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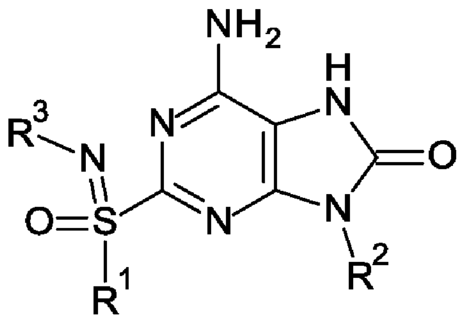

(I),

(57) Abstract: The present invention relates to compounds of formula (I), wherein R ^{1}, R^2 and R^3 are as described herein, and their prodrugs or pharmaceutically acceptable salt, enantiomer or diastereomer thereof, and compositions including the compounds and methods of using the compounds.

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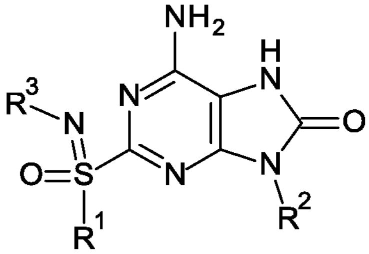
Novel sulfonimidoylpurinone compounds and derivatives for the treatment and prophylaxis of virus infection

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.

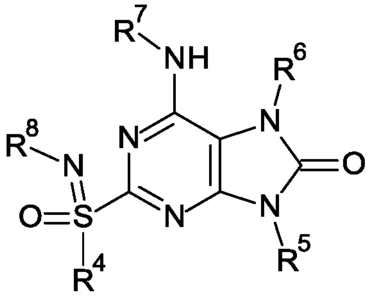
FIELD OF THE INVENTION

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



(I),

and their prodrugs, formula (Ia),



(Ia),

wherein R^1 to R^8 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 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 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-κB) 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).

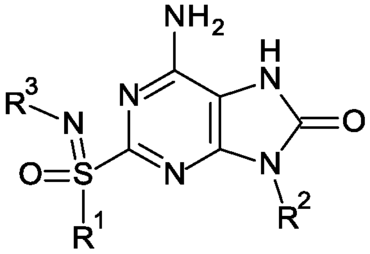
The current therapy of chronic HBV infection is based on two different types of drugs: the traditional antiviral nucleos(t)ide analogues and the more recent Pegylated IFN-α (PEG-IFN-α). The oral nucleos(t)ide analogues act by suppressing the HBV replication. This is a life-long course of treatment during 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 (ALDARA^{TM}) 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-7*H*-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) and/or (Ia) 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),



(I),

wherein

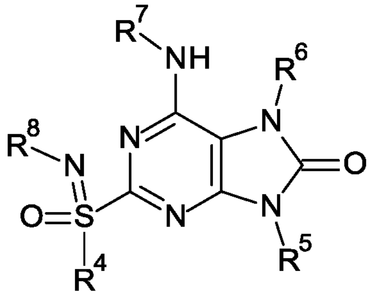
R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cylcoalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or pyrrolidinylC_{1-6}alkyl;

R^2 is C_{1-6}alkyl, phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl or pyrimidinylC_{1-6}alkyl, said phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl and pyrimidinylC_{1-6}alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

The present invention also relates to the prodrugs of formula (Ia),



(Ia),

wherein

R^4 is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cylcoalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or pyrrolidinylC_{1-6}alkyl;

R^5 is C_{1-6}alkyl, phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl or pyrimidinylC_{1-6}alkyl, said phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl and pyrimidinylC_{1-6}alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^6 is H or C_{1-6}alkyl-C(O)O-C_{1-6}alkyl-;

R^7 is H, C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-10}alkylcarbonyl;

R^8 is H, C_{1-6}alkylcarbonyl, carboxyC_{1-6}alkylcarbonyl, C_{1-6}alkyoxycarbonylC_{1-6}alkylcarbonyl or benzoyl;

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) or their prodrugs, formula (Ia), thereof as TLR7 agonist. Accordingly, the compounds of formula (I) or their prodrugs, formula (Ia), are useful for the 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 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 "C_{1-6}alkyl" denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups are methyl, ethyl and *n*-propyl.

The term "C_{1-10}alkyl" denotes a saturated, linear or branched chain alkyl group containing 1 to 10, particularly 1 to 7 carbon atoms, Particular "C_{1-10}alkyl" group is propylbutyl.

The term "C_{3-7}cycloalkyl" denotes to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular "C_{3-7}cycloalkyl" group is cyclopropyl.

The term "C_{1-6}alkoxy" denotes a group of the formula C_{1-6}alkyl-O-. Examples of C_{1-6}alkoxy group include, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and *tert*-butoxy. Particular "C_{1-6}alkoxy" groups are methoxy, ethoxy and isopropoxy. A more particular C_{1-6}alkoxy group is ethoxy.

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

The term “haloC_{1-6}alkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC_{1-6}alkyl include monofluoro-, difluoro-or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoroethyl.

The term “amino” denotes a group of the formula -NR’R” wherein R’ and R” are independently hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, heteroC_{3-7}cycloalkyl, aryl or heteroaryl. Alternatively, R’ and R”, together with the nitrogen to which they are attached, can form a heteroC_{3-7}cycloalkyl. The term “primary amino” denotes a group wherein both R’ and R” are hydrogen. The term “secondary amino” denotes a group wherein R’ is hydrogen and R” is not. The term “tertiary amino” denotes a group wherein both R’ and R” are not hydrogen. Particular secondary and tertiary amino are methylamino, ethylamino, propylamino, isopropylamino, phenylamino, benzylamino dimethylamino, diethylamino, dipropylamino, diisopropylamino, methoxyethylamino, methylethylamino, chlorobutylmethylamino, dibutylamino and methylbutylamino.

The term “carbonyl” alone or in combination refers to the group -C(O)-.

The term “C_{1-6}alkylcarbonyl” refers to a group C_{1-6}alkyl-C(O)-, wherein the “C_{1-6}alkyl” is as defined above. Particular “C_{1-6}alkylcarbonyl” group is acetyl.

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.

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

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, maloneic 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, ethanesulfonic acid, *p*-toluenesulfonic acid, and salicyclic 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 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, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, 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 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.

The term “prodrug” denotes a form or derivative of a compound which is metabolized in vivo, e.g., by biological fluids or enzymes by a subject after administration, into a pharmacologically active form of the compound in order to produce the desired pharmacological effect. Prodrugs are described e.g. in “The Organic Chemistry of Drug Design and Drug Action”, by Richard B. Silverman, Academic Press, San Diego, 2004, Chapter 8 Prodrugs and Drug Delivery Systems, pp. 497-558.

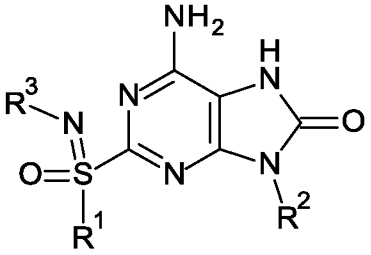
“A pharmaceutically active metabolite” is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. After entry into the body, most drugs are substrates for chemical reactions that may change their physical properties and biologic 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 AND PRODRUG

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



(I),

wherein

R^1 is $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, $C_{3\text{-}7}$cylcoalkyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl or pyrrolidinyl$C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl, phenyl$C_{1\text{-}6}$alkyl, pyridinyl$C_{1\text{-}6}$alkyl or pyrimidinyl$C_{1\text{-}6}$alkyl, said phenyl$C_{1\text{-}6}$alkyl, pyridinyl$C_{1\text{-}6}$alkyl and pyrimidinyl$C_{1\text{-}6}$alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

R^1 is methyl, ethyl, propyl, butyl, chloropropyl, cyclohexylmethyl, methoxyethyl, methoxypropyl, pyrrolidinylpropyl or trifluoroethyl;

R^2 is isobutyl, benzyl, chlorobenzyl, fluorobenzyl, bromobenzyl, chlorofluorobenzyl, chloromethylbenzyl, dichlorobenzyl, difluorobenzyl, methylbenzyl, methoxybenzyl, cyanobenzyl, carbamoylbenzyl, trifluoromethylbenzyl, methylsulfonylbenzyl, methoxycarbonylbenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, piperidinylcarbonylbenzyl, pyrrolidinylcarbonylbenzyl, pyridinylmethyl, chloropyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (iii) a compound of formula (I), wherein R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is a compound of formula (I), wherein R^1 is methyl, propyl, chloropropyl, methoxyethyl or trifluoroethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (iv) a compound of formula (I), wherein R^1 is methyl, ethyl, propyl, butyl, chloropropyl, trifluoroethyl, methoxyethyl or methoxypropyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (v) a compound of formula (I), wherein R^1 is C_{1-6}alkyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (vi) a compound of formula (I), wherein R^1 is methyl, ethyl or propyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (vii) a compound of formula (I), wherein R^1 is ethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is a compound of formula (I), wherein R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by one to three substituents independently selected from halogen, C_{1-6}alkyl, carboxy and C_{1-6}alkoxycarbonyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (viii) a compound of formula (I), wherein R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen, carbamoyl, C_{1-6}alkyl, carboxy, cyano, C_{1-6}alkoxy, C_{1-6}alkylsulfonyl and C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl; pyridinylC_{1-6}alkyl, said pyridinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl; or pyrimidinylC_{1-6}alkyl, said pyrimidinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (ix) a compound of formula (I), wherein R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, difluorobenzyl, cyanobenzyl, carboxybenzyl, methoxybenzyl, methylsulfonylbenzyl, methoxyethylaminocarbonylbenzyl, pyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is a compound of formula (I), wherein R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, bromobenzyl, chlorofluorobenzyl, chloromethylbenzyl, dichlorobenzyl, difluorobenzyl, carboxybenzyl or methoxycarbonylbenzyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (x) a compound of formula (I), wherein R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, difluorobenzyl, carboxybenzyl or methylpyridinylmethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xi) a compound of formula (I), wherein R^2 is methylbenzyl or chlorobenzyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is (xii) a compound of formula (I), wherein R^1 is C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen, carbamoyl, C_{1-6}alkyl, carboxy, cyano and C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl; or pyrimidinylC_{1-6}alkyl, said pyrimidinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

R^1 is methyl, ethyl, propyl, butyl or methoxyethyl;

R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, cyanobenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, pyrimidinylmethyl or methylpyrimidinylmethyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

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

R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen or C_{1-6}alkyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

R^1 is ethyl or propyl;

R^2 is benzyl, chlorobenzyl or methylbenzyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is that (xvi) particular compounds of formula (I) are the following:

6-Amino-9-benzyl-2-(methylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(ethylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(2-methoxyethylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(butylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(3-methoxypropylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(2,2,2-trifluoroethylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-benzyl-2-(cyclohexylmethylsulfonimidoyl)-7H-purin-8-one;

6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;

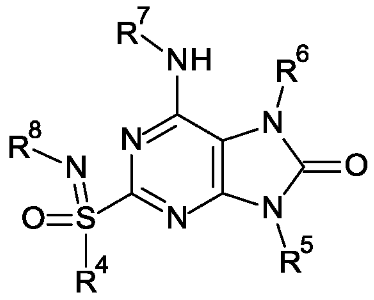
6-Amino-9-[(4-methoxyphenyl)methyl]-2-(methylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one;
6-Amino-9-[(4-methoxyphenyl)methyl]-2-(3-pyrrolidin-1-ylpropylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(methylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(methylsulfonimidoyl)-9-(3-pyridylmethyl)-7H-purin-8-one;
3-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzonitrile;
3-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzamide;
6-Amino-2-(methylsulfonimidoyl)-9-(2-pyridylmethyl)-7H-purin-8-one;
6-Amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7H-purin-8-one;
6-Amino-9-isobutyl-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7H-purin-8-one;
6-Amino-9-[(4-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-bromophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3,4-dichlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-(3,4-difluorophenylmethyl)-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
6-Amino-9-[(4-chloro-3-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2,4-difluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzonitrile;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzamide;
6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2-methyl-4-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
Methyl 4-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoate;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoic acid;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]-N-(2-methoxyethyl)benzamide;

6-Amino-9-[[4-(piperidine-1-carbonyl)phenyl]methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(S-propylsulfonimidoyl)-9-[[4-(pyrrolidine-1-carbonyl)phenyl]methyl]-7H-purin-8-one;
6-Methyl-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmethyl)-7H-purin-8-one;
6-Methyl-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7H-purin-8-one;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is that (xvii) more particular compounds of formula (I) are the following:
6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-bromophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
Methyl 4-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoate;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoic acid;
6-Methyl-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is that (xviii) the most particular compounds of formula (I) are the following:
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is (xix) a compound of formula (Ia),



(Ia),

wherein

R^4 is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cylcoalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or pyrrolidinylC_{1-6}alkyl;

R^5 is C_{1-6}alkyl, phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl or pyrimidinylC_{1-6}alkyl, said phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl and pyrimidinylC_{1-6}alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^6 is H or C_{1-6}alkyl-C(O)O-C_{1-6}alkyl-;

R^7 is H, C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-10}alkylcarbonyl;

R^8 is H, C_{1-6}alkylcarbonyl, carboxyC_{1-6}alkylcarbonyl, C_{1-6}alkyoxycarbonylC_{1-6}alkylcarbonyl or benzoyl;

provided that R^6, R^7 and R^8 are not H simultaneously;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xx) a compound of formula (Ia), wherein

R^4 is methyl, ethyl, propyl, butyl, chloropropyl, cyclohexylmethyl, methoxyethyl, methoxypropyl, pyrrolidinylpropyl or trifluoroethyl;

R^5 is isobutyl, benzyl, chlorobenzyl, fluorobenzyl, bromobenzyl, chlorofluorobenzyl, chloromethylbenzyl, dichlorobenzyl, difluorobenzyl, methylbenzyl, methoxybenzyl, cyanobenzyl, carbamoylbenzyl, trifluoromethylbenzyl, methylsulfonylbenzyl, methoxycarbonylbenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, piperidinylcarbonylbenzyl, pyrrolidinylcarbonylbenzyl, pyridinylmethyl, chloropyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl;

R^6 is H, acetoxymethyl, acetoxyethyl or dimethylpropanoyloxymethyl;

R^7 is H, ethyl, propyl, isopropyl, cyclopropyl, acetyl, pentanoyl, methylpentanoyl, propylpentanoyl, ethylbutanoyl, methylbutanoyl or dimethylpropanoyl;

R^8 is H, acetyl, pentanoyl, carboxypropanoyl, ethoxycarbonylpropanoyl or benzoyl;
provided that R^6, R^7 and R^8 are not H simultaneously;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxi) a compound of formula (Ia), wherein R^4 is C_{1-6}alkyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxii) a compound of formula (Ia), wherein R^4 is methyl or propyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxiii) a compound of formula (Ia), wherein R^5 is phenylC_{1-6}alkyl or pyridinylC_{1-6}alkyl, said phenylC_{1-6}alkyl and pyridinylC_{1-6}alkyl are unsubstituted or substituted by one to three substituents independently selected from halogen or C_{1-6}alkyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is a compound of formula (Ia), wherein R^5 is benzyl, methylbenzyl, chlorobenzyl or methylpyridinylmethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxiv) a compound of formula (Ia), wherein R^5 is benzyl, chlorobenzyl or methylpyridinylmethyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxv) a compound of formula (Ia), wherein R^7 is H, C_{1-6}alkyl or C_{1-10}alkylcarbonyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxvi) a compound of formula (Ia), wherein R^7 is H, ethyl, propyl, methylpentanoyl or propylpentanoyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxvii) a compound of formula (Ia), wherein R^8 is H, C_{1-6}alkylcarbonyl or carboxyC_{1-6}alkylcarbonyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A further embodiment of present invention is (xxviii) a compound of formula (Ia), wherein R^8 is H, pentanoyl or carboxypropanoyl; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is that (xix) particular compounds of formula (Ia) are the following:

N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]pentanamide;
N-[[6-Amino-9-[(4-chlorophenyl)methyl]-8-oxo-7H-purin-2-yl]-oxo-propyl-λ^4-sulfanylidene]acetamide;
N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-methyl-oxo-λ^4-sulfanylidene]acetamide;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-3-oxo-butanoate;
Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoate;
Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoate;
N-[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;
N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;
N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;
9-Benzyl-6-(ethylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-(Ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-(S-propylsulfonimidoyl)-7H-purin-8-one;
9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;
9-Benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;
9-Benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;
9-Benzyl-6-(cyclopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;
N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamide;
N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]acetamide;

N-[9-Benzyl-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]pentanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-ethylbutanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-3-methylbutanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-methylpentanamide;

N-[9-[(4-chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2,2-dimethylpropanamide;

N-[9-Benzyl-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamide;

[6-Amino-9-benzyl-2-(methylsulfonimidoyl)-8-oxo-purin-7-yl]methyl acetate;

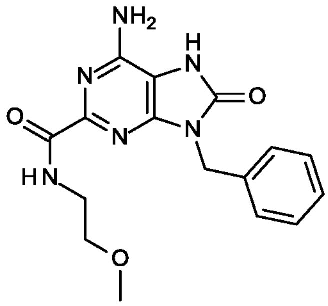
[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]methyl acetate;

[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]methyl 2,2-dimethylpropanoate; and

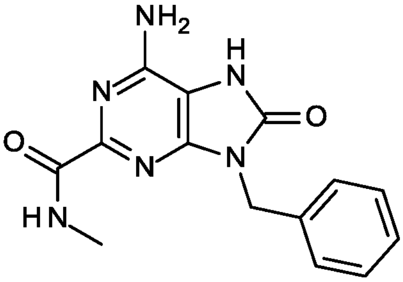
1-[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]ethyl acetate;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

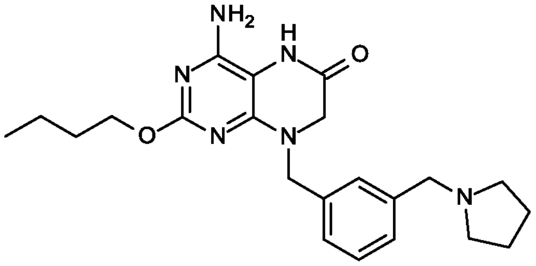
In some embodiments, compounds of present invention were tested and compared with the following reference compounds:



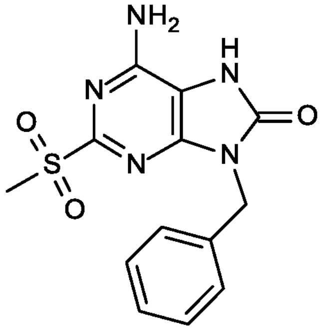
(P-2),



(P-5),



(GS-9620),



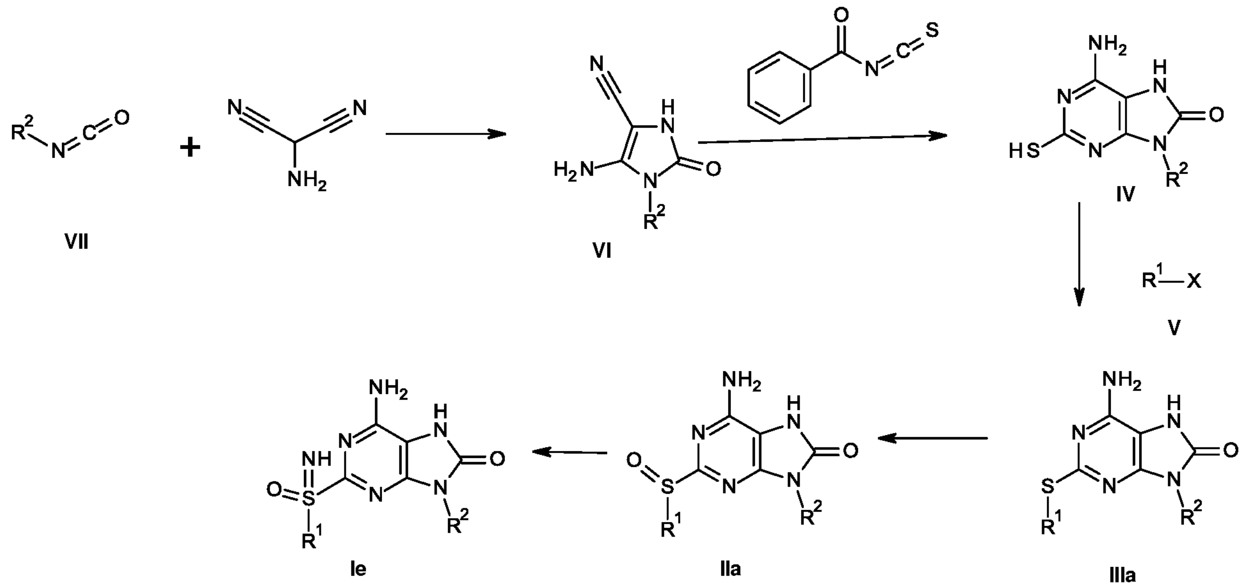
(S-1).

Compound P-2 and P-5 were disclosed in WO2006117670 as example 2 and 5 respectively, compound GS-9620 was disclosed in US20100143301 as example 49, compound S-1 was disclosed in JP1999193282.

SYNTHESIS

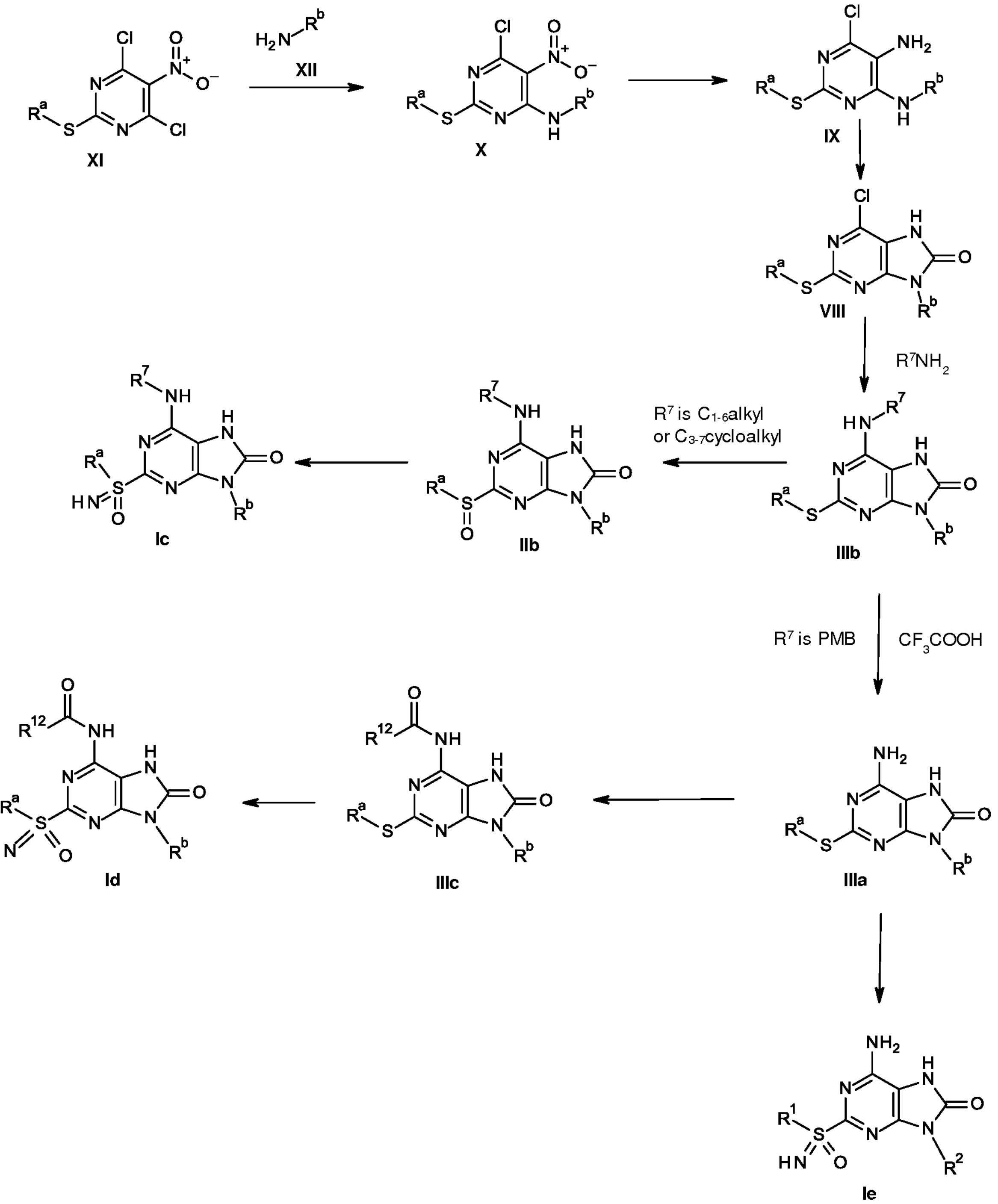
The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1 to R^{11} are as defined above unless otherwise 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



A compound of formula **VI** is prepared by cyclization of isocyanate **VII** with aminomalononitrile *p*-toluenesulfonate. Then bicycle **IV** is synthesized by reaction of compound of formula **VI** with benzoyl isothiocyanate with inorganic base, such as sodium hydroxide or potassium hydroxide. Alkylation of bicycle **IV** with alkylhalide **V** in the presence of base such as K_2CO_3, NaH or Cs_2CO_3, gives compound of formula **IIIa**. Then compound of formula **IIa** is prepared by oxidation of compound of formula **IIIa** with an oxidant, such as *meta*-chloroperoxybenzoic acid, urea-hydrogen peroxide adduct or HIO_4. Compound of formula **Ie** is obtained by imination of compound of formula **IIa** with imination reagent, such as sodium azide in acid, said acid is for example Eaton's reagent or PPA.

