33-3.41 (m, 1H), 3.10-3.18 (m, 1H), 2.22-2.34 (m, 1H), 2.26 (s, 3H), 2.11-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 359.

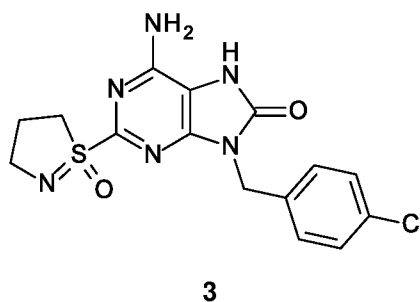
Separation of compound of **Example 2** (5.5 g) by chiral HPLC affords **Example 2-A** (faster eluting, 1.84 g) and **Example 2-B** (slower eluting, 2.04 g) as white solids with methanol
5 5%-40% (0.05%DEA)/CO₂ on ChiralPak OD-3 column.

Example 2-A: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.56 (br s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.99 (br s, 2H), 4.89 (s, 2H), 4.02-4.08 (m, 1H), 3.74-3.80 (m, 1H), 3.33-3.41 (m, 1H), 3.10-3.18 (m, 1H), 2.22-2.34 (m, 1H), 2.26 (s, 3H), 2.11-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 359.

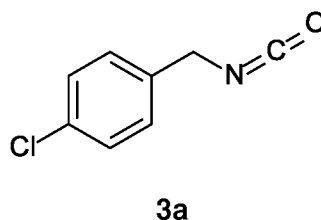
10 **Example 2-B:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.55 (br s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.98 (br s, 2H), 4.89 (s, 2H), 4.02-4.08 (m, 1H), 3.74-3.80 (m, 1H), 3.33-3.41 (m, 1H), 3.10-3.18 (m, 1H), 2.22-2.34 (m, 1H), 2.26 (s, 3H), 2.11-2.22 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 359.

Example 3

15 **6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one**



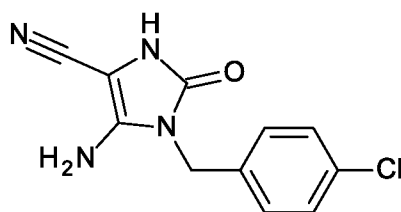
Step 1: Preparation of 1-chloro-4-(isocyanatomethyl)benzene



20 Compound **3a** was prepared in analogy to **Step 1** of **Example 2** by using (4-chlorophenyl)methanamine instead of *p*-tolylmethanamine. 1-Chloro-4-(isocyanatomethyl)benzene (38.7 g, compound **3a**) was obtained as a colorless oil.

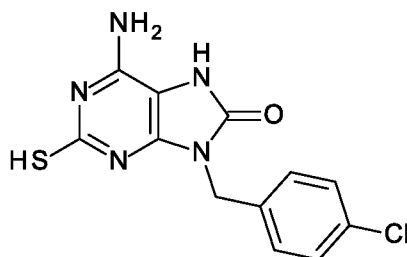
Step 2: Preparation of 4-amino-3-[(4-chlorophenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile

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**3b**

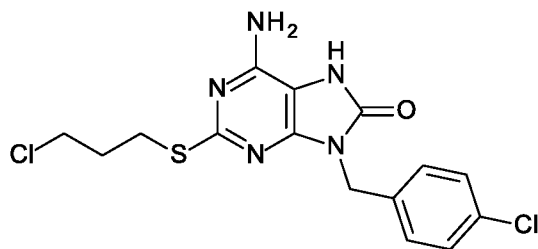
Compound **3b** was prepared in analogy to **Step 1** of **Example 1** by using 1-chloro-4-(isocyanatomethyl)benzene (compound **3a**) instead of isocyanatomethylbenzene. 4-Amino-3-[(4-chlorophenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (56.4 g, compound **3b**) was obtained as a grey solid. MS obsd. (ESI⁺) [(M+H)⁺]: 249.

Step 3: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7H-purin-8-one

**3c**

Compound **3c** was prepared in analogy to **Step 2** of **Example 1** by using 4-amino-3-[(4-chlorophenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (compound **3b**) instead of 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile (compound **1a**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7H-purin-8-one (16.3 g, compound **3c**) was obtained as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 308.

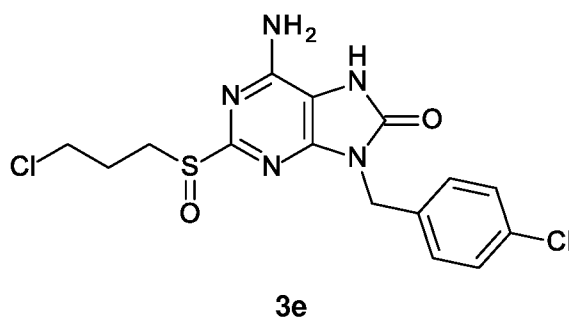
Step 4: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfanyl)-7H-purin-8-one

**3d**

Compound **3d** was prepared in analogy to **Step 3** of **Example 1** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7H-purin-8-one (compound **3c**) instead of 6-amino-9-benzyl-2-

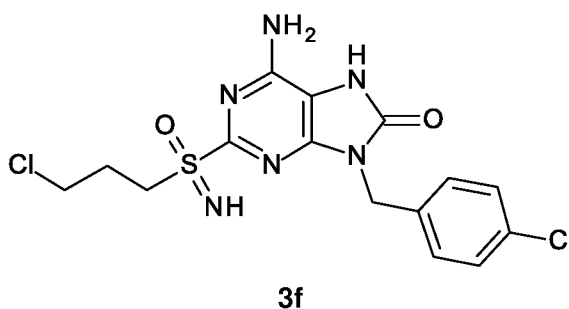
sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (14.3 g, compound **3d**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 384.