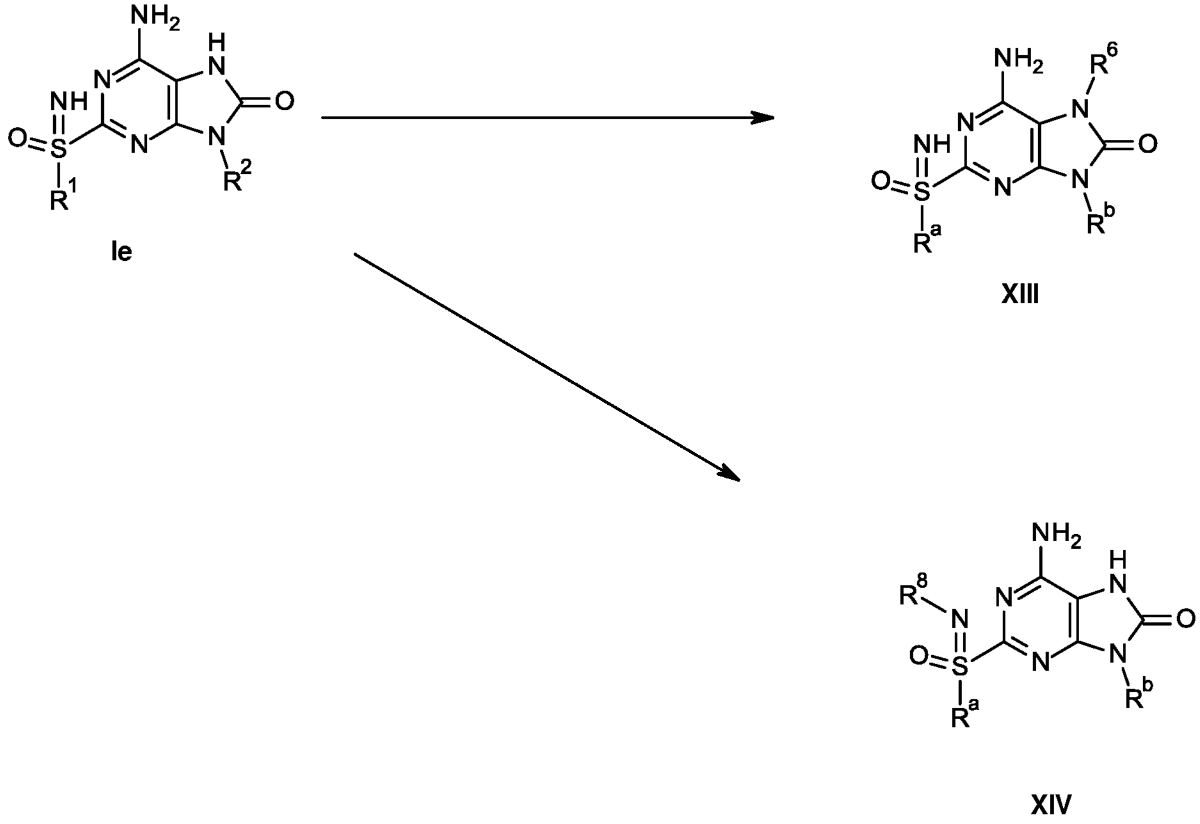
Scheme 2



R^a is R^1 or R^4, R^b is R^2 or R^5, R^7 is C_{1-6}alkyl, C_{3-7}cycloalkyl or PMB, R^{12} is C_{1-10}alkyl.

A compound of formula **X** is prepared by reaction of compound of formula **XI** with R^bNH_2. Reduction of compound **X** gives the compound of formula **IX**. Cyclization of compound of formula **IX** with cyclization reagents, such as phosgene, carbonyl diimidazole, diethyl carbonate or triphosgene affords compound of formula **VIII**. A compound of formula **IIIb** is prepared by treating the compound of formula **VIII** with R^7NH_2 upon heating. A compound of formula **Ie** is prepared by deprotection of compound of formula **IIIb** while R^7 is PMB with acid, such as CF_3COOH, followed by oxidation with an oxidant, such as *meta*-chloroperoxybenzoic acid, urea-hydrogen peroxide adduct or HIO_4, and imination with imination reagent, such as sodium azide in acid, said acid is for example Eaton's reagent or PPA. A compound of formula **Ic** is obtained by direct oxidation of compound of formula **IIIb** to give compound **IIb** while R^7 is alkyl or cycloalkyl, followed by imination with imination reagent, such as sodium azide in acid, said acid is for example Eaton's reagent or PPA. A compound of formula **Id** is obtained by acylation of compound of formula **IIIa** to give compound **IIIc**, followed by oxidation with an oxidant, such as *meta*-chloroperoxybenzoic acid, urea-hydrogen peroxide adduct or HIO_4, and imination with imination reagent, such as sodium azide in acid, said acid is for example Eaton's reagent or PPA.

Scheme 3



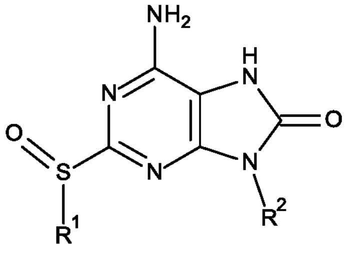
R^a is R^1, R^4 or R^9; R^b is R^2, R^5 or R^{10}.

Prodrugs of formula **XIII** or **XIV** can be prepared according **Scheme 3**.

Compound of formula **XIII** is synthesized by alkylation of active parent compounds of formula **Ie** with haloester, such as chloromethyl acetate. Compound of formula **XIV** is synthesized by reaction of active parent compound of formula **Ie** with carboxylic anhydride, such as acetic anhydride, or acylchloride, such as 4-chloro-4-*oxo*-butanoate.

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

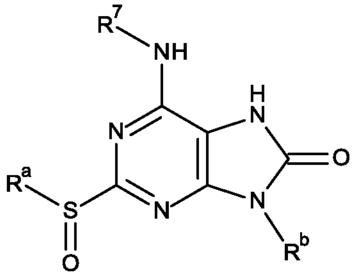
(a) the reaction of a compound of formula (IIa),



(IIa),

with an imination reagent;

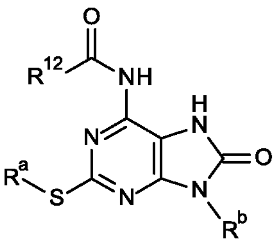
(b) the reaction of a compound of formula (IIb),



(IIb),

with an imination reagent; wherein R^a is R^1 or R^4, R^b is R^2 or R^5, R^7 is $C_{1\text{-}6}$alkyl or $C_{3\text{-}7}$cycloalkyl;

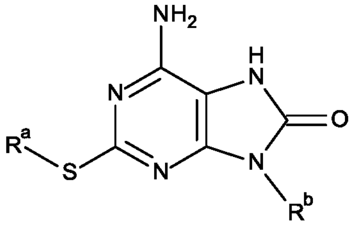
(c) the reaction of a compound of formula (IIIc),



(IIIc),

with an oxidant followed by an imination reagent, wherein R^a is R^1 or R^4, R^b is R^2 or R^5, R^{12} is C_{1-10}alkyl;

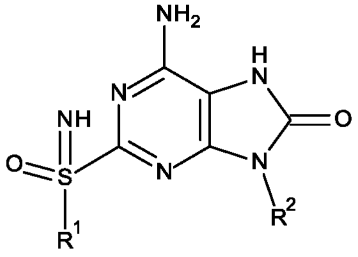
(d) the reaction of a compound of formula (IIIa),



(IIIa),

with an oxidant followed by an imination reagent, wherein R^a is R^1 or R^4, R^b is R^2 or R^5;

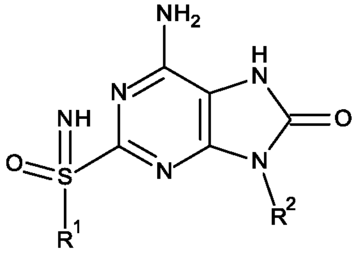
(e) the reaction of a compound of formula (Ie),



(Ie),

with haloester;

(f) the reaction of a compound of formula (Ie),



(Ie),

with carboxylic anhydride or acylchloride;

or wherein R^a, R^b, R^1, R^2, R^4 , R^5 , R^7 and R^{12} are defined above.

In step (a), (b), (c) and (d), the imination reagent can be for example sodium azide in acid, said acid can be for example Eaton's reagent or PPA.

In step (c) and (d), the oxidant can be for example *meta*-chloroperoxybenzoic acid, urea-hydrogen peroxide adduct or HIO_4.

In step (e), the haloester can be for example chloromethyl acetate.

In step (f), the carboxylic anhydride can be for example acetic anhydride; the acylchloride can be 4-chloro-4-*oxo*-butanoate.

A compound of formula (I) and (Ia) 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) or their prodrugs 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) or their prodrugs are formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (I) or their prodrugs 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 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 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 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 its prodrugs, formula (Ia), or pharmaceutically acceptable salts or enantiomers or diastereomers thereof.

In a further embodiment includes a pharmaceutical composition comprising a compound of formula (I) or its prodrugs, formula (Ia), 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 its prodrugs, formula (Ia), or pharmaceutically acceptable salts or enantiomers or diastereomers thereof for use 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 its prodrugs, 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
BSA:	*N, O*-bis(trimethylsilyl)acetamide
$CDCl_3$:	deuterated chloroform
CD_3OD:	deuterated methanol
CDI:	*N,N'*-carbonyl diimidazole
DIEPA:	*N, N*-diethylpropylamine
DMF:	dimethyl formamide
DMSO:	dimethyl sulfoxide
DBU:	1,8-Diazabicycloundec-7-ene
DPPA:	diphenylphosphoryl azide
EC_{50}:	the molar concentration of an agonist, which produces 50% of the maximum possible response for that agonist.
EDC:	*N*1-((ethylimino)methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine
EtOAc or EA:	ethyl acetate
HATU:	(1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
hr(s):	hour(s)
HPLC:	high performance liquid chromatography
HOBt:	*N*-hydroxybenzotriazole
MS (ESI):	mass spectroscopy (electron spray ionization)
m-CPBA:	3-chloroperbenzoic acid
min(s)	minute(s)
MTEB:	methyl *tert*-butyl ether

NMR:	nuclear magnetic resonance
NMP:	*N*-methylpyrrolidone
obsd.	observed
PE:	petroleum ether
PMB:	*p*-methoxybenzyl
PPA:	polyphosphoric acid
RT or rt:	room temperature
sat.	saturated
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran
TEA:	triethylamine
V/V	volume ratio

GENERAL EXPERIMENTAL CONDITIONS

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.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using X Bridge^{TM} Perp C_{18} (5 µm, OBD^{TM} 30 × 100 mm) column or SunFire^{TM} Perp C_{18} (5 µm, OBD^{TM} 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):

Acidic condition: A: 0.1% formic acid and 1% acetonitrile in H_2O; B: 0.1% formic acid in acetonitrile;

Basic condition: A: 0.05% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile.

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 $(M+H)^+$.

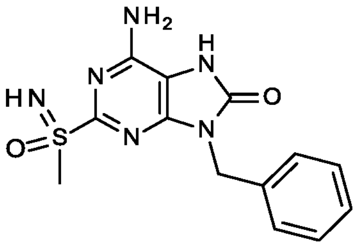
NMR Spectra were obtained using Bruker Avance 400MHz.

All reactions involving air-sensitive reagents were performed under an argon atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

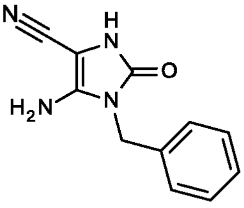
Example 1

6-Amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one



1

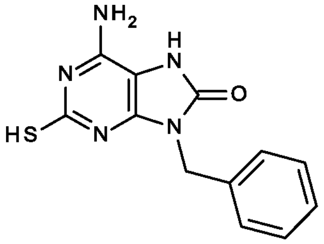
Step 1: Preparation of 4-amino-3-benzyl-2-*oxo*-1*H*-imidazole-5-carbonitrile



1a

To a solution of aminomalononitrile *p*-toluenesulfonate (25 g, 98.5 mmol, TCI, Catalog number: A1119-25G) in dry THF (100 mL) was added benzyl isocyanate (13.2 g, 98.5 mmol) and TEA (10.2 g, 79.0 mmol) at RT. After stirred at rt for 24 hrs, the reaction was concentrated *in vacuo* and the residue partitioned between EtOAc (500 mL) and water (250 mL). The separated organic layer was washed with brine (50 mL) two times, and extracted with sodium hydroxide solution (50 mL, 1*N*) two times. The combined sodium hydroxide solution layer was neutralized with 10 wt.% sodium hydrogen sulfate solution and extracted with EtOAc. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was triturated in 2-isopropoxypropane and then the suspension was filtered to give 4-amino-3-benzyl-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **1a**) as a yellow solid (15 g), the product was used in the next step without further purification. MS obsd. (ESI^+) [$(M+H)^+$]: 215.

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

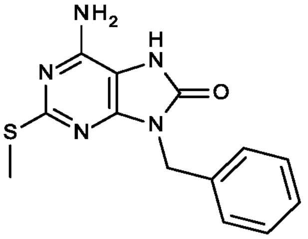


1b

To a solution of 4-amino-3-benzyl-2-*oxo*-1*H*-imidazole-5-carbonitrile (15.0 g, 70.0 mmol, compound **1a**) in THF (700 mL) was added benzoylisothiocyanate (28.6 g, 175.1 mmol, TCI, Catalog number: A11596-100G) dropwise. After stirred at RT for 12 hrs, the reaction mixture was concentrated *in vacuo*. The residue was triturated in diethyl ether (100 mL) and the resulting precipitate was collected by filtration.

To a solution of the obtained precipitate in THF (700 mL) was added sodium hydroxide (70 mL, 2 *N*). The mixture was refluxed for 50 hrs, and then acidified to pH3 with 10% wt. aqueous sodium hydrogen sulfate solution. The resulting precipitate was collected by filtration to give a crude product 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (8.1g, compound **1b**) as a yellow solid. The product was used in the next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 274.

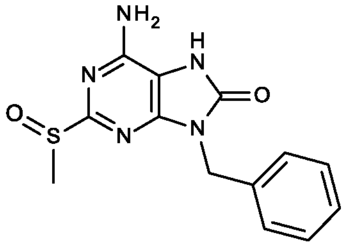
Step 3: Preparation of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one



1c

To a solution of 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (5.46 g, 20.0 mmol, compound **1b**) in DMF was added potassium carbonate (2.76 g, 20.0 mmol). And then methyl iodide (2.84 g, 20.0 mmol) in DMF (5.0 mL) was slowly added to previous solution. After stirred at RT for 12 hrs, the reaction mixture was poured into water (200 mL), then acidified with 10 wt.% aqueous sodium hydrogen sulfate solution and extracted with EtOAc (100 mL) two times. The organic layer was washed with brine, dried and concentrated *in vacuo* to give the crude product, which was purified by flash chromatography on silica gel to give 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (4.9 g, compound **1c**) as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 288.

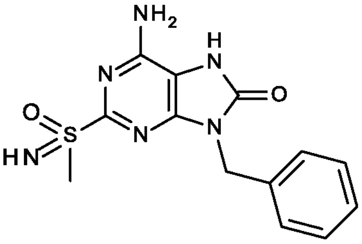
Step 4: Preparation of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one



1d

To a suspension of compound 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (2.5 g, 8.7 mmol, compound **1c**) in DCM/MeOH (500 mL, V/V = 1:1) was added 3-chloroperbenzoic acid (2.15 g, 8.7 mmol, 70% purity, Aldrich, Catalog number: 273031-100G). After reaction was stirred for 2 hrs, the volume of reaction mixture was reduced *in vacuo* to about 50 mL. The resulting precipitate was collected by filtration, washed with methanol and dried to give 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (1.0 g, compound **1d**) as a white solid. The product was used in the next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 304.

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



1

To a solution of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (1.4 g, 4.6 mmol, compound **1d**) in Eaton's reagent (40 mL, phosphorus pentoxide, 7.5 wt. % in methanesulphonic acid, Aldrich, Catalog number: 380814-100ML) was added sodium azide (360 mg, 5.5 mmol) at 50 °C. After being stirred at this temperature for 30 minutes, the reaction mixture was cooled to RT and poured into sat. aqueous sodium bicarbonate solution. The reaction mixture was extracted with *n*-BuOH (100 mL) two times, and the organic phase was concentrated *in vacuo*. The residue was submitted for purification by HPLC to give 6-amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one (900 mg, compound **1**) as a white solid. ^{1}H NMR (400

MHz, DMSO-d_6) δ ppm: 10.6 (br. s, 1H), 7.26-7.34 (m, 5H), 7.07 (br. s., 2H), 4.96 (s, 2H), 4.04 (s, 1H), 3.18 (s, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 319.

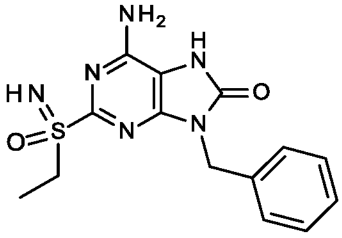
Separation of compound of **Example 1** by chiral HPLC afforded **Example 1-A** (faster eluting, 7.1 mg) and **Example 1-B** (slower eluting, 9.1 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak OJ-3 column.)

Example 1-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (br. s., 1H), 7.27-7.36 (m, 5H), 6.98 (br. s., 2H), 4.97 (s, 2H), 4.06 (br. s., 1H), 3.18 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 319.

Example 1-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.06 (br. s., 1H), 7.26-7.36 (m, 5H), 6.98 (br. s., 2H), 4.96 (s, 2H), 4.07 (br. s., 1H), 3.18 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 319.

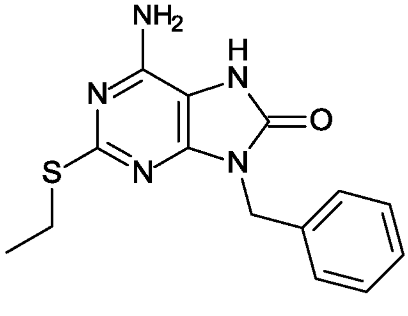
Example 2

6-Amino-9-benzyl-2-(ethylsulfonimidoyl)-7*H*-purin-8-one



2

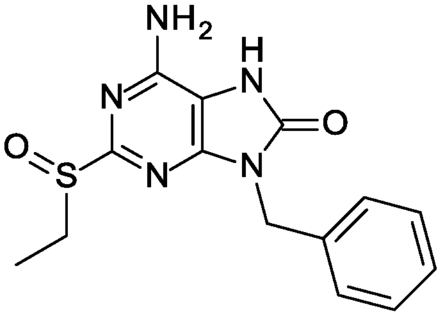
Step 1: Preparation of 6-amino-9-benzyl-2-ethylsulfanyl-7*H*-purin-8-one



2a

Compound **2a** was prepared in analogy to **Example 1, Step 3** by using ethyl bromide instead of methyl iodide. 6-Amino-9-benzyl-2-ethylsulfanyl-7*H*-purin-8-one (500 mg, compound **2a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 302.

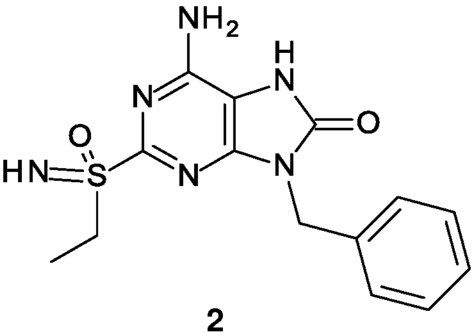
Step 2: Preparation of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one



2b

Compound **2b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-ethylsulfanyl-7*H*-purin-8-one (compound **2a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-ethylsulfinyl-7*H*-purin-8-one (300 mg, compound **2b**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 318.

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

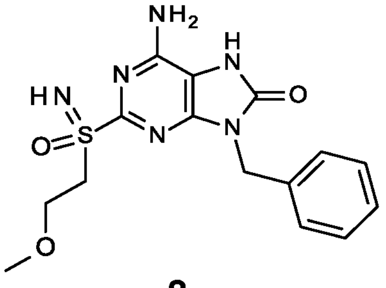


2

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-ethylsulfinyl-7*H*-purin-8-one (compound **2b**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(ethylsulfonimidoyl)-7*H*-purin-8-one (12 mg, compound **2**) was obtained as a white solid. ^1H NMR (400 MHz, CD_3OD) δ ppm: 7.43 (d, $J = 7.03$ Hz, 2H), 7.27-7.36 (m, 3H), 5.11 (s, 2H), 3.44-3.62 (m, 2H), 1.30 (t, $J = 7.40$ Hz, 3H). MS obsd. (ESI^+) $[(M+H)^+]$: 333.

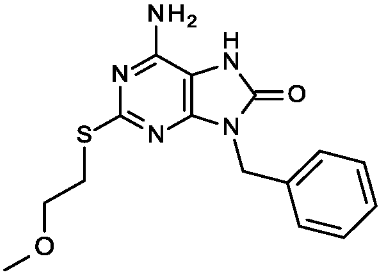
Example 3

6-Amino-9-benzyl-2-(2-methoxyethylsulfonimidoyl)-7*H*-purin-8-one



3

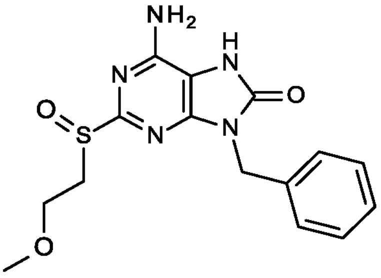
Step 1: Preparation of 6-amino-9-benzyl-2-(2-methoxyethylsulfanyl)-7*H*-purin-8-one



3a

Compound **3a** was prepared in analogy to **Example 1, Step 3** by using 2-bromoethyl methyl ether (TCI, Catalog number: B1242-250G) instead of methyl iodide. 6-Amino-9-benzyl-2-(2-methoxyethylsulfanyl)-7*H*-purin-8-one (600 mg, compound **3a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 332.

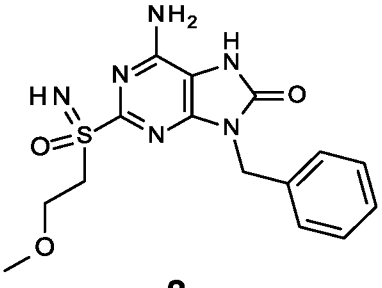
Step 2: Preparation of 6-amino-9-benzyl-2-(2-methoxyethylsulfinyl)-7*H*-purin-8-one



3b

Compound **3b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-(2-methoxyethylsulfanyl)-7*H*-purin-8-one (compound **3a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(2-methoxyethylsulfinyl)-7H-purin-8-one (350 mg, compound **3b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 348.

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



3

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-methoxyethylsulfinyl-7*H*-purin-8-one (compound **3b**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-amino-9-benzyl-2-(2-methoxyethylsulfonimidoyl)-7H-purin-8-one (21 mg, **Example 3**) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.44 (d, $J = 7.15$ Hz, 2H), 7.25-7.36 (m, 3H), 5.12 (s, 2H), 3.75-3.82 (m, 4H), 3.17 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 363.

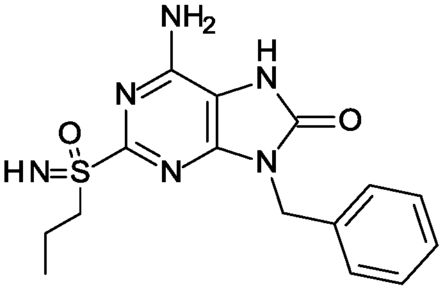
Separation of compound of **Example 3** by chiral HPLC afforded **Example 3-A** (faster eluting, 7.0 mg) and **Example 3-B** (slower eluting, 5.0 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak AS-3 column.)

Example 3-A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.43 (d, $J = 7.15$ Hz, 2H), 7.25-7.36 (m, 3H), 5.12 (s, 2H), 3.75-3.82 (m, 4H), 3.17 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 363.

Example 3-B: ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.44 (d, $J = 7.15$ Hz, 2H), 7.24-7.35 (m, 3H), 5.12 (s, 2H), 3.75-3.82 (m, 4H), 3.17 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 363.

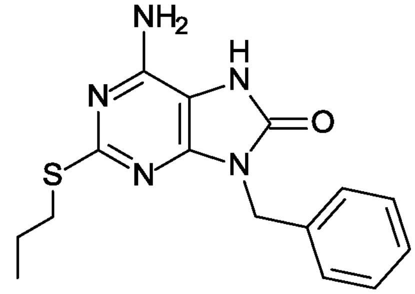
Example 4

6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one



4

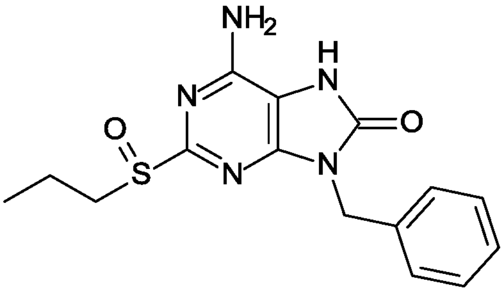
Step 1: Preparation of 6-amino-9-benzyl-2-(2-propylsulfanyl)-7*H*-purin-8-one



4a

Compound **4a** was prepared in analogy to **Example 1, Step 3** by using 1-bromopropane (TCI, Catalog number: B0638-500G) instead of methyl iodide. 6-Amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (240 mg, compound **4a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 316.

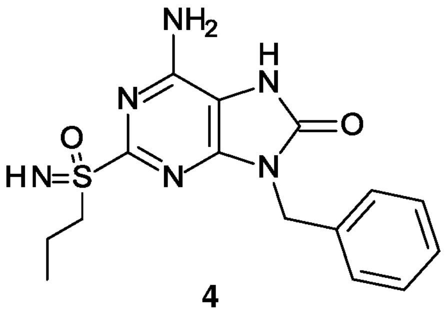
Step 2: Preparation of 6-amino-9-benzyl-2-propylsulfinyl-7*H*-purin-8-one



4b

Compound **4b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (compound **4a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7H-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(2-propylsulfinyl)-7*H*-purin-8-one (210 mg, compound **4b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 332.

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



4

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-(2-propylsulfinyl)-7*H*-purin-8-one (compound **4b**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (80 mg, **Example 4**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.65 (br. s., 1H), 7.26-7.37 (m, 5H), 6.98 (br. s., 2H), 4.97 (s, 2H), 4.02 (s, 1H), 3.33 (t, J = 7.53 Hz, 2H), 1.55-1.74 (m, 2H), 0.92 (t, J =7.53 Hz, 3H) MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 347.

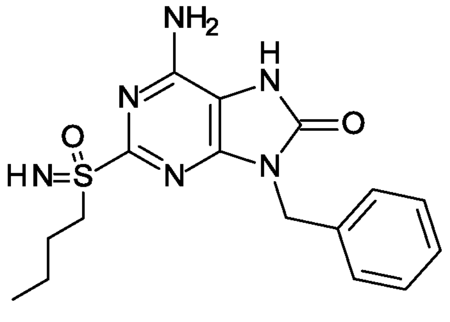
Separation of compound of **Example 4** by chiral HPLC afforded **Example 4-A** (slower eluting, 500 mg) and **Example 4-B** (faster eluting, 490 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO$_2$ on ChiralPak AS-3 column.)

Example 4-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.52 (br. s., 1H), 7.25-7.41 (m, 5H), 6.96 (br. s., 2H), 4.96 (s, 2H), 4.03 (s, 1H), 3.24-3.42 (m, 2H), 1.52-1.75 (m, 2H), 0.92 (t, J = 7.53 Hz, 3H).

Example 4-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.01 (br. s., 1H), 7.26-7.36 (m, 5H), 6.97 (br. s., 2H), 4.96 (s, 2H), 4.03 (s, 1H), 3.26-3.41 (m, 2H), 1.56-1.73 (m, 2H), 0.92 (t, J = 7.53 Hz, 3H).

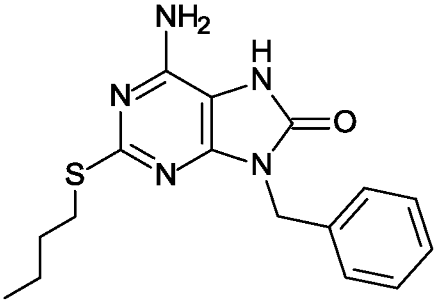
Example 5

6-Amino-9-benzyl-2-(butylsulfonimidoyl)-7*H*-purin-8-one



5

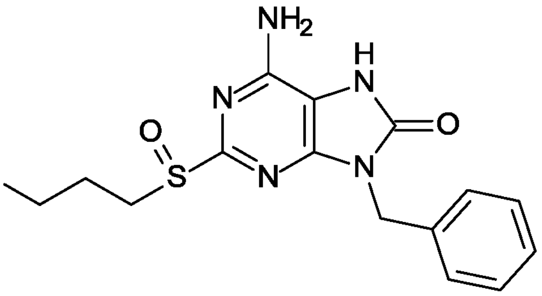
Step 1: Preparation of 6-amino-9-benzyl-2-butylsulfanyl-7*H*-purin-8-one



5a

Compound **5a** was prepared in analogy to **Example 1, Step 3** by using 1-bromobutane (TCI, Catalog number: B560-500G) instead of methyl iodide. 6-Amino-9-benzyl-2-butylsulfanyl-7*H*-purin-8-one (600 mg, compound **5a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 330.

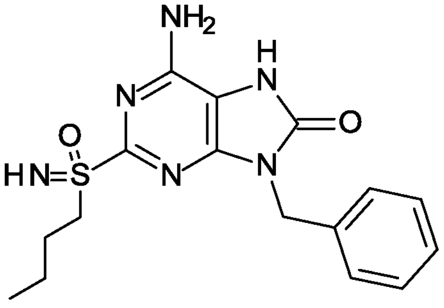
Step 2: Preparation of 6-amino-9-benzyl-2-butylsulfinyl-7*H*-purin-8-one



5b

Compound **5b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-butylsulfanyl-7*H*-purin-8-one (compound **5a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7H-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(2-butylsulfinyl)-7*H*-purin-8-one (400mg, compound **5b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 346.

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

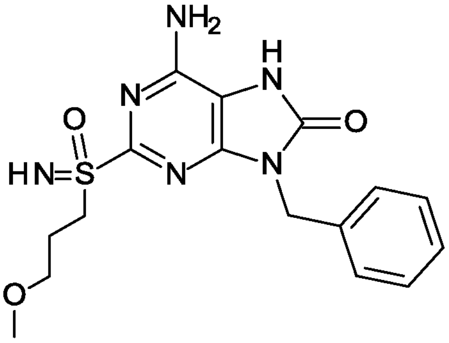


5

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-(2-butylsulfinyl)-7*H*-purin-8-one (compound **5b**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(butylsulfonimidoyl)-7*H*-purin-8-one (40 mg, **Example 5**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.59 (s, 1H), 7.24-7.39 (m, 5H), 6.97 (br. s., 2H), 4.96 (s, 2H), 4.03 (s, 1H), 3.35-3.46 (m, 2H),1.51-1.61 (m, 2H), 1.27-1.39 (m, 2H), 0.84 (t, J = 7.34 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

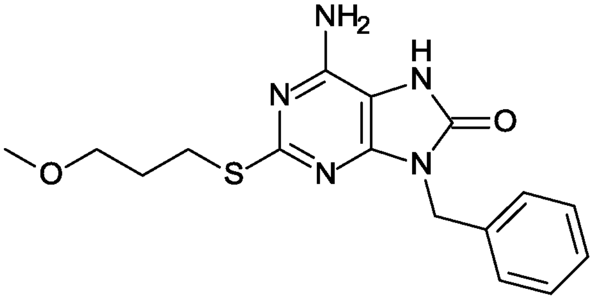
Example 6

6-Amino-9-benzyl-2-(3-methoxypropylsulfonimidoyl)-7*H*-purin-8-one



6

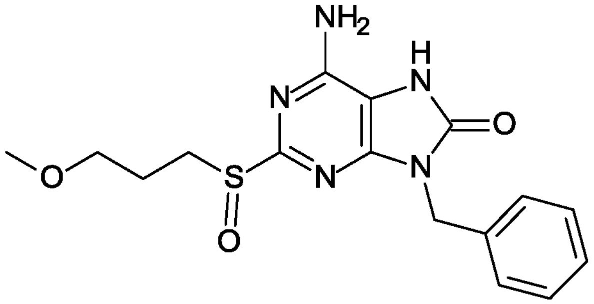
Step 1: Preparation of 6-amino-9-benzyl-2-(3-methoxypropylsulfanyl)-7*H*-purin-8-one



6a

Compound **6a** was prepared in analogy to **Example 1, Step 3** by using 1-bromo-3-methoxylpropane (TCI, Catalog number: B3499-25G) instead of methyl iodide. 6-Amino-9-benzyl-2-methoxypropylsulfanyl-7*H*-purin-8-one (220 mg, compound **6a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 346.

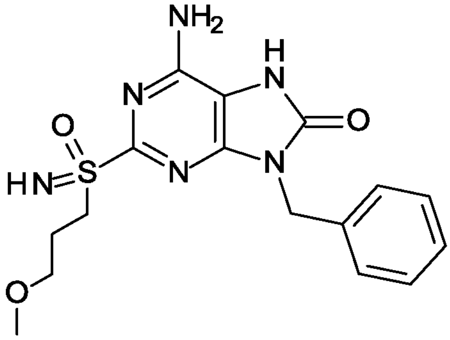
Step 2: Preparation of 6-amino-9-benzyl-2-(3-methoxypropylsulfinyl)-7*H*-purin-8-one



6b

Compound **6b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (compound **6a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7H-purin-8-one (compound **1c**). 6-amino-9-benzyl-2-(2-methoxypropylsulfinyl)-7*H*-purin-8-one (110 mg, compound **6b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 362.

Step 3: Preparation of 6-amino-9-benzyl-2-(butylsulfonimidoyl)-7*H*-purin8-one

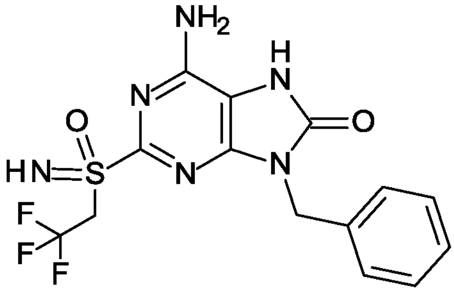


6

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-(2-methoxypropylsulfinyl)-7*H*-purin-8-one (compound **6b**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(methoxypropylsulfonimidoyl)-7*H*-purin-8-one (20 mg, **Example 6**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.59 (s, 1H), 7.29-7.34 (m, 5H), 7.00 (br. s., 2H), 4.96 (s, 2H), 4.13 (s, 1H), 4.10 (m, 4H), 3.20 (s, 3H), 1.86 (m, 2H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 377.

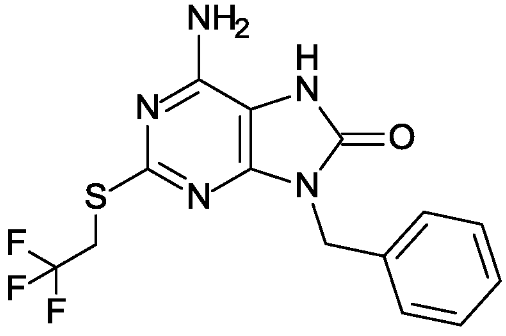
Example 7

6-Amino-9-benzyl-2-(2,2,2-trifluoroethylsulfonimidoyl)-7*H*-purin-8-one



7

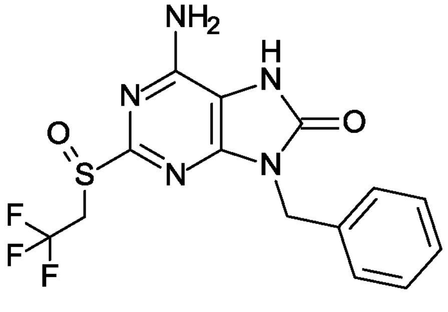
Step 1: Preparation of 6-amino-9-benzyl-2-(2,2,2-trifluoroethylsulfanyl)-7*H*-purin-8-one



7a

Compound **7a** was prepared in analogy to **Example 1, Step 3** by using 2,2,2-trifluoroethyl iodide (TCI, Catalog number: T1148-25G) instead of methyl iodide. 6-Amino-9-benzyl-2-(2,2,2-trifluoroethyl)sulfanyl-7*H*-purin-8-one (compound **7a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 356.

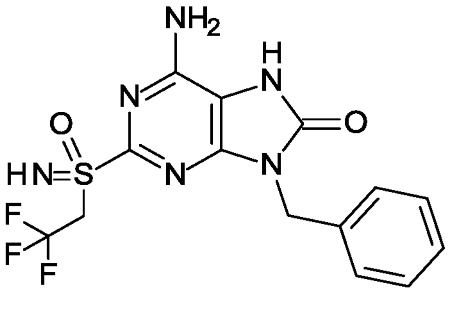
Step 2: Preparation of 6-amino-9-benzyl-2-(2,2,2-trifluoroethylsulfinyl)-7*H*-purin-8-one



7b

Compound **7b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-2,2,2-trifluoroethylsulfanyl sulfanyl-7*H*-purin-8-one (compound **7a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7H-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(2-2,2,2-trifluoroethylsulfinyl)-7*H*-purin-8-one (compound **7b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 372.

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

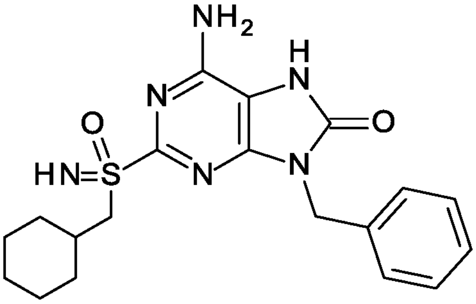


7

The title compound was prepared in analogy to **Example 1, Step 5** by using 6-amino-9-benzyl-2-(2-2,2,2-trifluoroethylsulfinyl)-7*H*-purin-8-one (compound **7b**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(2,2,2-trifluoroethylsulfonimidoyl)-7H-purin-8-one (20 mg, **Example 7**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.59 (br. s., 1H), 7.25-7.37 (m, 5H), 7.06 (br. s., 2H), 4.95-5.01 (m, 3H), 4.85 (qd, J = 10.02, 15.37 Hz, 1H), 4.63 (qd, J = 9.92, 15.40 Hz, 1H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

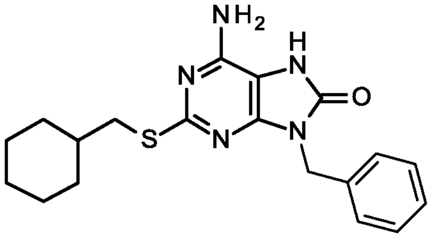
Example 8

6-Amino-9-benzyl-2-(cyclohexylmethylsulfonimidoyl)-7*H*-purin-8-one



8

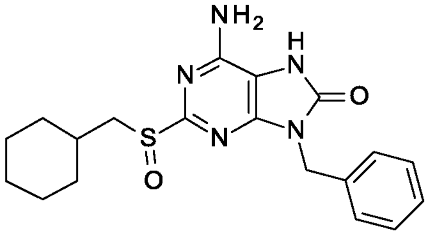
Step 1: Preparation of 6-amino-9-benzyl-2-(cyclohexylmethylsulfanyl)-7*H*-purin-8-one



8a

Compound **8a** was prepared in analogy to **Example 1, Step 3** by using cyclohexylmethyl bromide (TCI, Catalog number: B1708-25G) instead of methyl iodide. 6-Amino-9-benzyl-2-cyclohexylmethylsulfanyl-7*H*-purin-8-one (260 mg. compound **8a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 370.

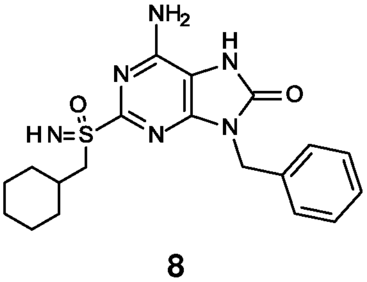
Step 2: Preparation of 6-amino-9-benzyl-2-(cyclohexylmethylsulfinyl)-7*H*-purin-8-one



8b

Compound **8b** was prepared in analogy to **Example 1, Step 4** by using 6-amino-9-benzyl-2-cyclohexylmethylsulfanyl-7*H*-purin-8-one (compound **8a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7H-purin-8-one (compound **1c**). 6-Amino-9-benzyl-2-(2-cyclohexylmethylsulfinyl)-7*H*-purin-8-one (120 mg, compound **8b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 386.

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

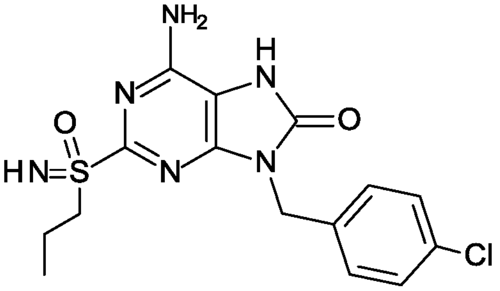


8

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-benzyl-2-(2-cyclohexylmethylsulfinyl)-7*H*-purin-8-one (compound **8b**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-9-benzyl-2-(cyclohexylmethylsulfonimidoyl)-7*H*-purin-8-one (40 mg, **Example 8**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.59 (br. s., 1H), 7.27-7.33 (m, 5H), 6.97 (br. s., 2H), 4.97 (s, 2H), 4.03 (s, 1H), 3.26-3.29 (m, 2H), 1.54-1.86 (m, 5H), 0.89-1.12 (m, 6H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 401.

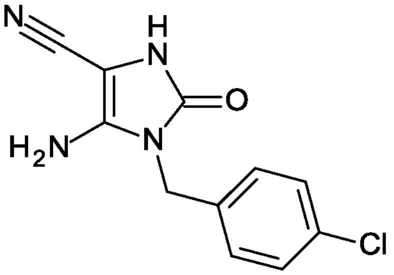
Example 9

6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



9

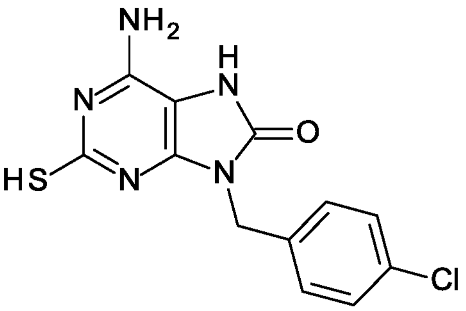
Step 1: Preparation of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile



9a

To a solution of triphosgene (5.9 g, 20 mmol) in dry THF (40 mL) was added (4-chlorophenyl)methylamine (8.5 g, 60 mmol, Accela ChemBio Inc, Catalog number: SY004062-25g) and DIPEA (12.4 g, 96 mmol) in dry THF (80 mL) at -80 °C. The solution was stirred at -80 °C for 15 min. A solution of aminomalononitrile *p*-toluenesulfonate (15.2 g, 60 mmol, TCI, Catalog number: A1119-25G) and DIPEA (6.2 g, 48 mmol) in dry THF (40 mL) was added at -80 °C. After stirred at RT for 24 hrs, the reaction was concentrated *in vacuo* and the residue was partitioned between EtOAc (300 mL) and water (150 mL). The separated organic layer was washed with brine (50 mL) two times, and extracted with sodium hydroxide solution (50 mL, 1 *N*) two times. The combined sodium hydroxide solution layer was neutralized with 10% wt. sodium hydrogen sulfate solution and extracted with EtOAc. Then the separated organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether and then the mixture was filtered to give 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (8.0 g, compound **9a**) as a yellow solid. MS obsd. (ESI^+) [$(M+H)^+$]: 249.

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

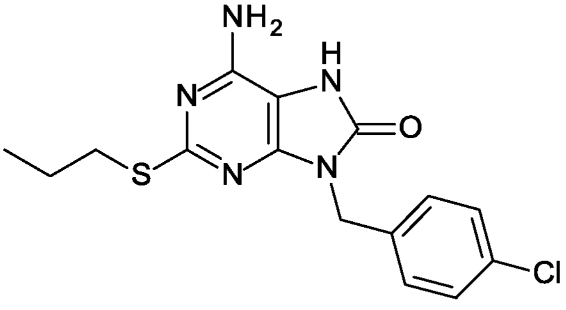


9b

To a solution of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (8.0 g, 32.0 mmol, compound **9a**) in THF (100 mL) was added benzoylisothiocyanate (11.5 g, 70.4 mmol, TCI, Catalog number: A11596-100G) dropwise. After stirred at RT for 12 hrs, the reaction mixture was concentrated *in vacuo*. The residue was triturated in diethyl ether (100 mL) and the resulting precipitate was collected by filtration.

To a solution of the obtained precipitate in THF (300 mL) was added sodium hydroxide (30 mL, 2 *N*). The mixture was refluxed for 50 hrs, and then acidified to pH 3 with 10 wt.% aqueous sodium hydrogen sulfate solution. The resulting precipitate was collected by filtration to give a crude product 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **9b**) as a yellow solid (6.4 g). The product was used in the next step without further purification. MS obsd. (ESI^+) [$(M+H)^+$]: 308.

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

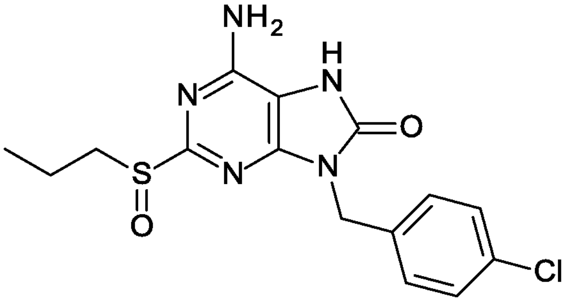


9c

Compound **9c** was prepared in analogy to **Example 1**, **Step 3** by using *n*-propyl bromide and 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **9b**) instead of methyl iodide and 6-amino-9-phenylmethyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-

Amino-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7H-purin-8-one (800 mg, compound **9c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

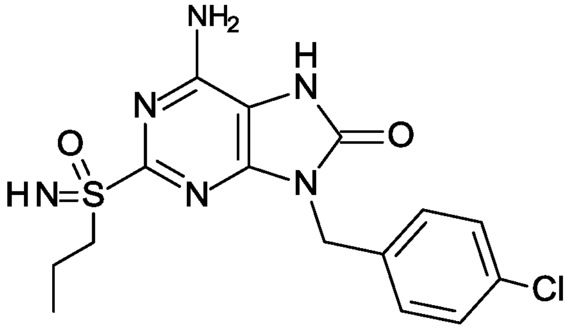
Step 4: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



9d

Compound **9d** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **9c**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (150 mg, compound **9d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 366.

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



9

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **9d**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (25 mg, **Example 9**) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.60 (br. s, 1H), 7.32-7.42 (m, 4H), 6.98 (br. s, 2H), 4.96 (s, 2H), 4.03 (s, 1H), 3.25-3.41 (m, 2H), 1.56-1.68 (m, 2H), 0.91 (t, J = 8 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 381.

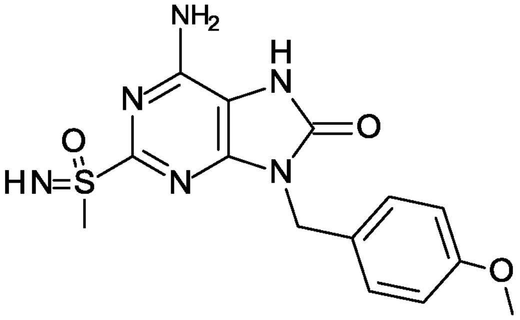
Separation of compound of **Example 9** by chiral HPLC afforded **Example 9-A** (faster eluting, 21 mg) and **Example 9-B** (slower eluting, 10 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak OJ-3 column.)