Step 5: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one



Compound **3e** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **3d**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **1c**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (10.5 g, compound **3e**) was obtained as a brown solid. MS obsd. (ESI⁺) [(M+H)⁺]: 400.

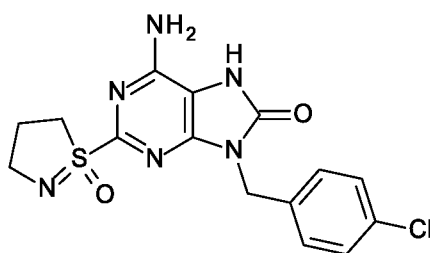
Step 6: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one



Compound **3f** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (compound **3e**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one (9.3 g, compound **3f**) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 415.

Step 7: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one

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**3**

Example 3 was prepared in analogy to **Step 6 of Example 1** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (compound **3f**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (compound **1e**).

6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one (4.7 g, compound **3**) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 10.81 (br s, 1H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.08 (br s, 2H), 4.94 (s, 2H), 4.01-4.07 (m, 1H), 3.72-3.82 (m, 1H), 3.34-3.41 (m, 1H), 3.11-3.19 (m, 1H), 2.25-2.32 (m, 1H), 2.11-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 379.

Separation of compound of **Example 3** (400 mg) by chiral HPLC affords **Example 3-A** (faster eluting, 64 mg) and **Example 3-B** (slower eluting, 95 mg) as white solids with methanol 5%-40% (0.05%DEA)/ CO_2 on ChiralPak OD-3 column.

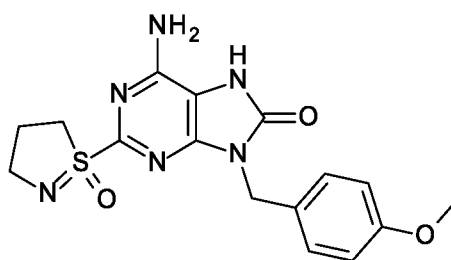
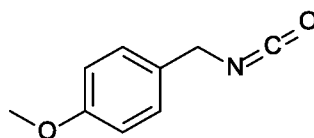
Example 3-A: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 10.81 (br s, 1H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.08 (br s, 2H), 4.94 (s, 2H), 3.99-4.08 (m, 1H), 3.72-3.82 (m, 1H), 3.36-3.44 (m, 1H), 3.10-3.17 (m, 1H), 2.25-2.32 (m, 1H), 2.11-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 379.

Example 3-B: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 10.80 (br s, 1H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.07 (br s, 2H), 4.92 (s, 2H), 3.98-4.08 (m, 1H), 3.72-3.82 (m, 1H), 3.36-3.44 (m, 1H), 3.10-3.17 (m, 1H), 2.25-2.32 (m, 1H), 2.11-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 379.

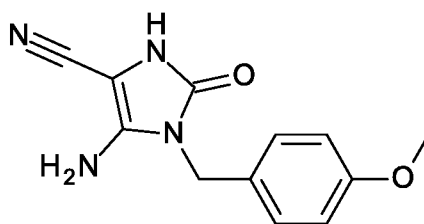
Example 4

6-Amino-9-[(4-methoxyphenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one

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**4****Step 1: Preparation of 1-(isocyanatomethyl)-4-methoxy-benzene****4a**

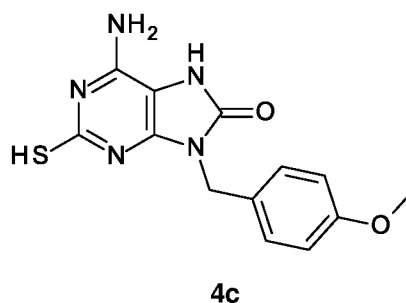
Compound **4a** was prepared in analogy to **Step 1** of **Example 2** by using (4-methoxyphenyl)methanamine instead of *p*-tolylmethanamine. 1-(isocyanatomethyl)-4-methoxybenzene (30.0 g, compound **4a**) was obtained as a colorless oil.

Step 2: Preparation of 4-amino-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile**4b**

Compound **4b** was prepared in analogy to **Step 1** of **Example 1** by using 1-(isocyanatomethyl)-4-methoxybenzene (compound **4a**) instead of isocyanatomethylbenzene. 4-amino-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (39 g, compound **4b**) was obtained as a grey solid. MS obsd. (ESI⁺) [(M+H)⁺]: 245.