Example 9-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.63 (br. s, 1H), 7.34-7.41 (m, 4H), 6.99 (br. s, 2H), 4.96 (s, 2H), 4.05 (br. s, 1H), 3.29-3.38 (m, 2H), 1.58-1.66 (m, 2H), 0.91 (t, J = 8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 381.

Example 9-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.63 (br. s, 1H), 7.34-7.41 (m, 4H), 6.99 (br. s, 2H), 4.96 (s, 2H), 4.05 (br. s, 1H), 3.29-3.38 (m, 2H), 1.58-1.66 (m, 2H), 0.91 (t, J = 8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 381.

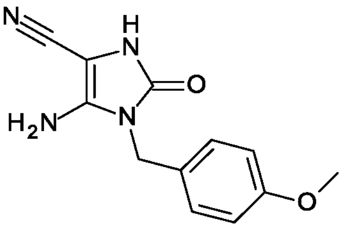
Example 10

6-Amino-9-[(4-methoxyphenyl)methyl]-2-(methylsulfonimidoyl)-7*H*-purin-8-one



10

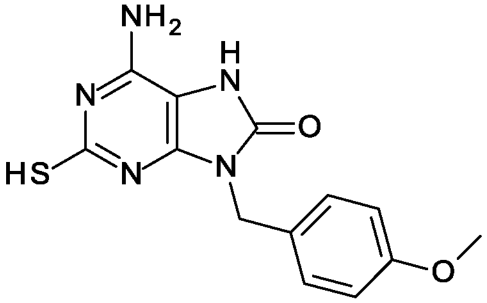
Step 1: Preparation of 4-amino-3-[(4-methoxyphenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile



10a

Compound **10a** was prepared in analogy to **Example 9**, **Step 1** by using (4-methoxyphenyl)methylamine instead of 4-chloropenylmethylamine. 4-Amino-3-[(4-methoxyphenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (7.5g, compound **10a**) was prepared as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 245.

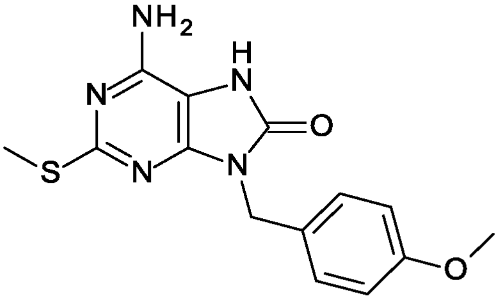
Step 2: Preparation of 6-amino-9-[(4-methoxyphenyl)methyl]-2-sulfanyl-7*H*-purin-8-one



10b

Compound **10b** was prepared in analogy to **Example 9**, **Step 2** by using 4-amino-3-[(4-methoxyphenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **10a**) instead of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **9a**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (11.4 g, compound **10b**) was prepared as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 304.

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

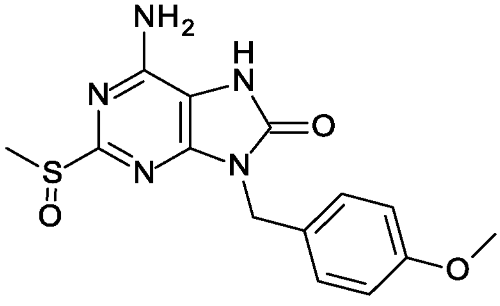


10c

Compound **10c** was prepared in analogy to **Example 1, Step 3** by using 6-amino-9-[(4-methoxyphenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **10b**) instead of 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-

methylsulfanyl-7*H*-purin-8-one (2.3 g, compound **10c**) was prepared as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 318.

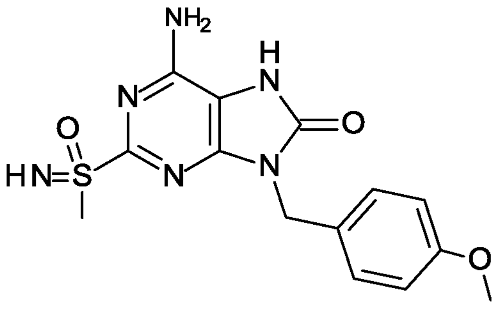
Step 4: Preparation of 6-amino-9-[(4-methoxyphenyl)methyl]-2-methylsulfinyl-7*H*-purin-8-one



10d

Compound **10d** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-9-[(4-methoxyphenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one (compound **10c**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-methylsulfinyl-7*H*-purin-8-one (130 mg, compound **10d**) was prepared as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 334.

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



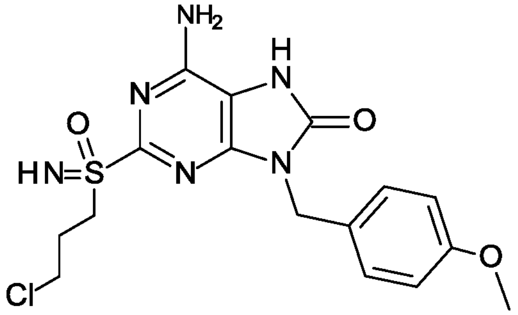
10

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-[(4-methoxyphenyl)methyl]-2-methylsulfinyl-7*H*-purin-8-one (compound **10d**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(4-methoxyphenyl)methyl]-2-(methylsulfonimidoyl)-7*H*-purin-8-one (10 mg, **Example 10**) was prepared as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (br. s, 1H), 7.32 (t, *J* =

6.41 Hz, 2H), 6.95 (br. s, 2H), 6.89 (t, *J* = 6.38 Hz, 2H), 4.89 (s, 2H), 4.07 (s, 1H), 3.72 (s, 3H), 3.21 (s, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 349.

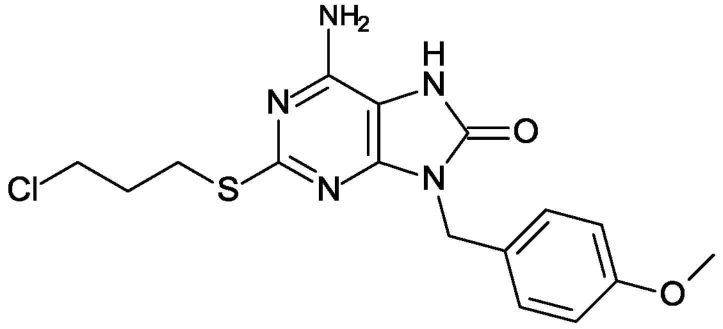
Example 11

6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one



11

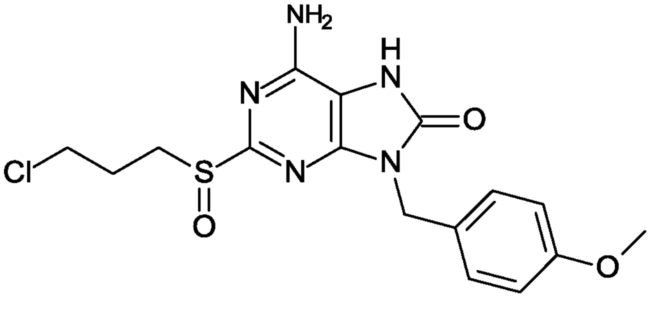
Step 1: Preparation of 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one



11a

Compound **11a** was prepared in analogy to **Example 1**, **Step 3** by using 1-bromo-3-chloro-propane and 6-amino-9-[(4-methoxyphenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **10b**) instead of methyl iodide and 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (3.2 g, compound **11a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 380.

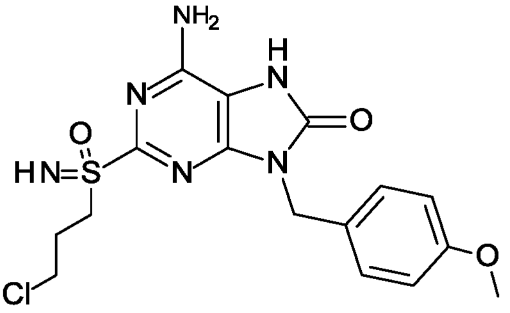
Step 2: Preparation of 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one



11b

Compound **11b** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-2-(3-chloropropylsulfanyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (compound **11a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-2-(3-chloropropylsulfinyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (1.3 g, compound **11b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 396.

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

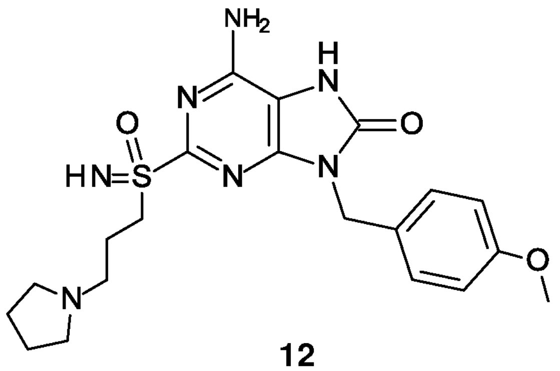


11

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-2-(3-chloropropylsulfinyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (compound **11b**) instead of 6-amino-9-benzyl-2-(2-methylsulfanyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (40 mg, **Example 11**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (br. s, 1H), 7.32 (t, $J = 6.41$ Hz, 2H), 6.95 (br. s, 2H), 6.89 (t, $J = 6.38$ Hz, 2H), 4.89 (s, 2H), 4.07 (s, 1H), 3.89 (m, 2H), 3.72 (s, 3H), 3.52 (m, 2H), 2.13 (m, 2H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 411.

Example 12

6-Amino-9-[(4-methoxyphenyl)methyl]-2-(3-pyrrolidin-1-ylpropylsulfonimidoyl)-7*H*-purin-8-one

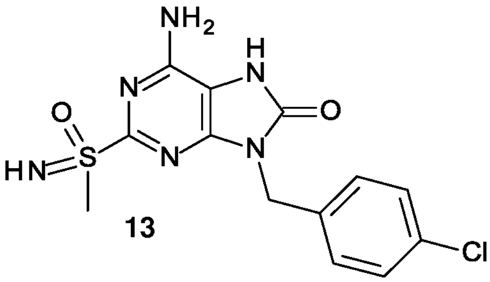


12

To a solution of 6-amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7*H*-purin-8-one (150 mg, compound **11**) in DMSO (5 mL) was added pyrrolidine (0.9 mL, 11.0 mmol) drop wise. The mixture was stirred at 80 °C for 2 hrs. The resulting mixture was diluted with brine (60 mL), extracted with EtOAc (60 mL) three times. The organic layer was combined, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-amino-9-[(4-methoxyphenyl)methyl]-2-(3-pyrrolidin-1-ylpropylsulfonimidoyl)-7*H*-purin-8-one (26 mg, **Example 12**) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.88 (br. s, 1H), 7.29 (t, J = 6.41 Hz, 2H), 7.05 (br. s, 2H), 6.88 (t, J = 6.38 Hz, 2H), 4.88 (s, 2H), 3.72 (m, 4H), 2.52 (m, 4H), 2.45 (m, 4H), 1.84 (m, 2H), 1.67 (m, 4H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 446.

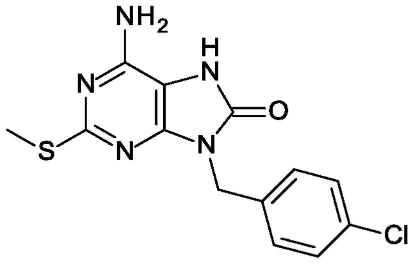
Example 13

6-Amino-9-[(4-chlorophenyl)methyl]-2-(methylsulfonimidoyl)-7*H*-purin-8-one



13

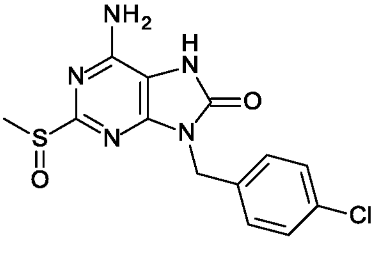
Step 1: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one



13a

Compound **13a** was prepared in analogy to **Example 1**, **Step 3** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **9b**) instead of 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one (1.2 g, compound **13a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 322.

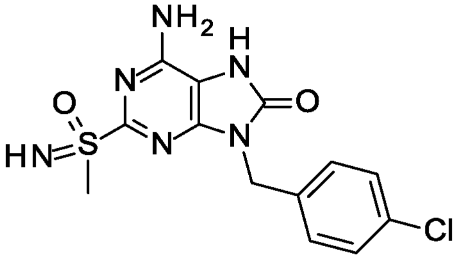
Step 2: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-methylsulfinyl-7*H*-purin-8-one



13b

Compound **13b** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one (compound **13a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one (148 mg, compound **13b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 338.

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

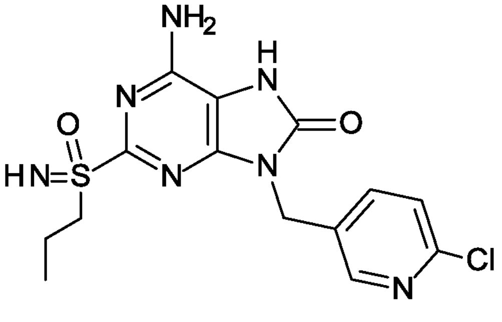


13

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-methylsulfanyl-7*H*-purin-8-one (compound **13b**) instead of using 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-methylsulfinyl-7*H*-purin-8-one (7 mg, **Example 13**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (br. s, 1H), 7.36-7.51 (m, 4H), 6.98 (br. s, 2H), 4.96 (s, 2H), 4.07 (s, 1H), 3.18 (s, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 353.

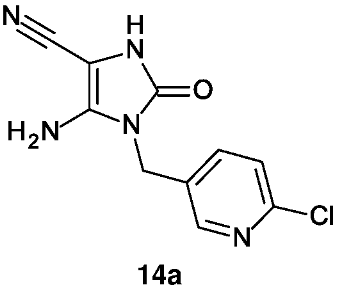
Example 14

6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



14

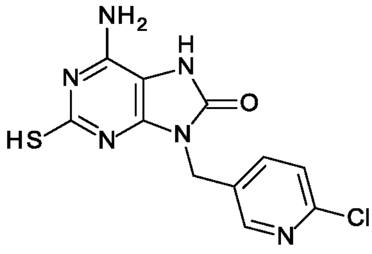
Step 1: Preparation of 4-amino-3-[(6-chloro-3-pyridyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile



14a

Compound **14a** was prepared in analogy to **Example 9**, **Step 1** by using (6-chloro-3-pyridyl)methanamine (Alfa Aesar (China) Co., Ltd., Catalog number: L19283-25 g) instead of (4-chlorophenyl)methylamine. 4-Amino-3-[(6-chloro-3-pyridyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (7.8 g, compound **14a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 250.

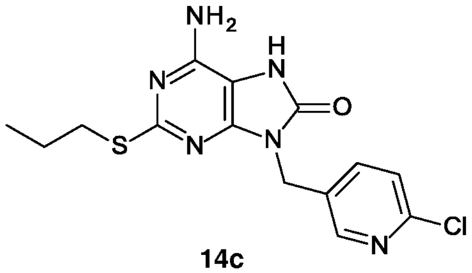
Step 2: Preparation of 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-sulfanyl-7*H*-purin-8-one



14b

Compound **14b** was prepared in analogy to **Example 9**, **Step 2** by using 4-amino-3-[(6-chloro-3-pyridyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **14a**) instead of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **9a**). 6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-sulfanyl-7*H*-purin-8-one (1.1 g, compound **14b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 309.

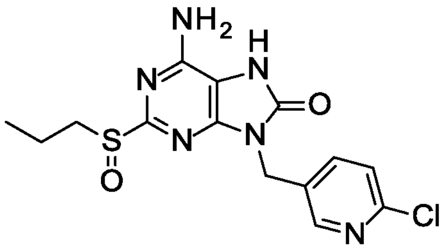
Step 3: Preparation of 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



14c

Compound **14c** was prepared in analogy to **Example 1**, **Step 3** by using 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **14b**) instead of 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (750 mg, compound **14c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 351.

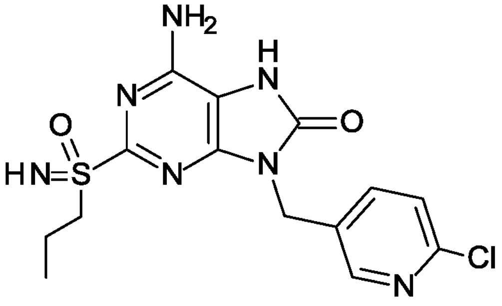
Step 4: Preparation of 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



14d

Compound **14d** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **14c**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (750 mg, compound **14d**). MS obsd. (ESI$^+$) [(M+H)$^+$]: 367.

Step 5: Preparation of 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one

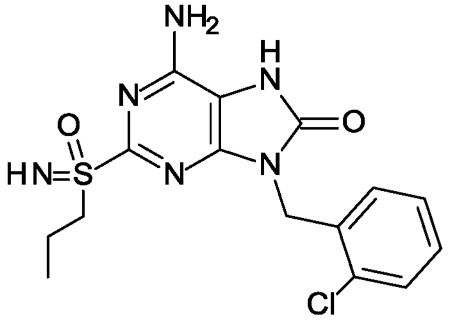


14

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-[(6-chloro-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **14d**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (4 mg, **Example 14**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.80 (br. s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 2.4, 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.04 (br. s, 2H), 5.01 (s, 2H), 4.06 (s, 1H), 3.24-3.43 (m, 2H), 1.53-1.73 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 382.

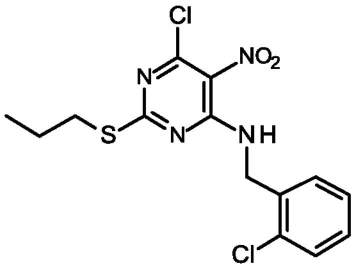
Example 15

6-Amino-9-[(2-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



15

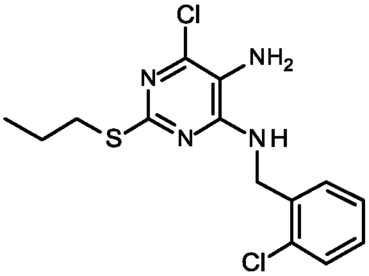
Step 1: Preparation of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



15a

To a solution of 4, 6-dichloro-5-nitro-2-propylsulfanyl-pyrimidine (10 g, 37.0 mmol, J & K scientific, Catalog number: J92_090911_25G) and DIPEA (5.8 g, 45 mmol) in THF (200 mL) was added a solution of (2-chlorophenyl)methylamine (5.5 g, 39 mmol) in THF (50 mL) at -78 °C. After the addition, the mixture was stirred at this temperature for 2 hrs. The resulting mixture was concentrated, extracted with EtOAc. The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluted with PE/ EtOAc from 20/1 to 5/1 (V/V) to give 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (11 g, compound **15a**) as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 373.

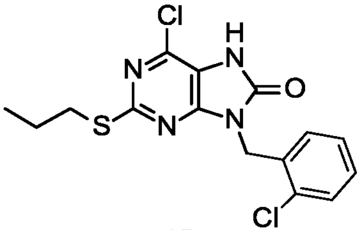
Step 2: Preparation of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



15b

To a solution of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (11 g, 29.5 mmol, compound **15a**) and HOAc (17.7 g, 295 mmol) in THF (400 mL) at 0 °C was added Zn dust (9.5 g, 147 mmol) in small portions. After the addition, the mixture was stirred at this temperature for 12 hrs and filtered. The filtrate was basified with $NaHCO_3$, extracted with DCM, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (9.0 g, compound **15b**). MS obsd. (ESI^+) $[(M+H)^+]$: 343.

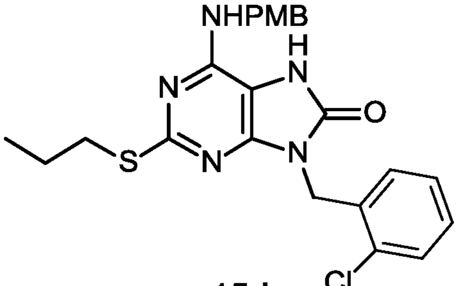
Step 3: Preparation of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



15c

To a solution of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (9.0 g, 26.2 mmol, compound **15b**) in THF (800 mg) was added CDI (21 g, 131 mmol). The reaction was kept at 80 °C for 12 hrs. The reaction mixture was cooled to RT, and then concentrated *in vacuo*. The residue was diluted with water (100 mL), extracted with EtOAc (125 mL) two times, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column eluted with PE / EtOAc from 10/1 to 1:1 (V/V) to give 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (9.5 g, compound **15c**) as a gray solid. MS obsd. (ESI^+) $[(M+H)^+]$: 369.

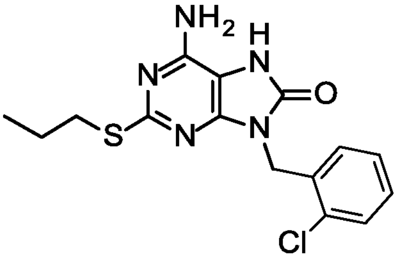
Step 4: Preparation of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



15d

To a solution of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (9.0 g, 26.2 mmol, compound **15c**) in *n*-BuOH (200 mL) was added PMBNH$_2$ (36 g, 262 mmol). The reaction was stirred at 130 °C for 12 hrs. The reaction mixture was cooled to 20 °C, poured into PE. The formed precipitate was collected by filtration to give 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one as a white solid (10.2 g, compound **15d**). MS obsd. (ESI$^+$) [(M+H)$^+$]: 470.

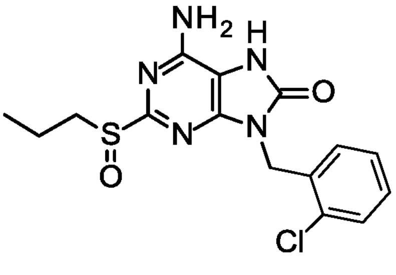
Step 5: Preparation of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



15e

9-[(2-Chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (2.0 g, 4.2 mmol, compound **15d**) was dissolved in TFA (10 mL) and stirred at 60 °C for 12 hrs. The reaction mixture was concentrated *in vacuo*, and basified with NaHCO$_3$ solution. The resulting precipitate was collected by filtration and purified to give 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (600 mg, compound **15e**). MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

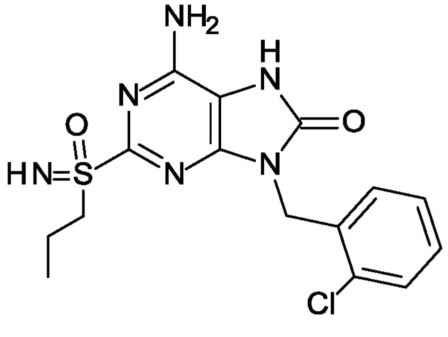
Step 6: Preparation of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



15f

To a solution of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (300 mg, 0.86 mmol, compound **15e**) in THF (7 mL) was added *m*-CPBA (221 mg,1.29 mmol) at 0 °C and the reaction mixture was stirred at 25 °C for 15 min. The mixture was filtered, and washed with THF (1 mL) three times. The obtained solid was co-evaporated with toluene two times to give 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (150 mg, compound **15f**) as a white solid. It was used in the next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 366.

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



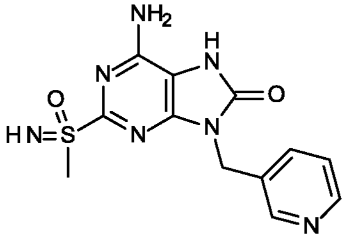
15

To a solution of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (100 mg, 0.27 mmol, compound **15f**) in Eaton's reagent (1 mL) was added NaN_3 (53 mg, 0.81 mmol) and the mixture was stirred at 60 °C for 0.5 hr. The reaction mixture was added to ice water and basified with 0.88 *N* ammonium hydroxide solution, extracted with *n*-BuOH (10 mL) four times and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-amino-9-[(2-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (35 mg, **Example 15**) as a white solid. ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 10.78 (br. s., 1H), 7.51-7.49 (m, 1H), 7.33-

7.28 (m, 2H), 7.14-7.12 (m, 1H), 7.04 (br. s., 2H), 5.05 (s, 2H), 3.98 (s, 1H), 3.35-3.24 (m, 2H), 1.62-1.55 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 381.

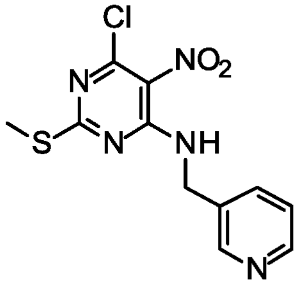
Example 16

6-Amino-2-(methylsulfonimidoyl)-9-(3-pyridylmethyl)-7*H*-purin-8-one



16

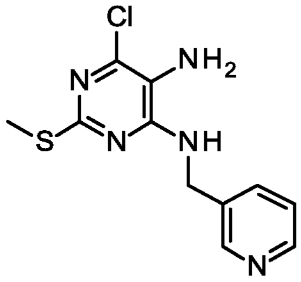
Step 1: Preparation of 6-chloro-2-methylsulfanyl-5-nitro-*N*-(3-pyridylmethyl)pyrimidin-4-amine



16a

Compound **16a** was prepared in analogy to **Example 15**, **Step 1** by using 4-pyridylmethylamine and 4,6-dichloro-2-methylsulfanyl-5-nitro-pyrimidine (J & K scientific, Catalog number: J92-058972-5G) instead of (2-chlorophenyl)methylamine and 4,6-dichloro-2-propylsulfanyl-5-nitro-pyrimidine. 6-Chloro-2-methylsulfanyl-5-nitro-*N*-(3-pyridylmethyl)pyrimidin-4-amine (compound **16a**), which was used in the next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 312.

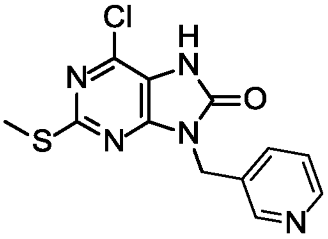
Step 2: Preparation of 6-chloro-2-methylsulfanyl-*N*4-(3-pyridylmethyl)pyrimidine-4,5-diamine



16b

Compound **16b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-2-methylsulfanyl-5-nitro-*N*-(3-pyridylmethyl)pyrimidin-4-amine (compound **16a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-2-methylsulfanyl-*N*4-(3-pyridylmethyl)pyrimidine-4,5-diamine (700 mg, compound **16b**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 282.

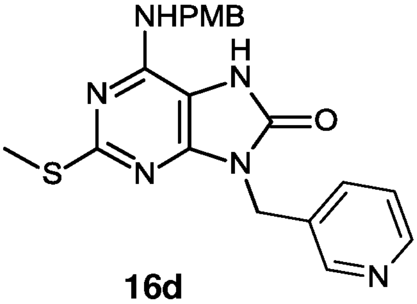
Step 3: Preparation of 6-chloro-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one



16c

Compound **16c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-2-methylsulfanyl-*N*4-(3-pyridylmethyl)pyrimidine-4,5-diamine (compound **16b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (600 mg, compound **16c**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 308.

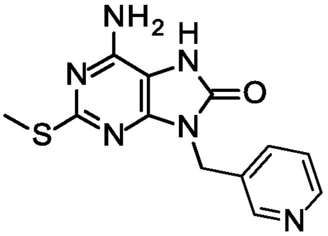
Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one



16d

Compound **16d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (compound **16c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (620 mg, compound **16d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 409.

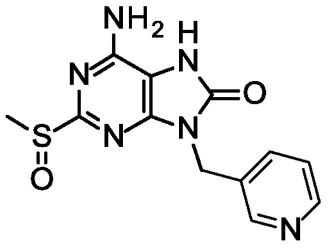
Step 5: Preparation of 6-amino-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one



16e

Compound **16e** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (compound **16d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (380 mg, compound **16e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 289.

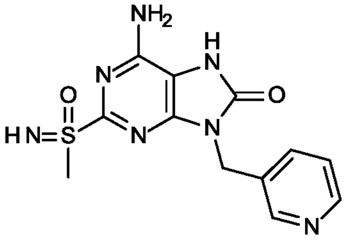
Step 6: Preparation of 6-amino-2-methylsulfinyl-9-(3-pyridylmethyl)-7*H*-purin-8-one



16f

Compound **16f** was prepared in analogy to **Example 15**, **Step 6** by 6-amino-2-methylsulfanyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (compound **16e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-methylsulfinyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (105 mg, compound **16f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 305.

Step 7: Preparation of 6-amino-2-(methylsulfonimidoyl)-9-(3-pyridylmethyl)-7*H*-purin-8-one



16

The title compound was prepared in analogy to **Example 15, Step 7** by using 6-amino-2-methylsulfinyl-9-(3-pyridylmethyl)-7*H*-purin-8-one (200 mg, compound **16f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(methylsulfonimidoyl)-9-(3-pyridylmethyl)-7*H*-purin-8-one (38.2 mg, **Example 16**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.63 (s, 1H), 8.50 (d, J = 4.52 Hz, 1H), 7.77 (d, J = 8.03 Hz, 1H), 7.38 (dd, J = 7.78, 5.02 Hz, 1H), 7.00 (br. s., 2H), 5.01 (s, 2H), 4.11 (br. s, 1H), 3.19 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

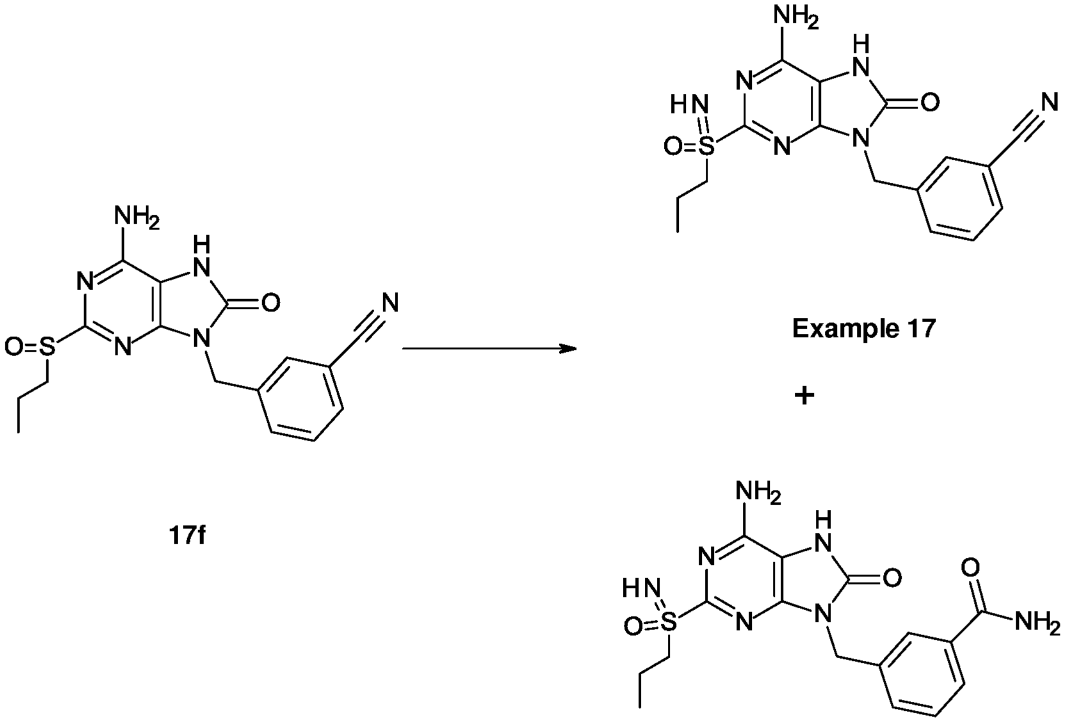
Separation of compound of **Example 16** by chiral HPLC afforded **Example 16-A** (faster eluting, 5.0 mg) and **Example 16-B** (slower eluting, 7.1 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak OJ-3 column.)

Example 16-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.63 (s, 1H), 8.50 (d, J = 4.52 Hz, 1H), 7.77 (d, J = 8.03 Hz, 1H), 7.38 (dd, J = 7.78, 5.02 Hz, 1H), 7.00 (br. s., 2H), 5.01 (s, 2H), 4.11 (br. s, 1H), 3.19 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

Example 16-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.63 (s, 1H), 8.50 (d, J = 4.52 Hz, 1H), 7.77 (d, J = 8.03 Hz, 1H), 7.38 (dd, J = 7.78, 5.02 Hz, 1H), 7.00 (br. s., 2H), 5.01 (s, 2H), 4.11 (br. s, 1H), 3.19 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

Example 17 and Example 18

3-[[6-Amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (compound 17) and 3-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (compound 18)

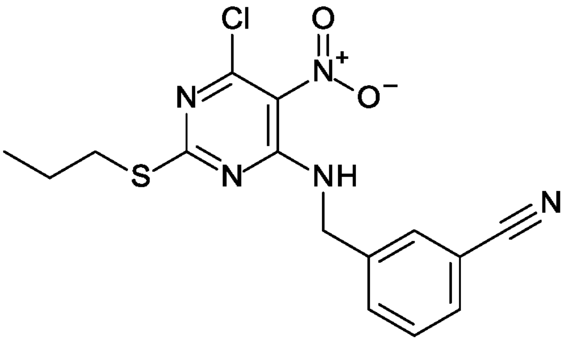


17f

Example 17

Example 18

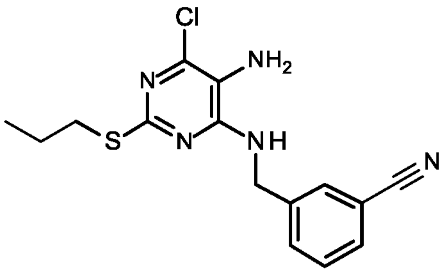
Step 1: Preparation of 3-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile



17a

Compound **17a** was prepared in analogy to **Example 15, Step 1** by using 3-(aminomethyl)benzonitrile instead of (2-chlorophenyl)methylamine. 3-[[(6-Chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (2.75g, compound **17a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 364.

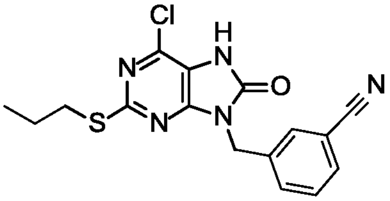
Step 2: Preparation of 3-[[(5-amino-6-chloro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile



17b

Compound **17b** was prepared in analogy to **Example 15**, **Step 2** by using 3-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (compound **17a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 3-[[(5-Amino-6-chloro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (1.1 g, compound **17b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 334.

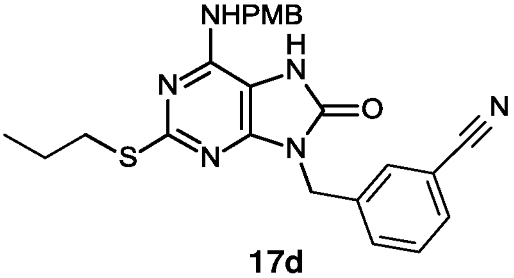
Step 3: Preparation of 3-[(6-chloro-2-propylsulfanyl-8-*oxo*-7*H*-purin-9-yl)methyl]benzonitrile



17c

Compound **17c** was prepared in analogy to **Example 15**, **Step 3** by using 3-[[(5-amino-6-chloro-2-methylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (compound **17b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 3-[(6-Chloro-2-methylsulfanyl-8-*oxo*-7*H*-purin-9-yl)methyl]benzonitrile (700 mg, compound **17c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 360.

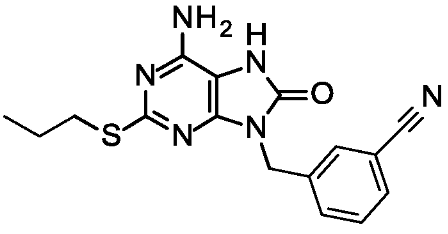
Step 4: Preparation of 3-[[6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-8-*oxo*-7*H*-purin-9-yl]methyl]benzonitrile



17d

Compound **17d** was prepared in analogy to **Example 15**, **Step 4** by using 3-[(6-chloro-2-methylsulfanyl-8-*oxo*-7*H*-purin-9-yl)methyl]benzonitrile (compound **17c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 3-[[6-[(4-Methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzonitrile (900 mg, compound **17d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 461.

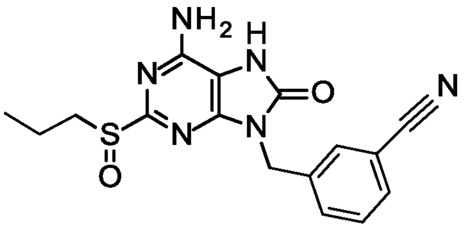
Step 5: Preparation of 3-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile



17e

Compound **17e** was prepared in analogy to **Example 15**, **Step 5** by using 3-[[6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-8-*oxo*-7*H*-purin-9-yl]methyl]benzonitrile (compound **17d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 3-[(6-Amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (600 mg, compound **17e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 341.

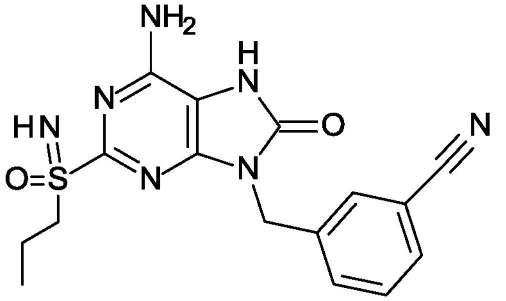
Step 6: Preparation of 3-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzonitrile



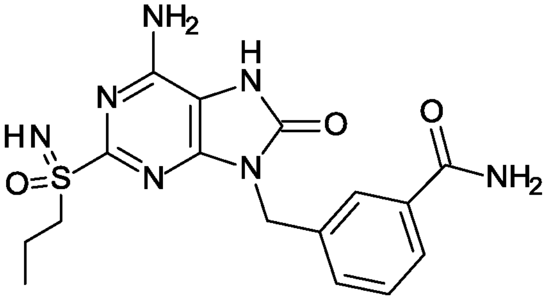
17f

Compound **17f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-2-propylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (compound **17e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 3-[(6-Amino-8-oxo-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzonitrile (610 mg, compound **17f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 357.

Step 7: Preparation of 3-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (compound 17) and 3-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (compound 18)



17



18

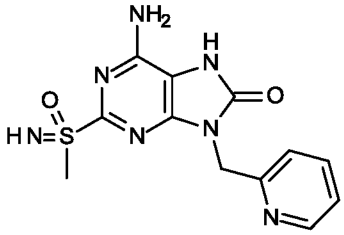
The title compound was prepared in analogy to **Example 15, Step 7** by using 6-amino-2-methylsulfinyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (270 mg, compound **17f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 3-[[6-Amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (5 mg, **Example 17**) and 3-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (41 mg, **Example 18**) was obtained as white solid.

Compound **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.62 (br. s, 1H), 7.76-7.80 (m, 2H), 7.66 (d, J = 8 Hz, 1H), 7.53-7.57 (m, 1H), 6.99 (br. s, 2H), 5.02 (s, 2H), 4.05 (s, 1H), 3.28-3.31 (m, 2H), 1.57-1.65 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 372.

Compound **18:** ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.85 (br. s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.77 (d, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.37-7.42 (m, 2H), 7.06 (br. s, 2H), 5.00 (s, 2H), 4.01 (s, 1H), 3.28-3.30 (m, 2H), 1.55-1.67 (m, 2H), 0.88 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 390.

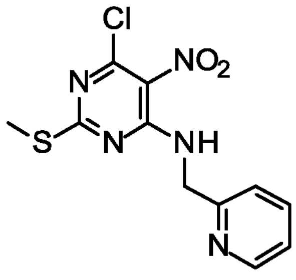
Example 19

6-Amino-2-(methylsulfonimidoyl)-9-(2-pyridylmethyl)-7*H*-purin-8-one



19

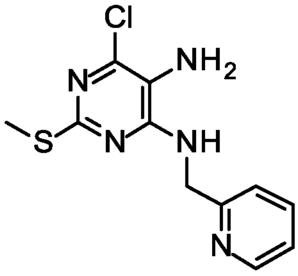
Step 1: Preparation of 6-chloro-2-methylsulfanyl-5-nitro-*N*-(2-pyridylmethyl)pyrimidin-4-amine



19a

Compound **19a** was prepared in analogy to **Example 15**, **Step 1** by using 2-pyridylmethylamine and 4,6-dichloro-2-methylsulfanyl-5-nitro-pyrimidine instead of (2-chlorophenyl)methylamine and 2-chlorophenylmethylamine and 4,6-dichloro-2-propylsulfanyl-5-nitro-pyrimidine. 6-Chloro-2-methylsulfanyl-5-nitro-*N*-(2-pyridylmethyl)pyrimidin-4-amine (4.64 g, compound **19a**) was obtained as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 312.

Step 2: Preparation of 6-chloro-2-methylsulfanyl-*N*4-(2-pyridylmethyl)pyrimidine-4,5-diamine

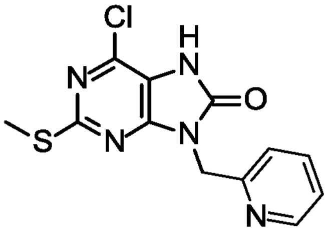


19b

Compound **19b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-2-methylsulfanyl-5-nitro-*N*-(2-pyridylmethyl)pyrimidin-4-amine (compound **19a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**).

6-Chloro-2-methylsulfanyl-*N*4-(2-pyridylmethyl)pyrimidine-4,5-diamine (2.3 g, compound **19b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 282.

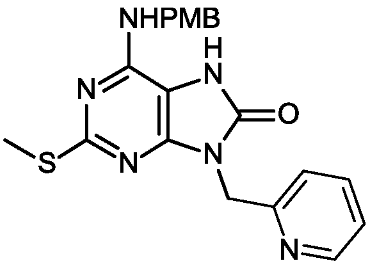
Step 3: Preparation of 6-chloro-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one



19c

Compound **19c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-2-methylsulfanyl-*N*4-(2-pyridylmethyl)pyrimidine-4,5-diamine (compound **19b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (2.0 g, compound **19c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 308.

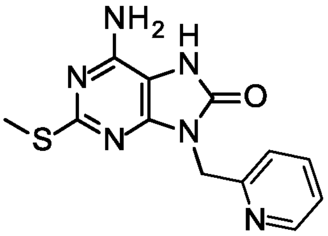
Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one



19d

Compound **19d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (compound **19c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (2.0 g, compound **19d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 409.

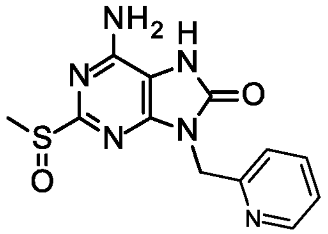
Step 5: Preparation of 6-amino-2-methylsulfanyl-9-(2-pyridylmethyl)-*7H*-purin-8-one



19e

Compound **19e** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (compound **19d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (1.14 g, compound **19e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 289.

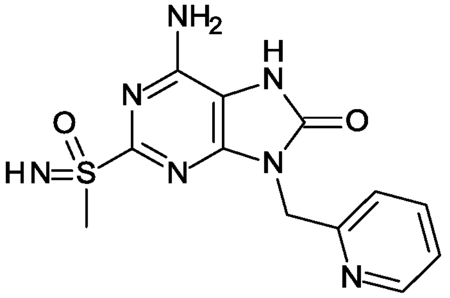
Step 6: Preparation of 6-amino-2-methylsulfinyl-9-(2-pyridylmethyl)-*7H*-purin-8-one



19f

Compound **19f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-2-methylsulfanyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (compound **19e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-methylsulfinyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (280 mg, compound **19f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 305.

Step 7: Preparation of 6-amino-2-(methylsulfonimidoyl)-9-(2-pyridylmethyl)-7*H*-purin-8-one

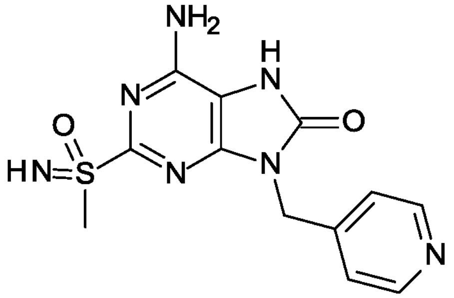


19

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-2-methylsulfinyl-9-(2-pyridylmethyl)-7*H*-purin-8-one (compound **19f**) instead 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(methylsulfonimidoyl)-9-(2-pyridylmethyl)-7*H*-purin-8-one (50 mg, **Example 19**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.47 (d, J = 4.27 Hz, 1H), 7.77 (td, J = 7.65, 1.51 Hz, 1H), 7.24-7.33 (m, 2H), 7.19 (br. s., 2H), 5.09 (s, 2H), 4.00 (br. s., 1H), 3.11 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

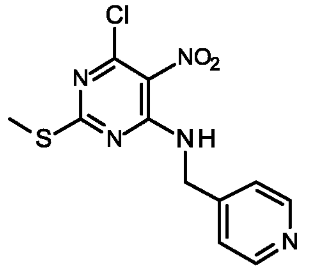
Example 20

6-Amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7*H*-purin-8-one



20

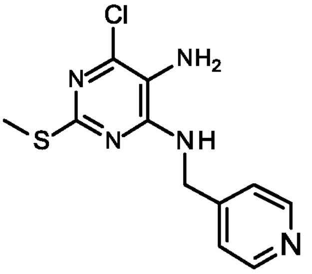
Step 1: Preparation of 6-chloro-2-methylsulfanyl-5-nitro-*N*-(4-pyridylmethyl)pyrimidin-4-amine



20a

Compound **20a** was prepared in analogy to **Example 15**, **Step 1** by using 4-pyridylmethylamine and 4,6-dichloro-2-methylsulfanyl-5-nitro-pyrimidine instead of (2-chlorophenyl)methylamine and 4,6-dichloro-2-propylsulfanyl-5-nitro-pyrimidine. 6-Chloro-2-methylsulfanyl-5-nitro-*N*-(4-pyridylmethyl)pyrimidin-4-amine (1.0 g, compound **20a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 312.

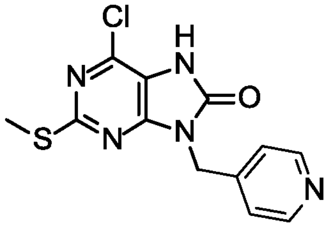
Step 2: Preparation of 6-chloro-2-methylsulfanyl-*N*4-(4-pyridylmethyl)pyrimidine-4,5-diamine



20b

Compound **20b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-2-methylsulfanyl-5-nitro-*N*-(4-pyridylmethyl)pyrimidin-4-amine (compound **20a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-2-methylsulfanyl-*N*4-(4-pyridylmethyl)pyrimidine-4,5-diamine (900 mg, compound **20b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 282.

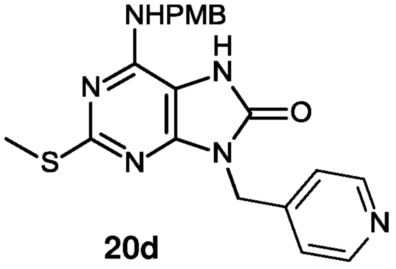
Step 3: Preparation of 6-chloro-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one



20c

Compound **20c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-2-methylsulfanyl-*N*4-(4-pyridylmethyl)pyrimidine-4,5-diamine (compound **20b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (620 mg, compound **20c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 308.

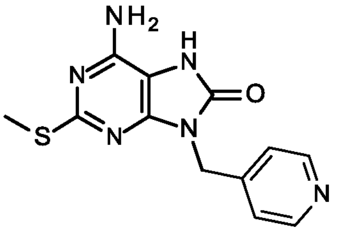
Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one



20d

Compound **20d** was prepared in analogy to **Example 15**, **Step 4** by using 6-Chloro-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (compound **20c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (700 mg, compound **20d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 409.

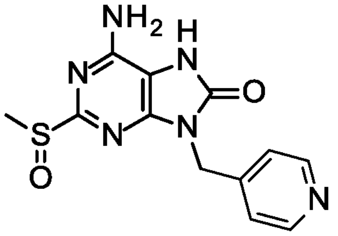
Step 5: Preparation of 6-amino-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one



20e

Compound **20e** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (compound **20d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (450 mg, compound **20e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 289.

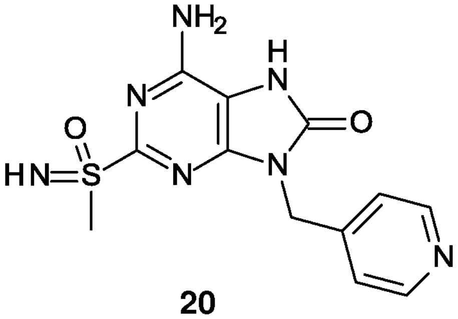
Step 6: Preparation of 6-amino-2-methylsulfinyl-9-(4-pyridylmethyl)-7*H*-purin-8-one



20f

Compound **20f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-2-methylsulfanyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (compound **20e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-methylsulfinyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (160 mg, compound **20f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 305.