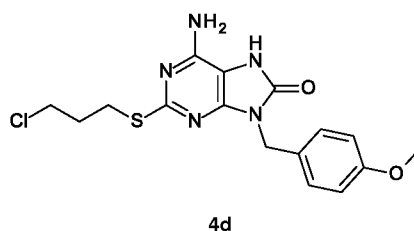
Step 3: Preparation of 6-amino-9-[(4-methoxyphenyl)methyl]-2-sulfanyl-7H-purin-8-one

-27-



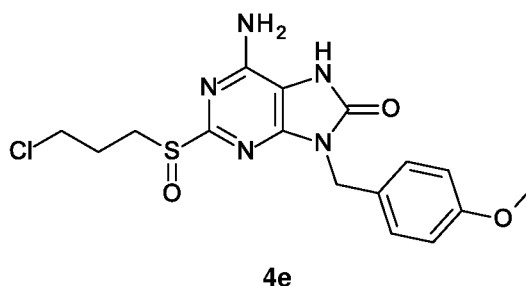
Compound **4c** was prepared in analogy to **Step 2** of **Example 1** by using 4-amino-3-[(4-methoxyphenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (compound **4b**) instead of 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile (compound **1a**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-sulfanylmethyl-7H-purin-8-one (19.5 g, compound **4c**) was obtained as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 304.

Step 4: Preparation of 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one



Compound **4d** was prepared in analogy to **Step 3** of **Example 1** by using 6-amino-9-[(4-methoxyphenyl)methyl]-2-sulfanylmethyl-7H-purin-8-one (compound **4c**) instead of 6-amino-9-benzyl-2-sulfanylmethyl-7H-purin-8-one (compound **1b**). 6-Amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one (18 g, compound **4d**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 380.

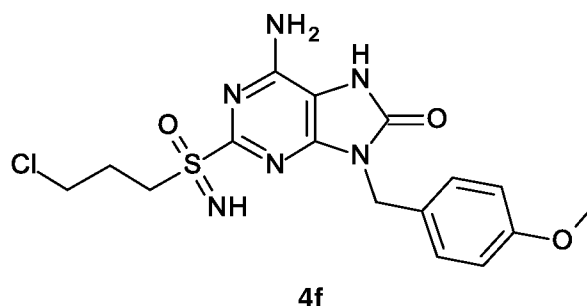
Step 5: Preparation of 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one



Compound **4e** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one (compound **4d**) instead of

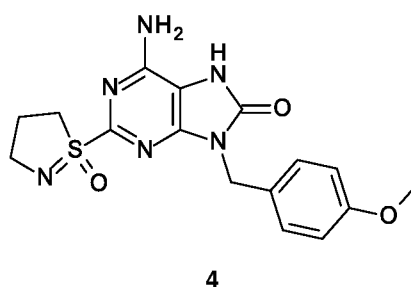
6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **1c**). 6-Amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (16.0 g, compound **4e**) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 396.

Step 6: Preparation of 6-amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one



Compound **4f** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (compound **4e**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (8.5 g, compound **4f**) was obtained as a grey solid. MS obsd. (ESI⁺) [(M+H)⁺]: 411.

Step 7: Preparation of 6-amino-9-[(4-methoxyphenyl)methyl]-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one



Example 4 was prepared in analogy to **Step 6** of **Example 1** by using 6-amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (compound **4f**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one (compound **1e**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one (5.0 g, **Example 4**) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.28 (d, *J* = 8.7 Hz, 2H), 6.99 (br s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.87 (s, 2H), 4.04-4.11 (m, 1H), 3.76-3.84 (m, 1H), 3.72 (s, 3H), 3.35-3.42 (m, 1H), 3.11-3.19 (m, 1H), 2.25-2.35 (m, 1H), 2.14-2.24 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 375.

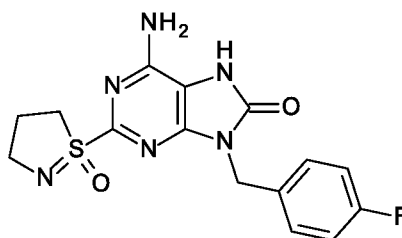
Separation of compound of **Example 4** (2.5 g) by chiral HPLC affords **Example 4-A** (faster eluting, 1.1 g) and **Example 4-B** (slower eluting, 0.7 g) as white solids with methanol 5%-40% (0.05%DEA)/CO₂ on ChiralPak OD-3 column.

Example 4-A: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.58 (br s, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.99 (br s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.86 (s, 2H), 4.02-4.11 (m, 1H), 3.74-3.82 (m, 1H), 3.71 (s, 3H), 3.35-3.42 (m, 1H), 3.11-3.19 (m, 1H), 2.25-2.35 (m, 1H), 2.14-2.24 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 375.

Example 4-B: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.78 (br s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.06 (br s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.87 (s, 2H), 4.02-4.11 (m, 1H), 3.74-3.82 (m, 1H), 3.72 (s, 3H), 3.35-3.42 (m, 1H), 3.11-3.19 (m, 1H), 2.27-2.35 (m, 1H), 2.14-2.26 (m, 1H). MS obsd. (ESI⁺) [(M+H)⁺]: 375.

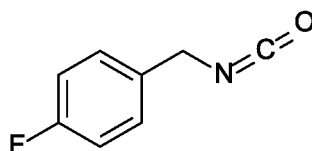
Example 5

6-Amino-9-[(4-fluorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one



5

Step 1: Preparation of 1-fluoro-4-(isocyanatomethyl)benzene

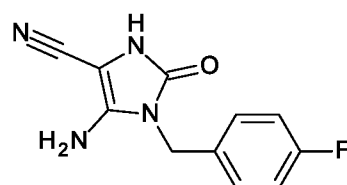


5a

Compound **5a** was prepared in analogy to **Step 1** of **Example 2** by using (4-fluorophenyl)methanamine instead of *p*-tolylmethanamine. 1-fluoro-4-(isocyanatomethyl)benzene (38.0 g, compound **5a**) was obtained as a colorless oil.