Step 7: Preparation of 6-amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7*H*-purin-8-one

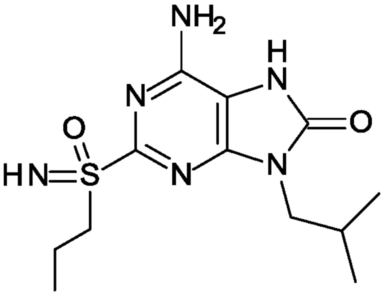


20

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-2-methylsulfinyl-9-(4-pyridylmethyl)-7*H*-purin-8-one (200 mg, compound **20f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7*H*-purin-8-one (27 mg, **Example 20**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.52 (d, J = 5.77 Hz, 2H), 7.29 (d, J = 5.52 Hz, 2H), 7.05 (br. s., 2H), 5.01 (s, 2H), 4.06 (s, 1H), 3.16 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

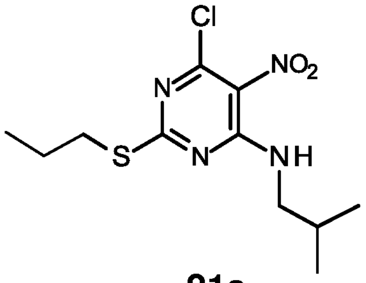
Example 21

6-Amino-9-isobutyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one



21

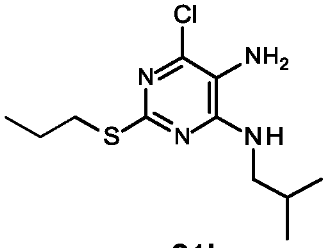
Step 1: Preparation of 6-chloro-*N*-isobutyl-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



21a

Compound **21a** was prepared in analogy to **Example 15**, **Step 1** by using 2-methylpropan-1-amine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-isobutyl-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **21a**) was obtained as a light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 305.

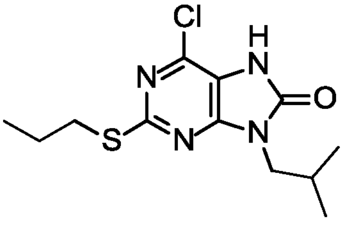
Step 2: Preparation of 6-chloro-*N*4-isobutyl-2-propylsulfanyl-pyrimidine-4,5-diamine



21b

Compound **21b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-isobutyl-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **21a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-isobutyl-2-propylsulfanyl-pyrimidine-4,5-diamine (4.5 g, compound **21b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 275.

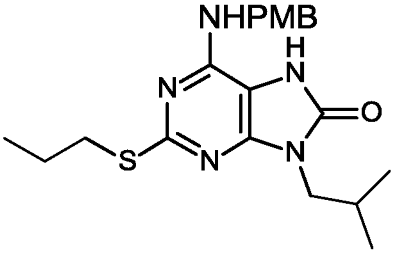
Step 3: Preparation of 6-chloro-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one



21c

Compound **21c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-isobutyl-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **21b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one (850 mg, compound **21c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 301.

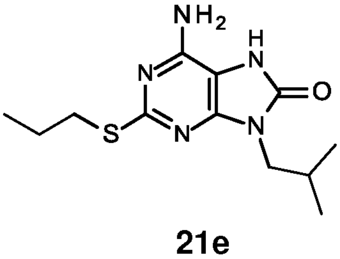
Step 4: Preparation of 9-isobutyl-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



21d

Compound **21d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one (compound **21c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-Isobutyl-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (570 mg, compound **21d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 402.

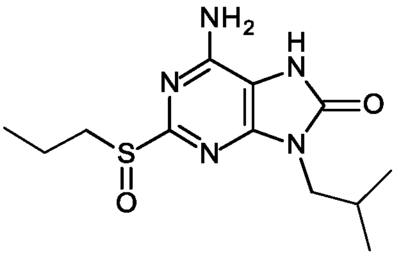
Step 5: Preparation of 6-amino-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one



21e

Compound **21e** was prepared in analogy to **Example 15**, **Step 5** by using 9-isobutyl-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **21d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one (300 mg, compound **21e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 282.

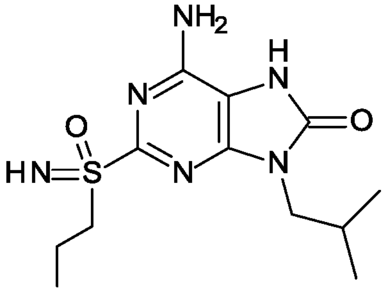
Step 6: Preparation of 6-amino-9-isobutyl-2-propylsulfinyl-7*H*-purin-8-one



21f

Compound **21f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-isobutyl-2-propylsulfanyl-7*H*-purin-8-one (compound **21e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-isobutyl-2-propylsulfinyl-7*H*-purin-8-one (125 mg, compound **21f**) was obtained as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 298.

Step 7: Preparation of 6-amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7*H*-purin-8-one

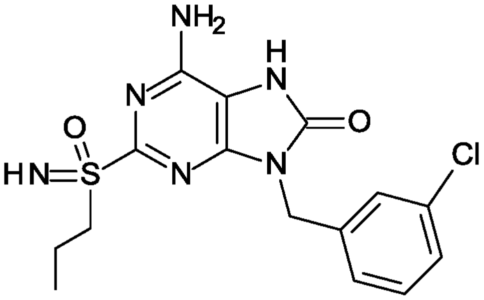


21

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-isobutyl-2-propylsulfinyl-7*H*-purin-8-one (compound **21f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-isobutyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (65.8 mg, **Example 21**) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.46 (s, 1H), 6.92 (br. s., 2H), 4.00 (s, 1H), 3.59 (d, J = 1.6 Hz, 2H), 3.32-3.38 (m, 2H), 2.15 (m, 1H), 1.65-1.73 (m, 2H), 0.97 (t, J = 73 Hz, 3H), 0.86 (m, 6H). MS obsd. (ESI^+) [$(M+H)^+$]: 313.

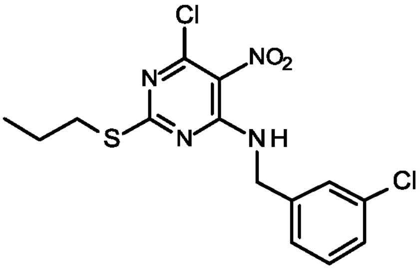
Example 22

6-Amino-9-[(3-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



22

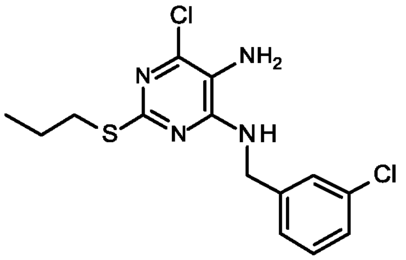
Step 1: Preparation of 6-chloro-*N*-[(3-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



22a

Compound **22a** was prepared in analogy to **Example 15**, **Step 1** by using (3-chlorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(3-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (13.9 g, compound **22a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 373.

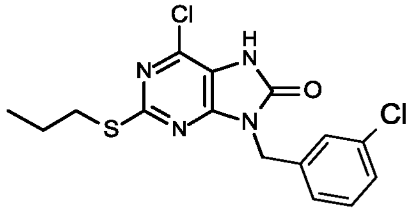
Step 2: Preparation of 6-chloro-*N*4-[(3-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



22b

Compound **22b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(3-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **22a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(3-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (13.0 g, compound **22b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 343.

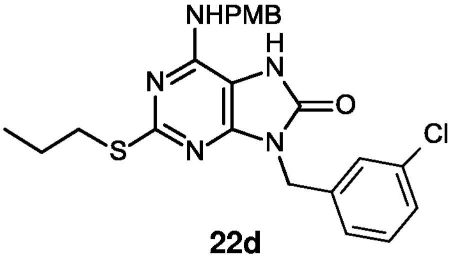
Step 3: Preparation of 6-chloro-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



22c

Compound **22c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(3-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **22b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (13.0 g, compound **22c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 369.

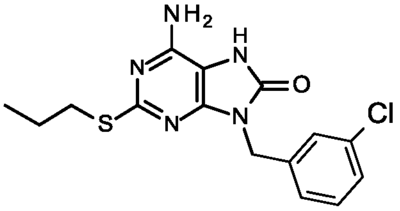
Step 4: Preparation of 9-[(3-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



22d

Compound **22d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **22c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(3-Chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (6.0 g, compound **22d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 470.

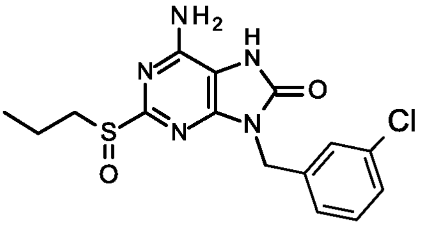
Step 5: Preparation of 6-amino-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



22e

Compound **22e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(3-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **22d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (300 mg, compound **22e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

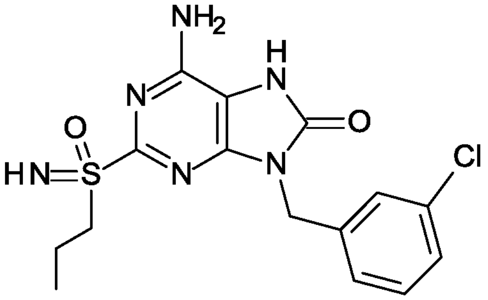
Step 6: Preparation of 6-amino-9-[(3-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



22f

Compound **22f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(3-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **22e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-[(3-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (150 mg, compound **22f**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 366.

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

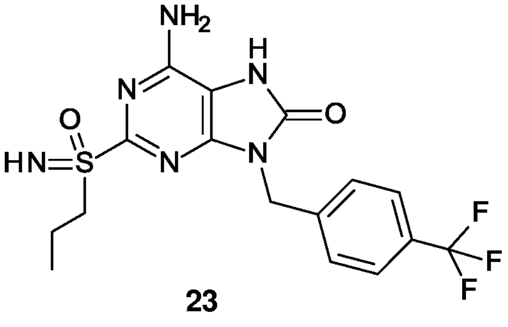


22

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(3-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (100 mg, compound **22f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-[(3-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (43 mg, **Example 22**) was obtained as a white solid. ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 7.41-7.36 (m, 3H), 7.030-7.28 (m, 1H), 7.01 (br. s., 2H), 4.96 (s, 2H), 4.03 (s, 1H), 3.34-3.27 (m, 2H), 1.67-1.59 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 381.

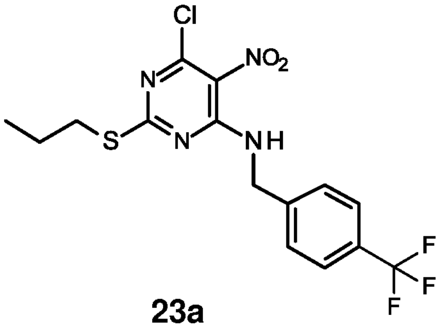
Example 23

6-Amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one



23

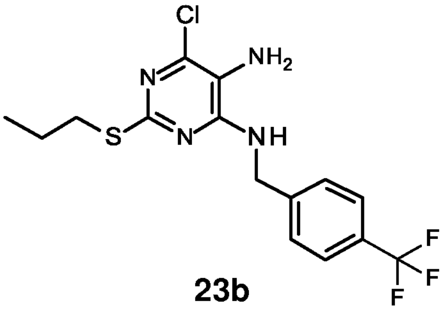
Step 1: Preparation of 6-chloro-*N*-[(4-trifluoromethylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



23a

Compound **23a** was prepared in analogy to **Example 15**, **Step 1** by using (4-trifluoromethylphenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-trifluoromethylphenylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (7.0 g, compound **23a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 407.

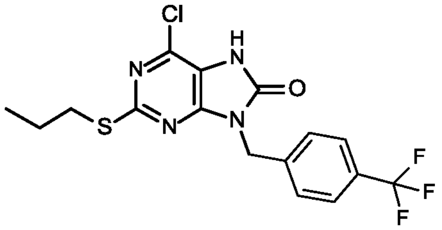
Step 2: Preparation of 6-chloro-2-propylsulfanyl-N4-[[4-(trifluoromethyl)phenyl]methyl] pyrimidine-4,5-diamine



23b

Compound **23b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-trifluoromethylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **23a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (3.1 g, compound **23b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 377.

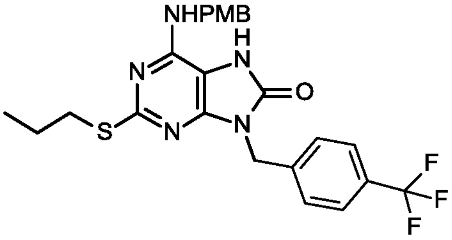
Step 3: Preparation of 6-chloro-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



23c

Compound **23c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **23b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.8 g, compound **23c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 403.

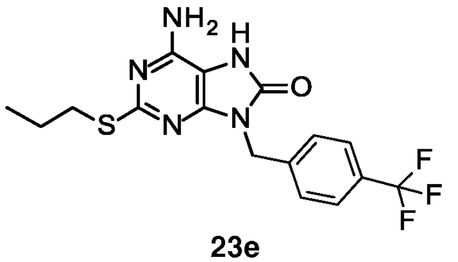
Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one



23d

Compound **23d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **23c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(4-Trifluoromethylphenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (1.2 g, compound **23d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 504.

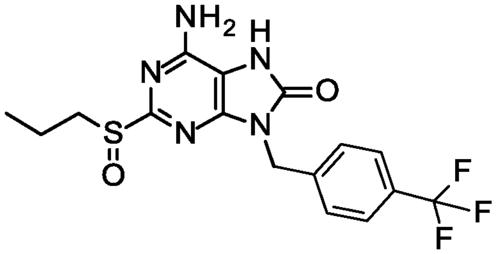
Step 5: Preparation of 6-amino-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



23e

Compound **23e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(4-trifluoromethylphenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **23d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (900 mg, compound **23e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 384.

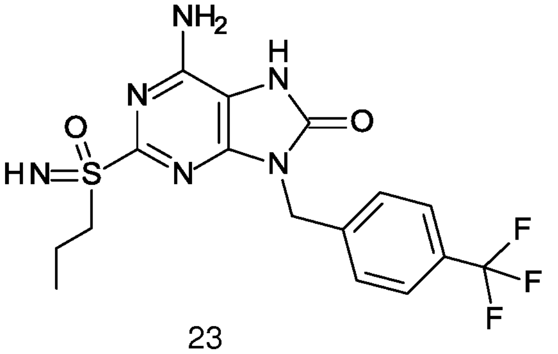
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one



23f

Compound 23f was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **23e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one (200 mg, compound **23f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 400.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one

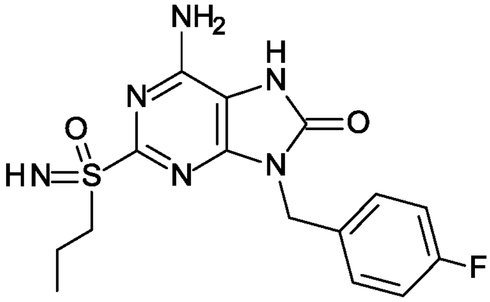


23

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(4-trifluoromethylphenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (200 mg, compound **23f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one (57 mg, **Example 23**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.70 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.01 (br. s., 2H), 5.07 (s, 2H), 4.06 (s, 1H), 3.41-3.27 (m, 2H), 1.6-1.57 (m, 2H), 0.86 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 415.

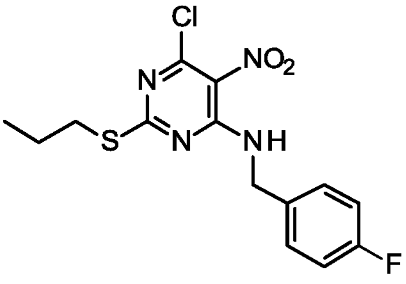
Example 24

6-Amino-9-[(4-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



24

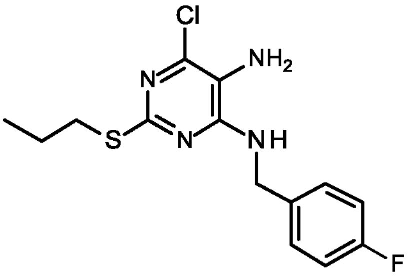
Step 1: Preparation of 6-chloro-*N*-[(4-fluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



24a

Compound **24a** was prepared in analogy to **Example 15**, **Step 1** by using (4-fluorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-fluorophenylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (6.4 g, compound **24a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 357.

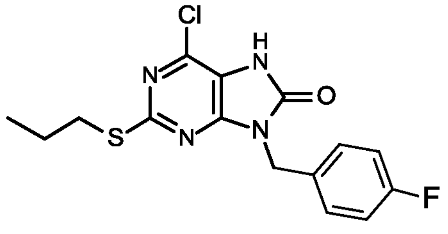
Step 2: Preparation of 6-chloro-*N*4-[(4-fluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



24b

Compound **24b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-fluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **24a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(4-fluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (6.0 g, compound **24b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 327.

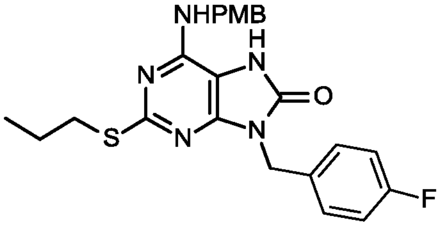
Step 3: Preparation of 6-chloro-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



24c

Compound **24c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(4-fluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **24b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (5.0 g, compound **24c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 353.

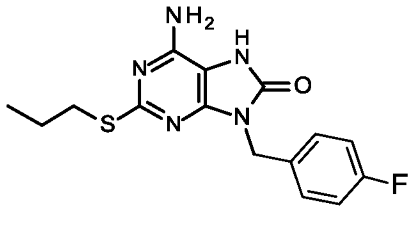
Step 4: Preparation of 9-[(4-fluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



24d

Compound **24d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **24c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(4-Fluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (5.5 g, compound **24d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 454.

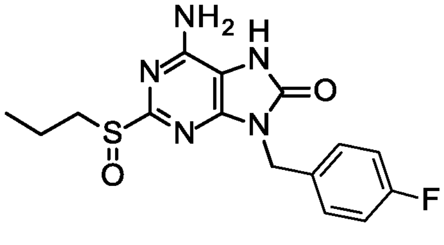
Step 5: Preparation of 6-amino-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



24e

Compound **24e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(4-fluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **24d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (600 mg, compound **24e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 334.

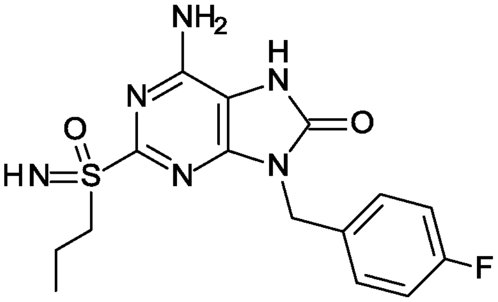
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[4-fluorophenylmethyl]-7*H*-purin-8-one



24f

Compound **24f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(4-fluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **24e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[4-fluorophenyl]methyl]-7*H*-purin-8-one (530 mg, compound **24f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7*H*-purin-8-one

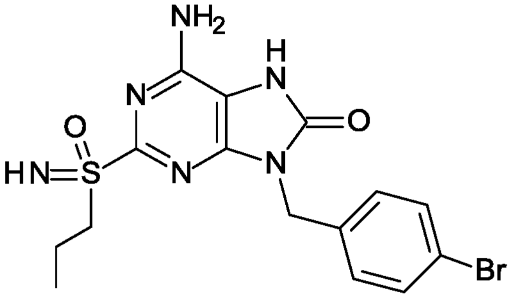


24

The title compound was prepared in analogy to **Example 15**, **Step 5** by using 6-amino-9-[(4-fluorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (250 mg, compound **24f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-[[4-fluorophenyl]methyl]-7*H*-purin-8-one (41.6 mg, **Example 24**) was obtained as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.62 (br. s., 1H), 7.40-7.38 (m, 2H), 7.18-7.16 (m, 2H), 7.00 (br. s., 2H), 4.95 (s, 2H), 4.05 (s, 1H), 3.33-3.30 (m, 2H), 1.74-1.55 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 365.

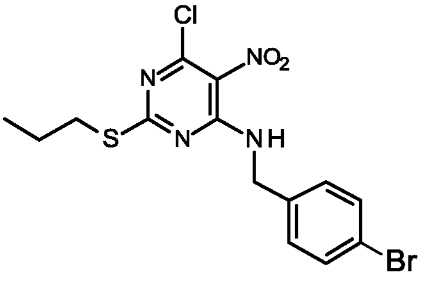
Example 25

6-Amino-9-[(4-bromophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



25

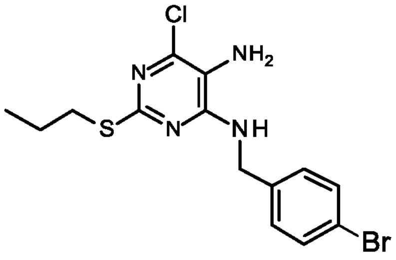
Step 1: Preparation of 6-chloro-*N*-[(4-bromophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



25a

Compound **25a** was prepared in analogy to **Example 15**, **Step 1** by using (4-bromophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-bromophenylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (7.0 g, compound **25a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 417.

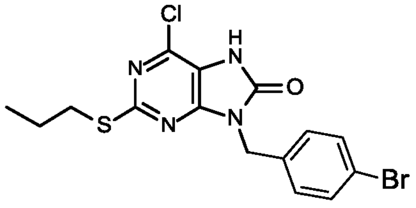
Step 2: Preparation of 6-chloro-*N*4-[(4-bromophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



25b

Compound **25b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-bromophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **25a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(4-bromophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (3.2 g, compound **25b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

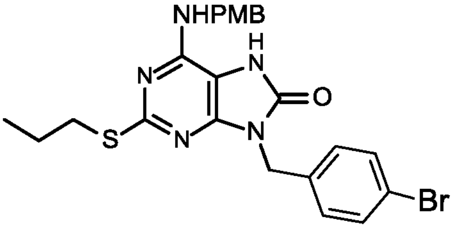
Step 3: Preparation of 6-chloro-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



25c

Compound **25c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(4-bromophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **25b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (2.5 g, compound **25c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 413.

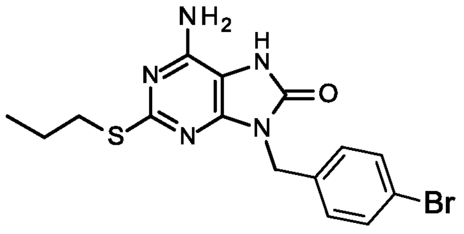
Step 4: Preparation of 9-[(4-bromophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



25d

Compound **25d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **25c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(4-Bromophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (3.1 g, compound **25d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 514.

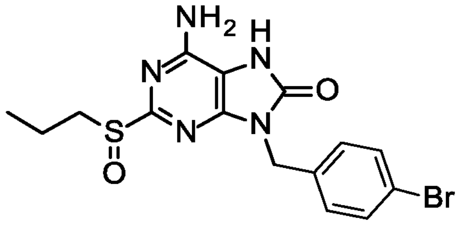
Step 5: Preparation of 6-amino-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



25e

Compound **25e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(4-bromophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **25d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.1 g, compound **25e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 394.

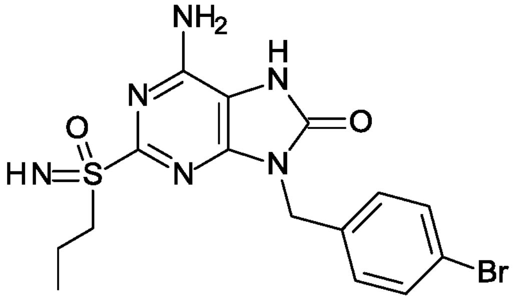
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[4-bromophenylmethyl]-7*H*-purin-8-one



25f

Compound **25f** was prepared in analogy to **Example 15**, **Step 5** by using 6-amino-9-[(4-bromophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **25e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[4-bromophenyl]methyl]-7*H*-purin-8-one (250 mg, compound **25f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 410.