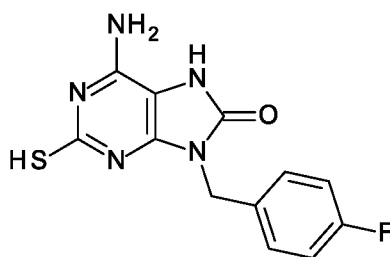
Step 2: Preparation of 4-amino-3-[(4-fluorophenyl)methyl]-2-oxo-1*H*-imidazole-5-carbonitrile

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**5b**

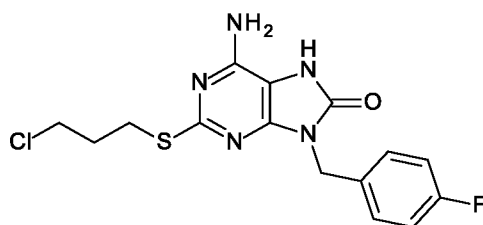
Compound **5b** was prepared in analogy to **Step 1** of **Example 1** by using 1-fluoro-4-(isocyanatomethyl)benzene (compound **5a**) instead of isocyanatomethylbenzene. 4-amino-3-[(4-fluorophenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (48.0 g, compound **5b**) was obtained as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 233.

Step 3: Preparation of 6-amino-9-[(4-fluorophenyl)methyl]-2-sulfanyl-7H-purin-8-one

**5c**

Compound **5c** was prepared in analogy to **Step 2** of **Example 1** by using 4-amino-3-[(4-fluorophenyl)methyl]-2-oxo-1H-imidazole-5-carbonitrile (compound **5b**) instead of 4-amino-3-benzyl-2-oxo-1H-imidazole-5-carbonitrile (compound **1a**). 6-Amino-9-[(4-fluorophenyl)methyl]-2-sulfanyl-7H-purin-8-one (32.0 g, compound **5c**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 292.

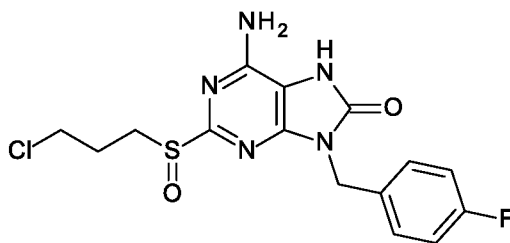
Step 4: Preparation of 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-fluorophenyl)methyl]-7H-purin-8-one

**5d**

Compound **5d** was prepared in analogy to **Step 3** of **Example 1** by using 6-amino-9-[(4-fluorophenyl)methyl]-2-sulfanyl-7H-purin-8-one (compound **5c**) instead of 6-amino-9-benzyl-2-sulfanyl-7H-purin-8-one (compound **1b**). 6-Amino-2-(3-chloropropylsulfanyl)-9-[(4-

fluorophenyl)methyl]-7*H*-purin-8-one (1.0 g, compound **5d**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 368.

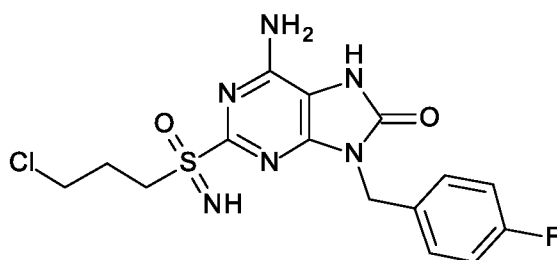
Step 5: Preparation of 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one



5e

Compound **5e** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (compound **5d**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (compound **1c**). 6-Amino-2-(3-chloropropylsulfinyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (8.1 g, compound **5e**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 384.

Step 6: Preparation of 6-amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one

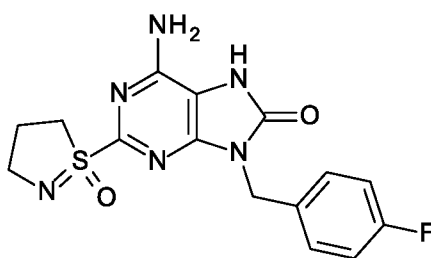


5f

Compound **5f** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (compound **5e**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (2.2 g, compound **5f**) was obtained as an off-white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 399.

Step 7: Preparation of 6-amino-9-[(4-fluorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3*H*-isothiazol-1-yl)-7*H*-purin-8-one

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**5**

Example 5 was prepared in analogy to **Step 6** of **Example 1** by using 6-amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7H-purin-8-one (compound **5f**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (compound **1e**).

6-Amino-9-[(4-fluorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one (1.9 g, **Compound 5**) was obtained as a white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm: 10.59 (br s, 1H), 7.38 (dd, $J = 8.5, 5.7$ Hz, 2H), 7.17 (t, $J = 8.9$ Hz, 2H), 7.00 (br s, 2H), 4.93 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.79 (m, 1H), 3.34-3.39 (m, 1H), 3.11-3.19 (m, 1H), 2.22-2.32 (m, 1H), 2.11-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 363.