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

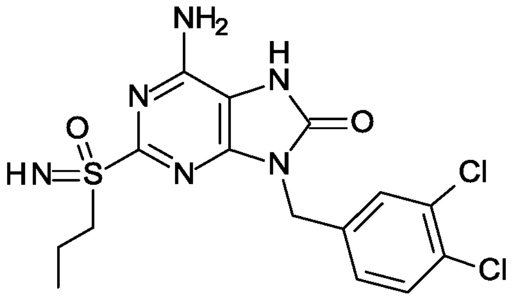


25

The title compound was prepared in analogy to **Example 15**, **Step 5** by using 6-amino-9-[(4-bromophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (260 mg, compound **25f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-[[4-bromophenyl]methyl]-7*H*-purin-8-one (70 mg, **Example 25**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.62 (br. s., 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.99 (br. s., 2H), 4.94 (s, 2H), 4.04 (s, 1H), 3.35 - 3.25 (m, 2H), 1.67-1.56 (m, 2H), 0.90 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 425.

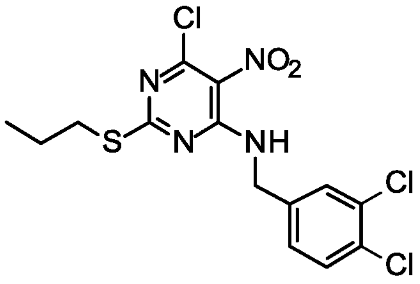
Example 26

6-Amino-9-[(3,4-dichlorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



26

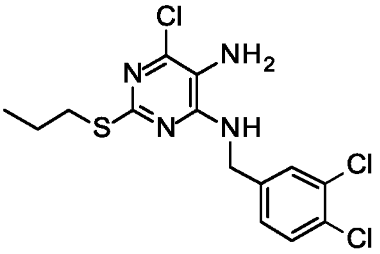
Step 1: Preparation of 6-chloro-*N*-[(3,4-dichlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



26a

Compound **26a** was prepared in analogy to **Example 15**, **Step 1** by using (3,4-dichlorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-bromophenylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (3.6 g, compound **26a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 425.

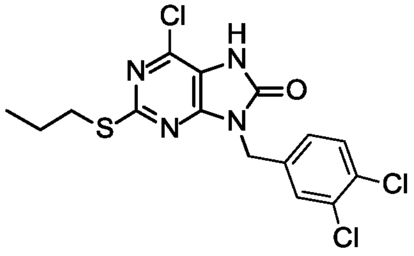
Step 2: Preparation of 6-chloro-*N*4-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



26b

Compound **26b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(3,4-dichlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **26a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (3.1 g, compound **26b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 377.

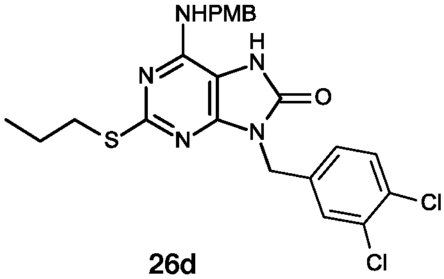
Step 3: Preparation of 6-chloro-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



26c

Compound 26**c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **26b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.8 g, compound **26c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 403.

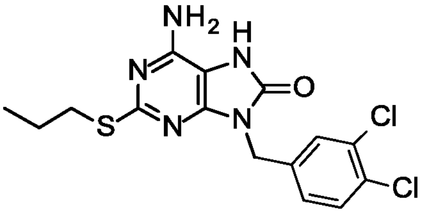
Step 4: Preparation of 9-[(3,4-dichlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



26d

Compound **26d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **26c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(3,4-Dichlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (1.6 g, compound **26d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 504.

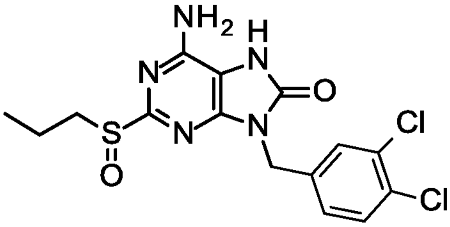
Step 5: Preparation of 6-amino-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



26e

Compound **26e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(3,4-dichlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **26d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (900 mg, compound **26e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 384.

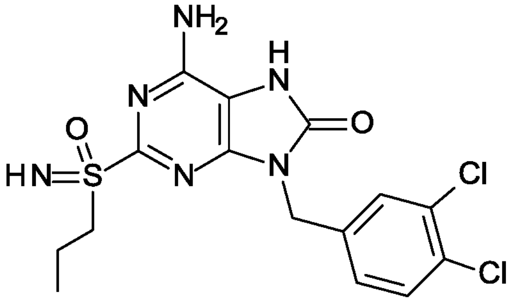
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[3,4-dichlorophenyl]-7*H*-purin-8-one



26f

Compound **26f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(3,4-dichlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **26e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[3,4-dichlorophenyl]methyl]-7*H*-purin-8-one (210 mg, compound **26f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 401.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-(3,4-dichlorophenylmethyl)-7*H*-purin-8-one

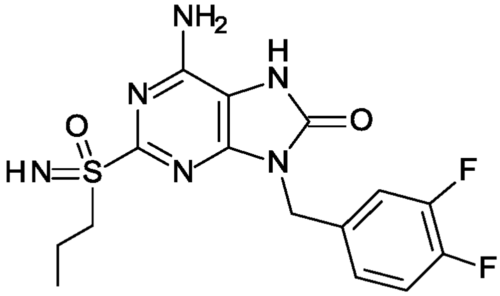


26

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(3,4-dichlorophenylmethyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **26f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-(3,4-dichlorophenylmethyl)-7*H*-purin-8-one (47 mg, **Example 26**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.67 (br. s., 1H), 7.63 - 7.59 (m, 2H), 7.32 - 7.29 (m, 1H), 7.01 (br. s., 2H), 4.98 (s, 2H), 4.05 (s, 1H), 3.35 - 3.30 (m, 2H), 1.67-1.56 (m, 2H), 0.90 (t, $J = 8.0$ Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 415.

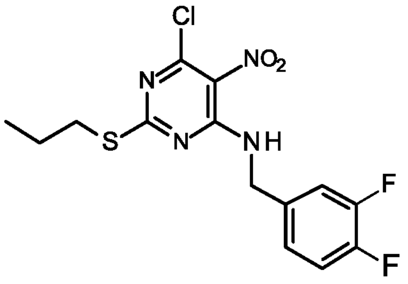
Example 27

6-Amino-9-(3,4-difluorophenylmethyl)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



27

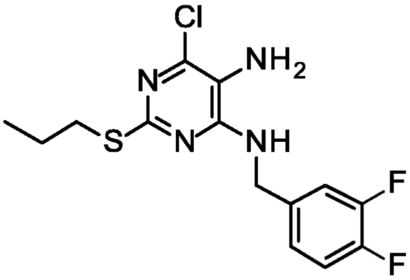
Step 1: Preparation of 6-chloro-*N*-[(3,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



27a

Compound **27a** was prepared in analogy to **Example 15**, **Step 1** by using (3,4-difluorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(3,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (3.1 g, compound **27a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 375.

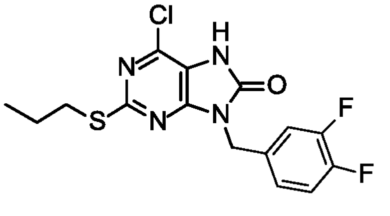
Step 2: Preparation of 6-chloro-*N*4-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



27b

Compound **27b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(3,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **27a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*-4-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (2.2 g, compound **27b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 345.

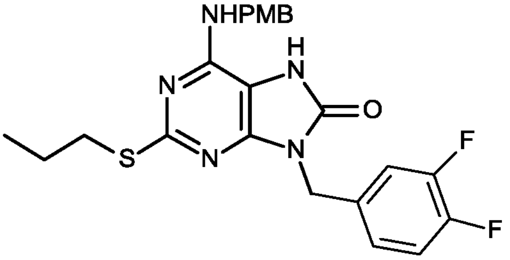
Step 3: Preparation of 6-chloro-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



27c

Compound **27c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **27b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.6 g, compound **27c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 371.

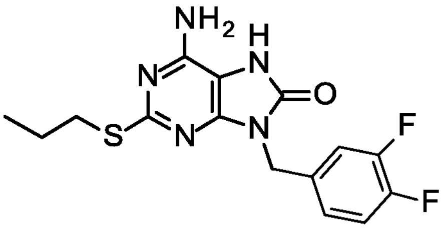
Step 4: Preparation of 9-[(3,4-difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



27d

Compound **27d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **27c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(3,4-Difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (1.5 g, compound **27d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 472.

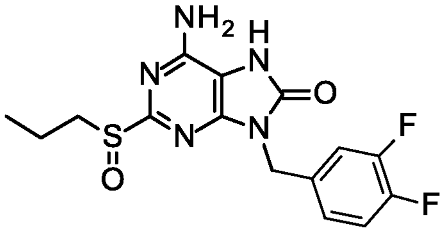
Step 5: Preparation of 6-amino-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



27e

Compound **27e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(3,4-difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **27d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (600 mg, compound **27e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 352.

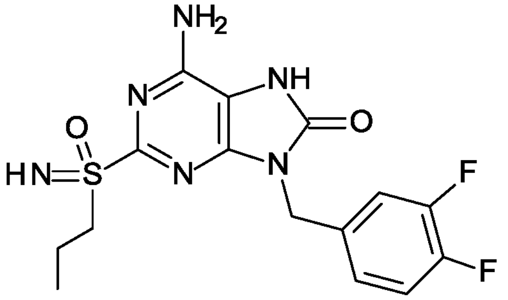
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[3,4-difluorophenyl)methyl]-7*H*-purin-8-one



27f

Compound **27f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(3,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **27e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[3,4-difluorophenyl)methyl]-7*H*-purin-8-one (150 mg, compound **27f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 368.

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

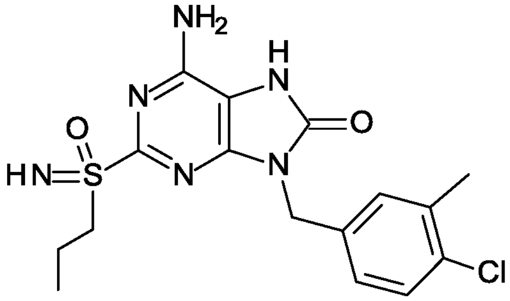


27

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(3,4-difluorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **27f**) instead 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-[[3,4-difluorophenyl)methyl]-7*H*-purin-8-one (60 mg, **Example 27**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.65 (br. s.,1H), 7.46 - 7.36 (m, 2H), 7.19 - 7.18 (m, 1H), 6.98 (br. s., 2H), 4.96 (s, 2H), 4.04 (s, 1H), 3.35 - 3.26 (m, 2H), 1.67-1.57 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 383.

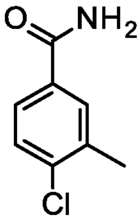
Example 28

6-Amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



28

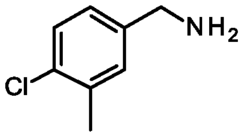
Step 1: Preparation of 4-chloro-3-methylbenzamide



28a

To an ice cooled solution of 4-chloro-3-methylbenzoic acid (20.0 g, 117.2 mmol), HOBt (15.8 g, 117.2 mmol) and NH_4Cl (18.8 g, 351.7 mmol) in anhydrous DMF (200 mL) was added DIPEA (45.5 g, 351.7 mmol) followed by EDC·HCl (27.4 g, 152.4 mmol), then the mixture was warmed to 25 °C and stirred for 20 hrs. The reaction mixture was diluted with water (1.2 L) and extracted with EtOAC (200 mL) three times. The combined organic layer was washed with 1*N* HCl aq., sat. Na_2CO_3 aq., brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was triturated with MTBE to give 4-chloro-3-methylbenzamide (15 g, compound **28a**) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.00 (s, 1H), 7.86 (s, 1H), 7.71 (dd, $J = 8.3$ Hz, 1.5 Hz, 1H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.42 (s, 1H), 2.37 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 170.

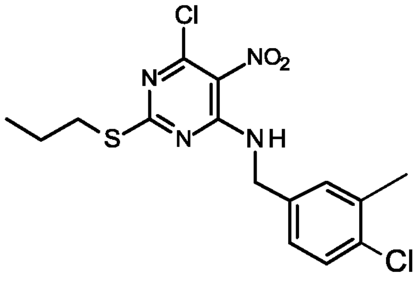
Step 2: Preparation of (4-chloro-3-methylphenyl)methylamine



28b

To a suspension of $LiAlH_4$ (11.2 g, 294.8 mmol) in anhydrous THF (100 mL) was added 3-chloro-4-methyl-benzamide (10 g, 58.96 mmol) in THF (100 mL) drop-wise. After the addition, the mixture was stirred at 28 °C for 2 hrs and then heated to 60 °C for 12 hrs. After the reaction mixture was cooled to 0 °C, then 11.2 mL of water, 11.2 mL of 15% NaOH aq. and 33.6 mL of water was added sequentially. Anhydrous sodium sulfate (20 g) was added, and the resulting suspension was stirred for 30 min, and filtered. The filtrate was concentrated *in vacuo* to obtain (4-chloro-3-methyl-phenyl)methylamine as a colorless oil (8g, compound **28b**). MS obsd. (ESI$^+$) [(M+H)$^+$]: 156.

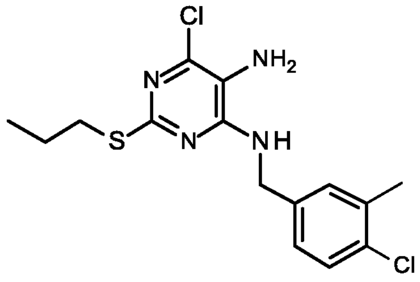
Step 3: Preparation of 6-chloro-*N*-[(4-chloro-3-methyl-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



28c

Compound **28c** was prepared in analogy to **Example 15**, **Step 1** by using (4-chloro-3-methyl-phenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-chloro-3-methylphenylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (8.0 g, compound **28c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

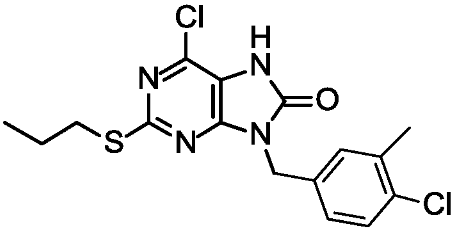
Step 4: Preparation of 6-chloro-*N*4-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



28d

Compound **28d** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-chloro-3-methylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **28c**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*-4-[(4-chloro-3-methylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (4.4 g, compound **28d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 357.

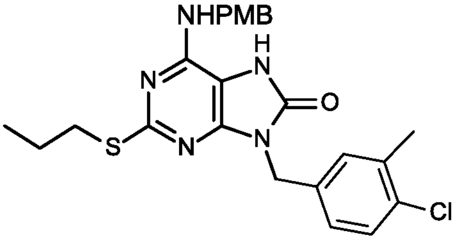
Step 5: Preparation of 6-chloro-9-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



28e

Compound **28e** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(4-chloro-3-methylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **28d**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfanyl-7H-purin-8-one (4.6 g, compound **28e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 383.

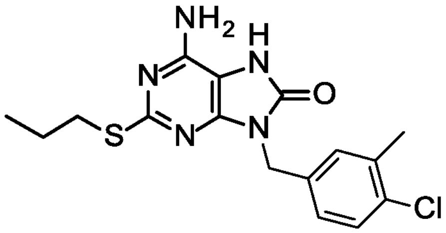
Step 6: Preparation of 9-[(4-chloro-3-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



28f

Compound **28f** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-chloro-3-methylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **28e**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(3-Chloro-4-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (9 g, compound **28f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 484.

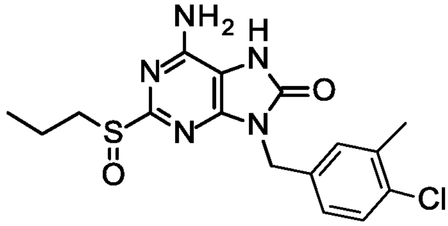
Step 7: Preparation of 6-amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



28g

Compound **28g** was prepared in analogy to **Example 15, Step 5** by using 9-[(4-chloro-3-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **28f**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (4.5 g, compound **28g**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 364.

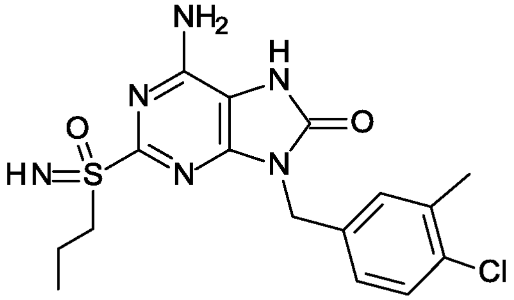
Step 8: Preparation of 6-amino-2-propylsulfinyl-9-[4-chloro-3-methyl-phenyl methyl]-7*H*-purin-8-one



28h

Compound **28h** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **28g**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[4-chloro-3-methyl-phenyl]methyl]-7*H*-purin-8-one (340 mg, compound **28h**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 380.

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

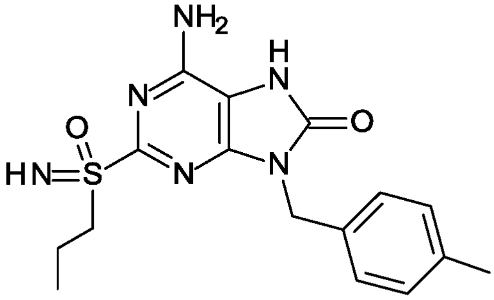


28

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **28h**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one. 6-Amino-2-(propylsulfonimidoyl)-9-[[4-chloro-3-methyl-phenyl]methyl]-7*H*-purin-8-one (80 mg, **Example 28**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.37-7.33 (m, 2H), 7.18-7.16 (m, 2H), 6.97 (br. s., 2H), 4.92 (s, 2H), 4.04 (s, 1H), 3.33-3.31 (m, 2H), 2.29 (s, 3H),1.65-1.61 (m, 2H), 0.90 (t, *J* = 7.6 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 395.

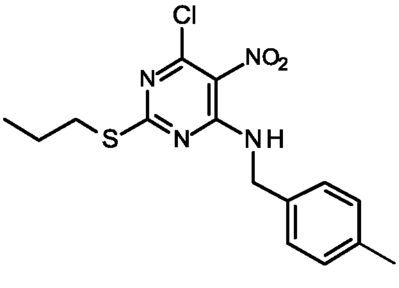
Example 29

6-Amino-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one



29

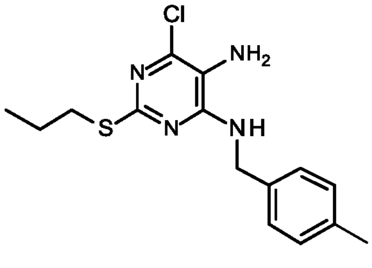
Step 1: Preparation of 6-chloro-*N*-[(*p*-tolylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



29a

Compound **29a** was prepared in analogy to **Example 15**, **Step 1** by using *p*-tolylmethylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(*p*-tolylmethyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (3.9 g, compound **29a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 353.

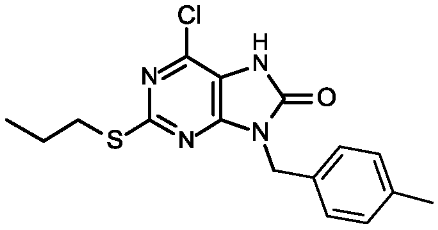
Step 2: Preparation of 6-chloro-*N*4-[(*p*-tolylmethyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



29b

Compound **29b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(*p*-tolylmethyl-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **29a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-(*p*-tolylmethyl)-2-propylsulfanyl-pyrimidine-4,5-diamine (2.2 g, compound **29b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 323.

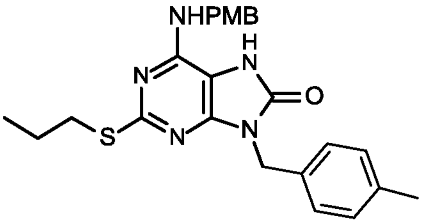
Step 3: Preparation of 6-chloro-9-[(*p*-tolylmethyl]-2-propylsulfanyl-7*H*-purin-8-one



29c

Compound **29c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(*p*-tolylmethyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **29b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(*p*-tolylmethyl]-2-propylsulfanyl-7*H*-purin-8-one (2.2 g, compound **29c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 349.

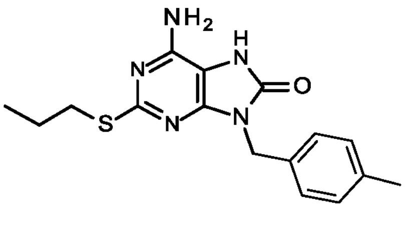
Step 4: Preparation of 9-[(*p*-tolylmethyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one:



29d

Compound **29d** was prepared in analogy to **Example 15**, **Step 4**, by using 6-chloro-9-[(*p*-tolylmethyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **29c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(*p*-Tolylmethyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (2.0 g, compound **29d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 450.

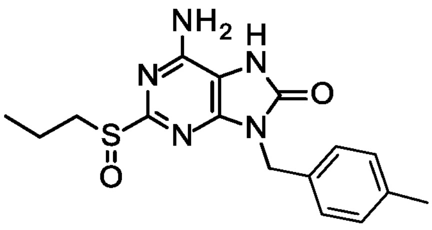
Step 5: Preparation of 6-amino-2-propylsulfanyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one



29e

Compound **29e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(*p*-tolylmethyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **29d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(*p*-tolylmethyl]-2-propylsulfanyl-7*H*-purin-8-one (1.0 g, compound **29e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 330.

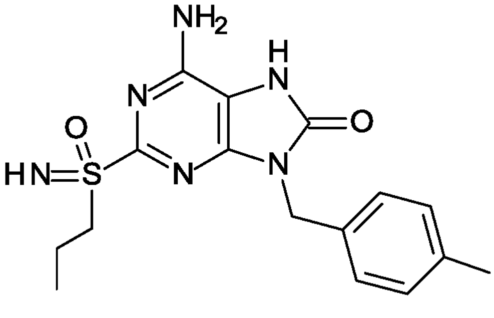
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[*p*-tolylmethyl]-7*H*-purin-8-one



29f

Compound **29f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(*p*-tolylmethyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **29e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[*p*-tolylmethyl]-7*H*-purin-8-one (220 mg, compound **29f**) was obtained as a white solid MS obsd. (ESI$^+$) [(M+H)$^+$]: 345.

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



29

The title compound was prepared in analogy to **Example15**, **Step 7** by using 6-amino-9-[(*p*-tolylmethyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **29f**) instead 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one. 6-Amino-2-(propylsulfonimidoyl)-9-[[*p*-tolylmethyl]-7*H*-purin-8-one (127 mg, **Example 29**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.67 (br. s., 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.98 (br. s., 2H), 4.91 (s, 2H), 4.05 (s, 1H), 3.34-3.27 (m, 2H), 2.26 (s, 3H), 1.67-1.62 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

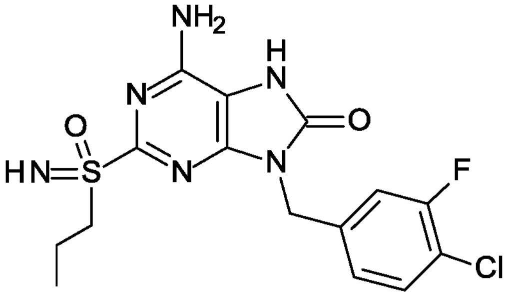
Separation of compound of **Example 29** by chiral HPLC afforded **Example 29-A** (faster eluting, 50 mg) and **Example 29-B** (slower eluting, 49 mg) as white solid. (Separation condition: 30% isopropanol (0.05%DEA)/CO_2 on ChiralPak AD-3 column.)

Example 29-A: ^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm: 10.51 (s, 1 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.00 (s, 2 H), 4.91 (s, 2 H), 4.03 (s, 1 H), 3.35 - 3.31 (m, 2 H), 2.26 (s, 3 H), 1.70 - 1.58 (m, 2 H), 0.93 (t, J = 7.40 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

Example 29-B: ^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm: 10.54 (s, 1 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.97 (s, 2 H), 4.91 (s, 2 H), 4.04 (s, 1 H), 3.34 - 3.30 (m, 2 H), 2.26 (s, 3 H), 1.72 - 1.57 (m, 2 H), 0.93 (t, J = 7.40 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

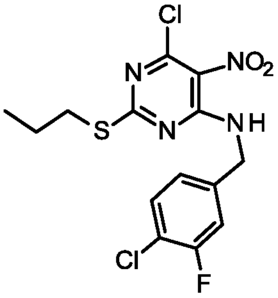
Example 30

6-Amino-9-[(4-chloro-3-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



30

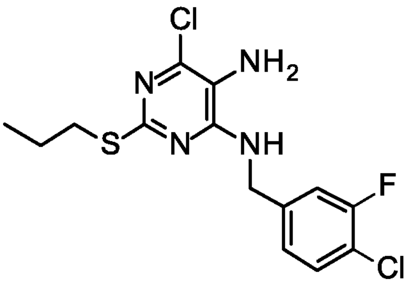
Step 1: Preparation of 6-chloro-*N*-[(4-chloro-3-fluoro-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



30a

Compound **30a** was prepared in analogy to **Example 15**, **Step 1** by using 4-chloro-3-fluorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-chloro-3-fluoro-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (6.2 g, compound **30a**) was obtained. MS obsd. (ESI$^+$) [(M+H)$^+$]: 391.