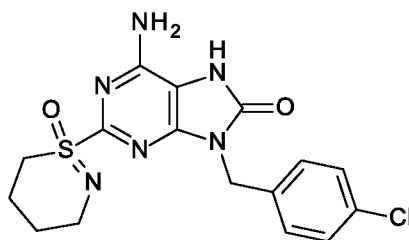
Separation of compound of **Example 5** (300 mg) by chiral HPLC affords **Example 5-A** (faster eluting, 40 mg) and **Example 5-B** (slower eluting, 20 mg) as white solids with methanol 5%-40% (0.05%DEA)/ CO_2 on ChiralPak OD-3 column.

Example 5-A: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm: 7.37 (dd, $J = 8.5, 5.7$ Hz, 2H), 7.17 (t, $J = 8.9$ Hz, 2H), 7.09 (br s, 2H), 4.93 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.79 (m, 1H), 3.34-3.39 (m, 1H), 3.11-3.19 (m, 1H), 2.22-2.32 (m, 1H), 2.11-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 363.

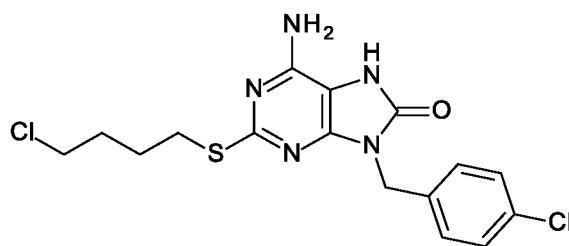
Example 5-B: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm: 7.37 (dd, $J = 8.4, 5.7$ Hz, 2H), 7.17 (t, $J = 8.8$ Hz, 2H), 7.07 (br s, 2H), 4.93 (s, 2H), 4.01-4.08 (m, 1H), 3.74-3.79 (m, 1H), 3.34-3.39 (m, 1H), 3.11-3.19 (m, 1H), 2.22-2.32 (m, 1H), 2.12-2.22 (m, 1H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 363.

Example 6

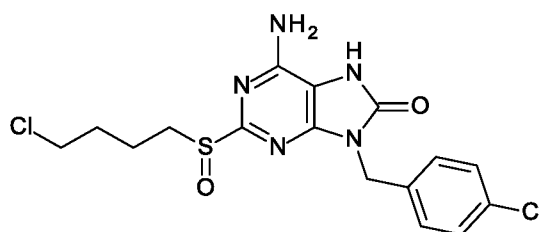
6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo- λ^6 -thia-2-azacyclohexen-1-yl)-7H-purin-8-one

**6**

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Step 1: Preparation of 6-amino-2-(4-chlorobutylsulfanyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one**6a**

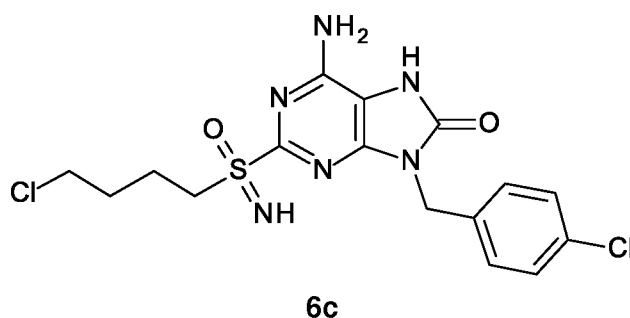
Compound **6a** was prepared in analogy to **Step 3** of **Example 1** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7H-purin-8-one (compound **3c**) and 1-bromo-4-chlorobutane instead of 6-amino-9-benzyl-2-sulfanyl-7H-purin-8-one (compound **1b**) and 1-bromo-3-chloropropane. 6-Amino-2-(4-chlorobutylsulfanyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (1.5 g, compound **6a**) was obtained as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 398.

Step 2: Preparation of 6-amino-2-(4-chlorobutylsulfinyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one**6b**

Compound **6b** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-2-(4-chlorobutylsulfanyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (compound **6a**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7H-purin-8-one (compound **1c**). 6-Amino-2-(4-chlorobutylsulfinyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (370 mg, compound **6b**) was obtained as a brown solid. MS obsd. (ESI⁺) [(M+H)⁺]: 414.

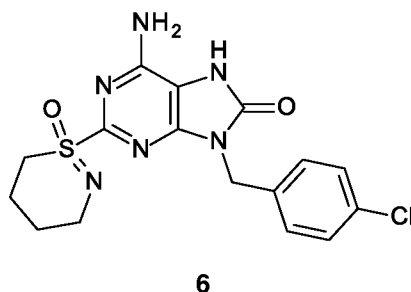
Step 3: Preparation of 6-amino-2-(4-chlorobutylsulfonimidoyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one

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Compound **6c** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-2-(4-chlorobutylsulfonimidoyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (compound **6b**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (compound **1d**). 6-Amino-2-(4-chlorobutylsulfonimidoyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (125 mg, compound **6c**) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 429.

Step 4: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo- λ^6 -thia-2-azacyclohexen-1-yl)-7H-purin-8-one

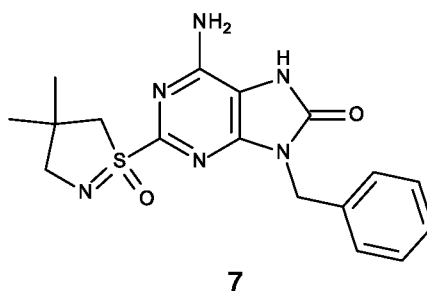
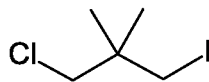


Example 6 was prepared in analogy to **Step 6** of **Example 1** by using 6-amino-2-(4-chlorobutylsulfonimidoyl)-9-[(4-chlorophenyl)methyl]-7H-purin-8-one (compound **6c**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7H-purin-8-one (compound **1e**). 6-amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo- λ^6 -thia-2-azacyclohexen-1-yl)-7H-purin-8-one (25 mg, **Example 6**) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.69 (br s, 1H), 7.33-7.42 (m, 4H), 7.05 (br s, 2H), 4.96 (s, 2H), 3.83 (ddd, *J* = 12.9, 6.3, 4.1 Hz, 1H), 3.06-3.28 (m, 1H), 2.64-2.75 (m, 1H), 2.53-2.56 (m, 1H), 2.14 (br dd, *J* = 10.2, 4.1 Hz, 1H), 1.79-1.92 (m, 1H), 1.41-1.56 (m, 2H). MS obsd. (ESI⁺) [(M+H)⁺]: 393.

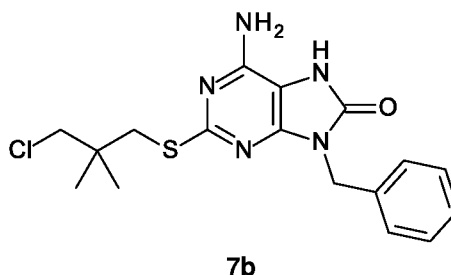
Example 7

6-Amino-9-benzyl-2-(4,4-dimethyl-1-oxo-3,5-dihydroisothiazol-1-yl)-7H-purin-8-one

-35-

**Step 1: Preparation of 1-chloro-3-iodo-2,2-dimethyl-propane**

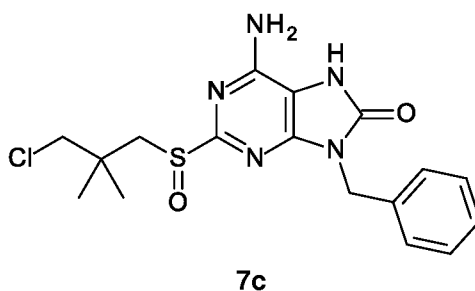
Iodine (3.31 g, 13.0 mmol), imidazole (0.88 g, 13.0 mmol), and triphenylphosphane (3.16 g, 12.0 mmol) were added to a solution of 3-chloro-2,2-dimethylpropan-1-ol (1.23 g, 10.0 mmol) in dry toluene (50 mL) and the reaction mixture was stirred at 120 °C for 3 hrs. After cooling, the reaction was filtered and the filtrate was concentrated to give crude product. The crude was suspended in 2-methoxy-2-methyl-propane (30 mL) and filtered. The filtrate was concentrated to give 1-chloro-3-iodo-2,2-dimethylpropane (2.3 g, compound **7a**) as a colorless oil. The product was used for the next step without further purification.

Step 2: Preparation of 6-amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfanyl-7H-purin-8-one

Compound **7b** was prepared in analogy to **Step 3** of **Example 1** by using 1-chloro-3-iodo-2,2-dimethylpropane (compound **7a**) instead of 1-bromo-3-chloropropane. 6-Amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfanyl-7H-purin-8-one (1.9 g, compound **7b**) was obtained as an off white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 378.

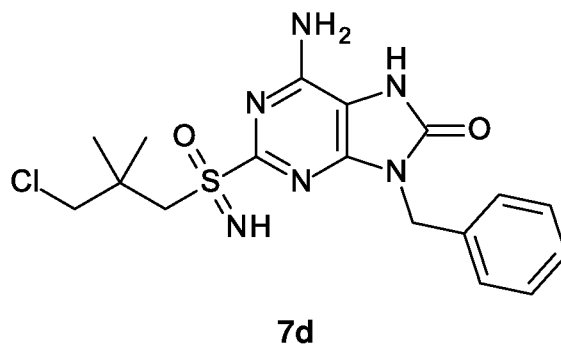
Step 3: Preparation of 6-amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfinyl-7H-purin-8-one

-36-



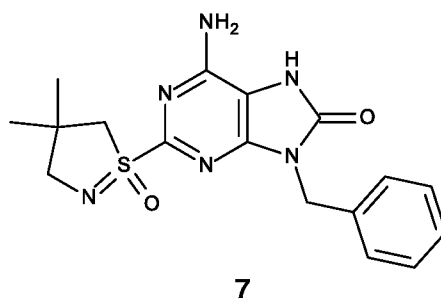
Compound **7c** was prepared in analogy to **Step 4** of **Example 1** by using 6-amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfanyl-7H-purin-8-one (compound **7b**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfanyl)-7H-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfinyl-7H-purin-8-one (520 mg, compound **7c**) was obtained as an off white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 394.

Step 4: Preparation of 6-amino-9-benzyl-2-[(3-chloro-2,2-dimethyl-propyl)sulfonimidoyl]-7H-purin-8-one



Compound **7d** was prepared in analogy to **Step 5** of **Example 1** by using 6-amino-9-benzyl-2-(3-chloro-2,2-dimethyl-propyl)sulfinyl-7H-purin-8-one (compound **7c**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfinyl)-7H-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-[(3-chloro-2,2-dimethyl-propyl)sulfonimidoyl]-7H-purin-8-one (380 mg, compound **7d**) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 409.

Step 5: Preparation of 6-amino-9-benzyl-2-(4,4-dimethyl-1-oxo-3,5-dihydroisothiazol-1-yl)-7H-purin-8-one



Example 7 was prepared in analogy to **Step 6** of **Example 1** by using 6-amino-9-benzyl-2-[(3-chloro-2,2-dimethyl-propyl)sulfonimidoyl]-7*H*-purin-8-one (**compound 7d**) instead of 6-amino-9-benzyl-2-(3-chloropropylsulfonimidoyl)-7*H*-purin-8-one (**compound 1e**). 6-Amino-9-benzyl-2-(4,4-dimethyl-1-oxo-3,5-dihydroisothiazol-1-yl)-7*H*-purin-8-one (73 mg, **Example 7**) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.58 (br s, 1H), 7.26-7.37 (m, 5H), 7.02 (br s, 2H), 4.95 (s, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.02 (d, *J* = 12.0 Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 373.

Separation of compound of **Example 7** (70 mg) by chiral HPLC affords **Example 7-A** (faster eluting, 25 mg) and **Example 7-B** (slower eluting, 34 mg) as white solids with methanol 5%-40% (0.05%DEA)/CO₂ on ChiralPak OD-3 column.

Example 7-A: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.60 (br s, 1H), 7.26-7.36 (m, 5H), 7.02 (br s, 2H), 4.95 (s, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.02 (d, *J* = 12.0 Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 373.

Example 7-B: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.58 (br s, 1H), 7.26-7.36 (m, 5H), 7.02 (br s, 2H), 4.95 (s, 2H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.02 (d, *J* = 12.0 Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 373.

Example 8

Activity of Compounds and Examples in HEK293-hTLR-7 assay

HEK293-Blue-hTLR-7 cells assay:

A stable HEK293-Blue-hTLR-7 cell line was purchased from InvivoGen (Cat.#: hkb-hltr7, San Diego, California, USA). These cells were designed for studying the stimulation of human TLR7 by monitoring the activation of NF- κ B. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN- β minimal promoter fused to five NF- κ B and AP-1-binding sites. The SEAP was induced by activating NF- κ B and AP-1 *via* stimulating HEK-Blue hTLR7 cells with TLR7 ligands. Therefore the reporter expression was regulated by the NF- κ B promoter upon stimulation of human TLR7 for 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qbl, Invivogen, San Diego, Ca, USA) at a wavelength of 640 nm, a detection medium that turns purple or blue in the presence of alkaline phosphatase.

HEK293-Blue-hTLR7 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 180 μ L in a 96-well plate in Dulbecco's Modified Eagle's medium (DMEM) containing 4.5 g/L glucose, 50 U/mL penicillin, 50 mg/mL streptomycin, 100 mg/mL Normocin, 2 mM L-glutamine, 10% (V/V) heat-inactivated fetal bovine serum for 24 hrs. Then the

- 5 HEK293-Blue-hTLR-7 cells were incubated with addition of 20 μ L test compound in a serial dilution in the presence of final DMSO at 1% and perform incubation under 37 °C in a CO₂ incubator for 20 hrs. Then 20 μ L of the supernatant from each well was incubated with 180 μ L Quanti-blue substrate solution at 37°C for 2 hrs and the absorbance was read at 620~655 nm using a spectrophotometer. The signalling pathway that TLR7 activation leads to downstream
- 10 NF- κ B activation has been widely accepted, and therefore similar reporter assay was also widely used for evaluating TLR7 agonist (Tsuneyasu Kaisho and Takashi Tanaka, Trends in Immunology, Volume 29, Issue 7, July 2008, Pages 329.sci; Hiroaki Hemmi *et al*, Nature Immunology 3, 196 - 200 (2002)).

- The Compounds and Examples of the present invention were tested in HEK293-hTLR-7
- 15 assay for their TLR7 agonism activity as described herein and results are listed in Table 1. The compounds of the invention were found to have EC₅₀ of about 0.1 μ M to about 0.9 μ M

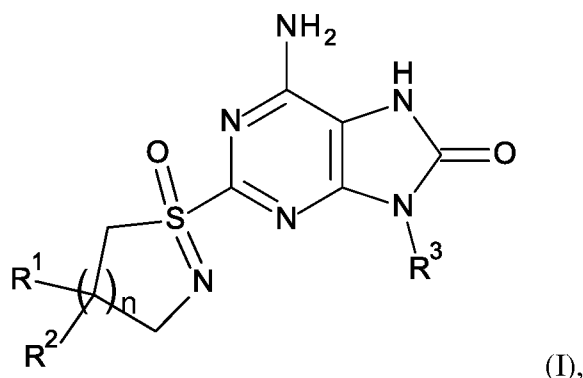
Table 1. Activity of Examples and Compounds of present invention in HEK293-hTLR-7 assay

Example	HEK293-hTLR-7 EC ₅₀ (μ M)
Example 1	0.74
Example 1-A	0.39
Example 1-B	0.85
Example 2-A	0.16
Example 2-B	0.25
Example 3	0.09
Example 3-A	<0.1
Example 3-B	0.30
Example 4	0.14
Example 4-A	0.39
Example 4-B	0.81
Example 5	0.19

Example 5-A	0.63
Example 5-B	0.71
Example 6	0.40
Example 7	0.5
Example 7-A	0.16
Example 7-B	0.23

Claims

1. A compound of formula (I),



5 wherein

R^1 and R^2 are independently selected from H and C_{1-6} alkyl;

R^3 is benzyl, said benzyl being unsubstituted or substituted by halogen, cyano, C_{1-6} alkyl or C_{1-6} alkoxy;

n is 0, 1, 2, 3, 4, 5 or 6;

10 or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

2. A compound according to claim 1, wherein

R^1 and R^2 are simultaneously H or C_{1-6} alkyl;

R^3 is benzyl, said benzyl being unsubstituted or substituted by halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

15 n is 1, 2 or 3;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

3. A compound according to claim 1, wherein R^1 and R^2 are independently selected from H and methyl.

20

4. A compound according to claim 2 or 3, wherein R^1 and R^2 are simultaneously H or methyl.

5. A compound according to claim 3 or 4, wherein R^3 is benzyl, methylbenzyl, fluorobenzyl, chlorobenzyl or methoxybenzyl.

25

6. A compound according to any one of claims 1 to 5, wherein n is 1 or 2.

7 A compound according to claim 2, wherein

R^1 and R^2 are simultaneously H or methyl;

R^3 is benzyl, methylbenzyl, fluorobenzyl, chlorobenzyl or methoxybenzyl;

5 n is 1 or 2;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

8. A compound according to claim 1 or 2 selected from:

6-Amino-9-benzyl-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one;

10 6-Amino-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-9-(p-tolylmethyl)-7H-purin-8-one;

6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one;

6-Amino-9-[(4-methoxyphenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one;

6-Amino-9-[(4-fluorophenyl)methyl]-2-(1-oxo-4,5-dihydro-3H-isothiazol-1-yl)-7H-purin-8-one;

15 6-Amino-9-[(4-chlorophenyl)methyl]-2-(1-oxo- λ^6 -thia-2-azacyclohexen-1-yl)-7H-purin-8-one;

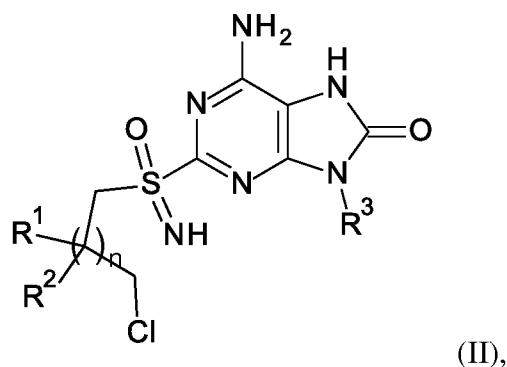
and

6-Amino-9-benzyl-2-(4,4-dimethyl-1-oxo-3,5-dihydroisothiazol-1-yl)-7H-purin-8-one;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 9. A process for the preparation of a compound according to any one of claims 1 to 8 comprising the following step:

(a) the reaction of a compound of formula (II),



with a base;

25 wherein R^1 , R^2 , R^3 and n are defined as in any one of claims 1 to 8.

10. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8 for use as therapeutically active substance.

11. A pharmaceutical composition comprising a compound in accordance with any one of claims
5 1 to 8 and a therapeutically inert carrier.

12. The use of a compound according to any one of claims 1 to 8 for the treatment or prophylaxis of hepatitis B virus infection.

10 13. The use of a compound according to any one of claims 1 to 8 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

14. The use of a compound according to any one of claims 1 to 8 as the TLR7 agonist.

15 15. The use of a compound according to any one of claims 1 to 8 to induce production of interferon- α .

16. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8 for the treatment or prophylaxis of hepatitis B virus infection.

20

17. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8, when manufactured according to a process of claim 9.

18. A method for the treatment or prophylaxis of hepatitis B virus infection, which method
25 comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/077707

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/00 C07D487/04 A61K31/522 A61P31/20
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 practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/023511 A1 (CHIA TAI TIANQING PHARMACEUTICAL GROUP CO LTD [CN]) 18 February 2016 (2016-02-18) claim 1	1-18
A	----- EP 2 138 497 A1 (DAINIPPON SUMITOMO PHARMA CO [JP]; ASTRAZENECA AB [SE]) 30 December 2009 (2009-12-30) claim 1 -----	1-18



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

23 November 2017

Date of mailing of the international search report

02/01/2018

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Authorized officer

Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/077707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016023511	A1	18-02-2016	
		AU 2015303558 A1	30-03-2017
		CA 2958097 A1	18-02-2016
		CN 106661034 A	10-05-2017
		EA 201790389 A1	30-06-2017
		EP 3190113 A1	12-07-2017
		JP 2017524037 A	24-08-2017
		KR 20170041913 A	17-04-2017
		PH 12017500281 A1	03-07-2017
		SG 11201701169X A	30-03-2017
		US 2017273983 A1	28-09-2017
		WO 2016023511 A1	18-02-2016

EP 2138497	A1	30-12-2009	
		EP 2138497 A1	30-12-2009
		JP W02008114819 A1	08-07-2010
		US 2010099870 A1	22-04-2010
		WO 2008114819 A1	25-09-2008