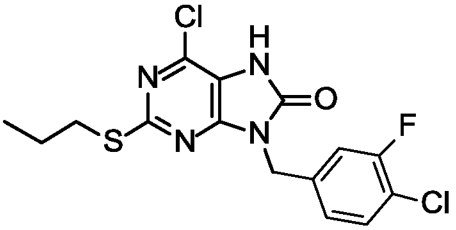
Step 2: Preparation of 6-chloro-*N*4-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



30b

Compound **30b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-chloro-3-fluoro-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **30a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (4.7 g, compound **30b**) was obtained as a brown solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

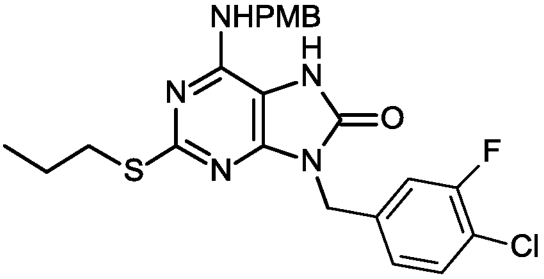
Step 3: Preparation of 6-chloro-9-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



30c

Compound **30c** was prepared in analogy to **Example 15, Step 3** by using 6-chloro-*N*-4-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **30b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (3.8 g, compound **30c**) was obtained as a gray solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

Step 4: Preparation of 9-[(4-chloro-3-fluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one

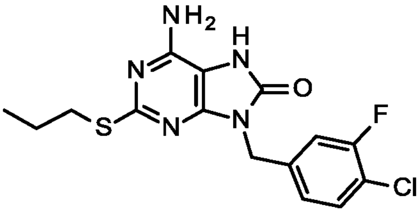


30d

Compound **30d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **30c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(4-

Chloro-3-fluoro-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (2.3 g, compound **30d**) was obtained as a light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 488.

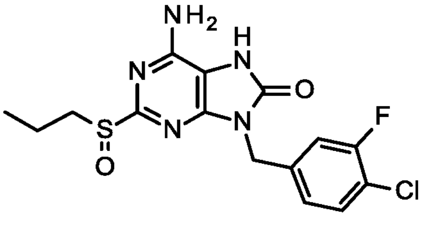
Step 5: Preparation of 6-amino-9-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



30e

Compound **30e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(4-chloro-3-fluoro-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **30d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(4-chloro-3-fluoro-phenyl)methyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.4 g, compound **30e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 368.

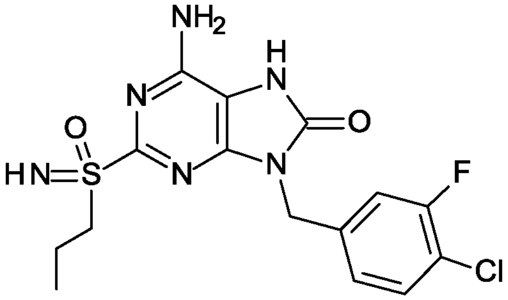
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[4-chloro-3-fluoro-phenyl)methyl]-7*H*-purin-8-one



30f

Compound **30f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(4-chloro-3-fluoro-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **30e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[4-chloro-3-fluoro-phenyl)methyl]-7*H*-purin-8-one (300 mg, compound **30f**) was obtained as a white solid MS obsd. (ESI$^+$) [(M+H)$^+$]: 384.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-[[4-chloro-3-fluoro-phenyl)methyl]methyl]-7*H*-purin-8-one

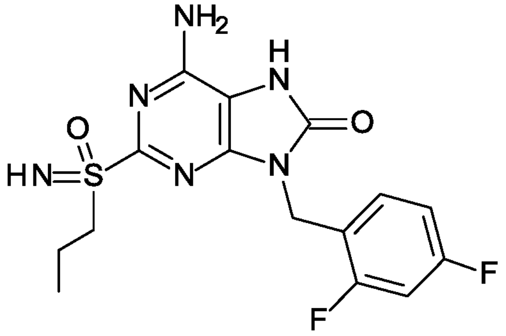


30

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(4-chloro-3-fluoro-phenyl)methyl 2-propylsulfinyl-7*H*-purin-8-one (compound **30f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (**Example 30**). 6-Amino-2-(propylsulfonimidoyl)-9-[[4-chloro-3-fluoro-phenyl)methyl]-7*H*-purin-8-one (63 mg, **Example 30**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.67 (br. s., 1H), 7.45-7. 34 (m, 1H)), 7.31-7.22 (m, 1H), 7.09-7.03 (m, 1H), 7.00 (br. s., 2H), 4.99 (s, 2H), 3.98 (s, 1H), 3.31-3.26 (m, 2H), 1.72-1.50 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 399.

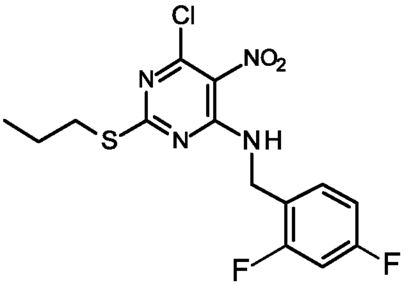
Example 31

6-Amino-9-[(2,4-difluorophenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



31

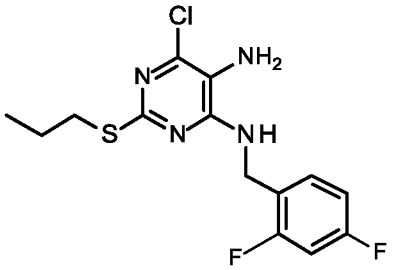
Step 1: Preparation of 6-chloro-*N*-[(2,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



31a

Compound **31a** was prepared in analogy to **Example 15**, **Step 1** by using (2,4-difluorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(2,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (5.0 g, compound 31**a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 375.

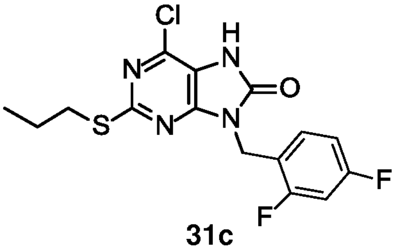
Step 2: Preparation of 6-chloro-*N*4-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



31b

Compound **31b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(2,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **31a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (4.0 g, compound **31b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 345.

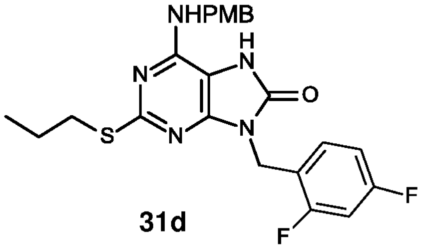
Step 3: Preparation of 6-chloro-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



31c

Compound **31c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **31b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (4.0 g, compound **31c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 371.

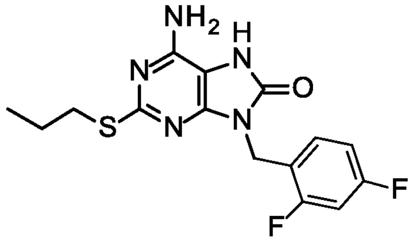
Step 4: Preparation of 9-[(2,4-difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



31d

Compound **31d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound 3**1c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(2,4-Difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (2.9 g, compound **31d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 472.

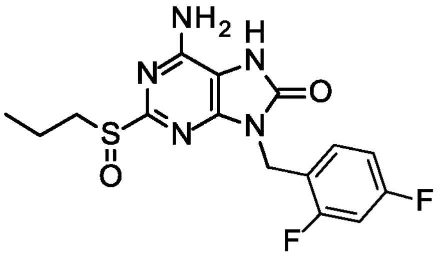
Step 5: Preparation of 6-amino-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



31e

Compound **31e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(2,4-difluorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **31d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.4 g, compound **31e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 352.

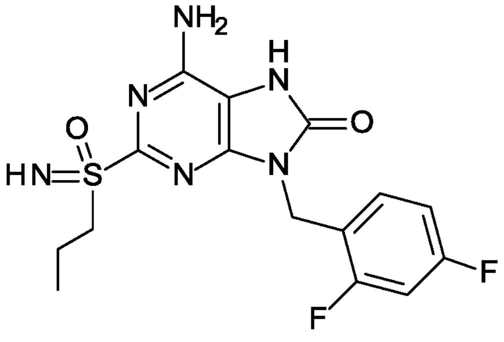
Step 6: Preparation of 6-amino-2-propylsulfinyl-9-[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one



31f

Compound **31f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(2,4-difluorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **31e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-2-propylsulfinyl-9-[[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one (290 mg, compound **31f)** was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 368.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-[[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one

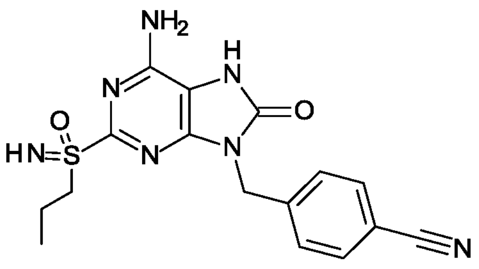


31

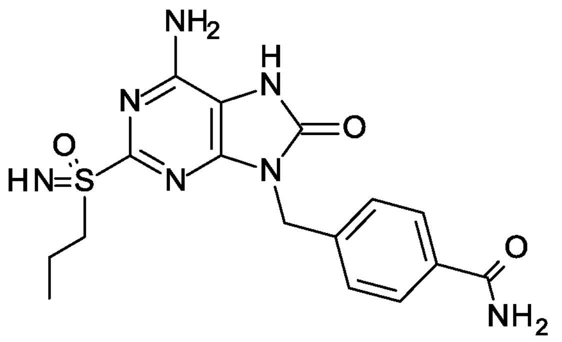
The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(2,4-difluorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **31f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-[[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one (33 mg, compound **31**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.68 (br. s., 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.24-7.14 (m, 1H), 7.01 (br. s., 2H), 4.98 (s, 2H), 4.05 (s, 1H), 3.32-3.24 (m, 2H), 1.71-1.52 (m, 2H), 0.90 (t, $J = 8.0$ Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 383.

Example 32 & Example 33

4-[[6-Amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (compound 32) and 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (compound 33)

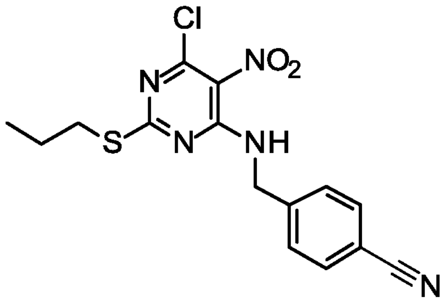


32



33

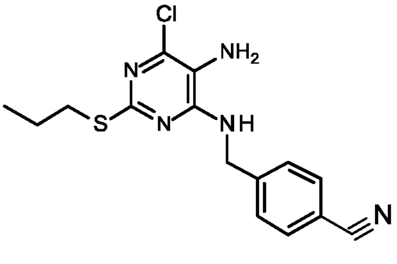
Step 1: Preparation of 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile



32a

Compound **32a** was prepared in analogy to **Example 15**, **Step 1** by using 4-(aminomethyl)benzonitrile instead of (2-chlorophenyl)methylamine. 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (5.5 g, compound **32a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 364.

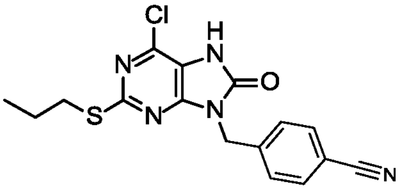
Step 2: Preparation of 4-[[(5-amino-6-chloro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile



32b

Compound **32b** was prepared in analogy to **Example 15**, **Step 2** by using 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (compound **32a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 4-[[(5-Amino-6-chloro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (2.7 g, compound **32b**) was obtained as a brown oil. MS obsd. (ESI$^+$) [(M+H)$^+$]: 334.

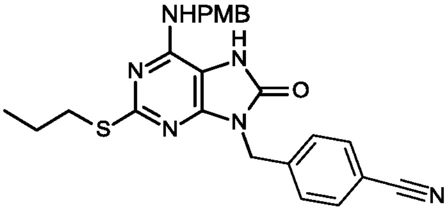
Step 3: Preparation of 4-[(6-chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile



32c

Compound **32c** was prepared in analogy to **Example 15**, **Step 3** by using 4-[[(5-amino-6-chloro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzonitrile (2.7 g, compound **32b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 4-[(6-Chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (2.5 g, compound **32c**) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.14 (br. s., 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2 H), 5.06 (s, 2H), 3.01 (t, J = 8.0 Hz, 2H), 1.68-1.53 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 360.

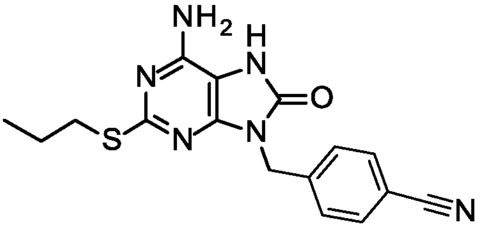
Step 4: Preparation of 4-[[6-[(4-methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzonitrile



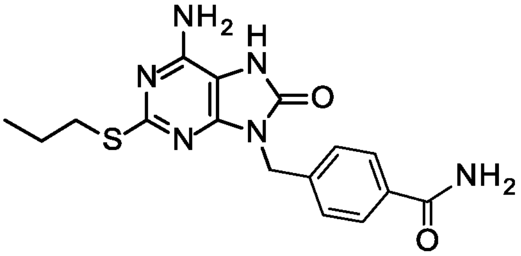
32d

Compound **32d** was prepared in analogy to **Example 15**, **Step 4** by using 4-[(6-chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (compound **32c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 4-[[6-[(4-Methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzonitrile (3.0 g, compound **32d**) was obtained as a light red solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 461.

Step 5: Preparation of 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (compound 32e)and 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzamide (compound 33a)



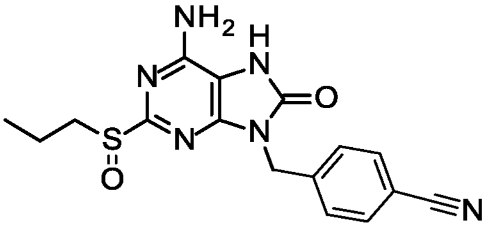
32e



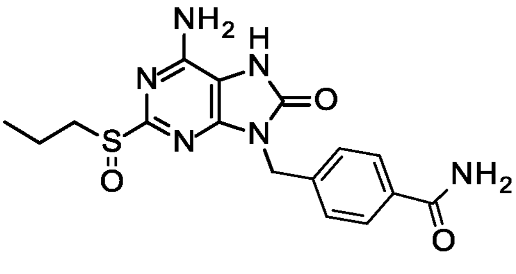
33a

Compound **32e**, **33a** were prepared in analogy to **Example 15**, **Step 5** by using 4-[[6-[(4-methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzonitrile (compound **32d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 4-[(6-Amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (compound **32e**) and 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzamide (compound **33a**) was obtained as a mixture (1.5g).

Step 6: Preparation of 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzonitrile (compound 32f) and 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzamide (compound 33b)



32f

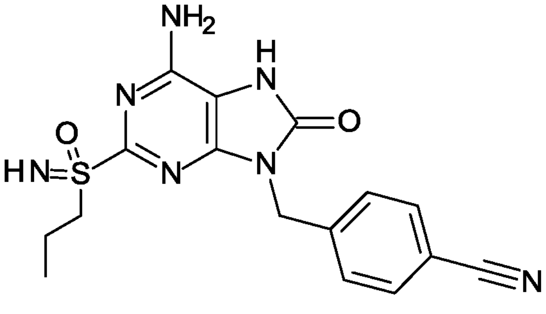


33b

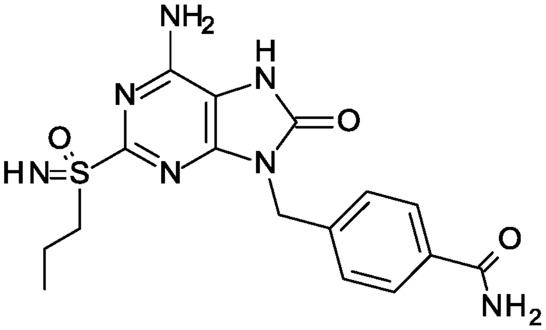
Compound **32f**, **33b** were prepared in analogy to **Example 15**, **Step 6** by using the mixture of 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzonitrile (compound **32e**) and 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzamide (compound **33a**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 4-[(6-Amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzonitrile (compound **32f**) and 4-[(6-

amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzamide (250 mg, compound **33b**) was obtained as a mixture of white solid.

Step 7: Preparation of 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (compound 32) and 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (compound 33)



32



33

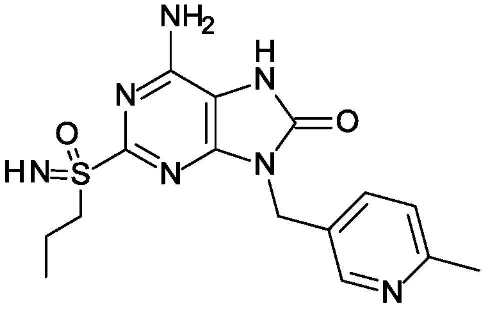
The title compound was prepared in analogy to **Example 15**, **Step 7** by using the mixture of 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzonitrile (compound **32f**) and 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzamide (compound **33b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). The residue was purified by prep-HPLC to give 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzonitrile (24.7 mg, **Example 32**) and 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzamide (18.8 mg, **Example 33**).

Example 32: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.82 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.04 (br. s., 2H), 5.06 (s, 2H), 4.02 (s, 1H), 3.29-3.26 (m, 2H), 1.66-1.54 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 372.

Example 33: ^{1}H NMR(400 MHz DMSO-d_6) δ ppm: 10.73 (br. s., 1H), 7.94 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.34 (s, 1H), 7.02 (br. s., 2H), 5.01 (s, 2H), 4.03 (s, 1H), 3.31-3.27 (m, 2H), 1.68-1.56 (m, 2H), 0.90 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 390.

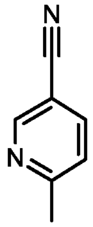
Example 34

6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



34

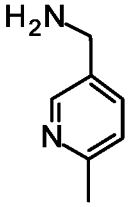
Step 1: Preparation of 6-methylpyridine-3-carbonitrile



34a

To a suspension of 6-methylpyridine-3-carboxylic acid (17.0 g, 125 mmol) in toluene (200 mL) was added phosphoryl trichloride (84.24 g, 708 mmol) drop-wise. After the addition, the reaction mixture was stirred at 100 °C for 12 hrs. The mixture was cooled to RT and the solvent was removed *in vacuo*. The residue was suspended in EtOAc (400 mL), basified with sat. $NaHCO_3$ (400 mL), and extracted with EtOAc (300 mL) two times. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with (PE / EtOAc from 10/1 to 5/1) to give 6-methylpyridine-3-carbonitrile (10.5 g, compound **34a**) as a light yellow solid. MS obsd. (ESI^+) $[(M+H)^+]$: 119.

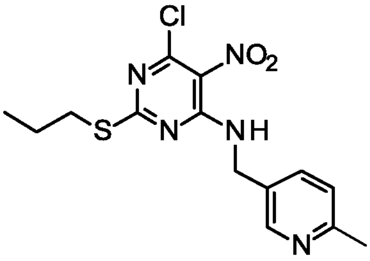
Step 2: Preparation of (6-methyl-3-pyridyl)methylamine



34b

To a solution of 6-methylpyridine-3-carbonitrile (10.5 g, 25.7 mmol) in MeOH (80 mL) and NH_3/MeOH (20 mL, 7 *M*) was added Raney-Ni (2.0 g) under N_2 atmosphere. The suspension was degassed *in vacuo* and refilled with H_2. The mixture was stirred for 12 hrs at 40 °C under H_2 (50 psi) atmosphere. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give (6-methyl-3-pyridyl)methylamine (9.5 g, compound **34b**) as a light oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.36 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 3.69 (s, 2H), 2.42 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 123.

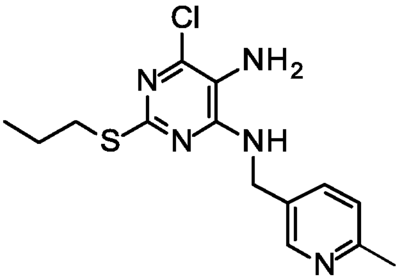
Step 3: Preparation of 6-chloro-*N*-[(6-methyl-3-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



34c

Compound **34c** was prepared in analogy to **Example 15**, **Step 1** by using (6-methyl-3-pyridyl)methylamine (compound **34b**) instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(6-methyl-3-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (15.5 mg, compound **34c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 354.

Step 4: Preparation of 6-chloro-*N*-4-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine

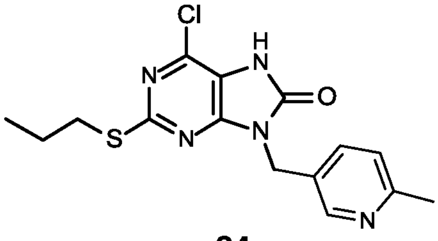


34d

Compound **34d** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(6-methyl-3-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **34c**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound

15a). 6-Chloro-*N*-4-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (10.9 g, compound **34d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 324.

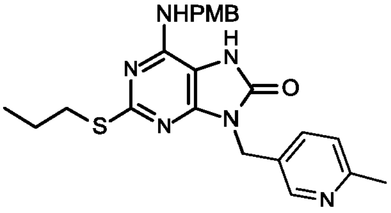
Step 5: Preparation of 6-chloro-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



34e

Compound **34e** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*-4-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **34d**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (12.0 g, compound **34e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

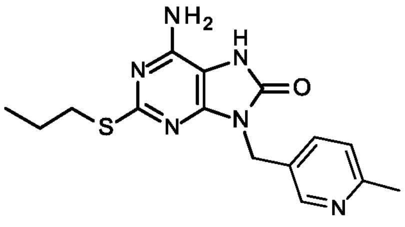
Step 6: Preparation of 6-[(4-methoxyphenyl)methylamino]-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



34f

Compound **34f** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **34e**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (15.0 g, compound **34f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 451.

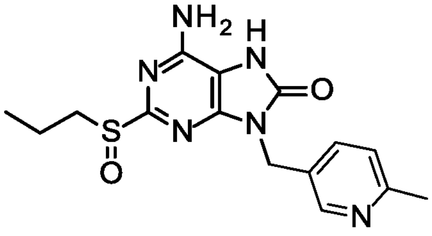
Step 7: Preparation of 6-amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



34g

Compound **34g** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **34f**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (7.9 g, compound **34g**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 331.

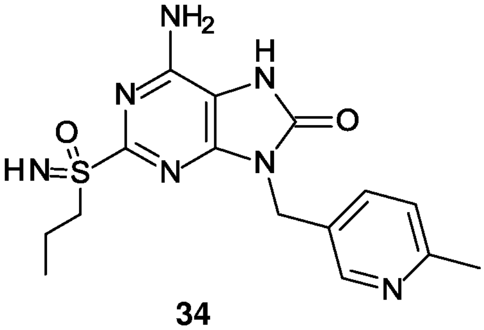
Step 8: Preparation of 6-amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



34h

Compound **34h** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **34g**) instead 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (300 mg, compound **34h**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 347.

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

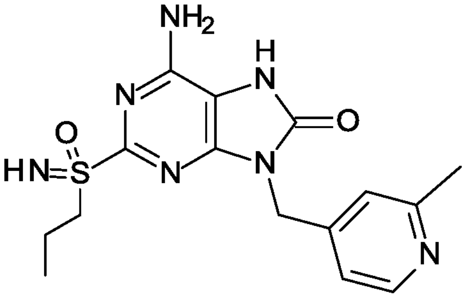


34

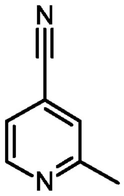
The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **34h**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (13 mg, **Example 34**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.47 (s, 1H), 7.63 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.07 (s, 2H), 4.95 (s, 2H), 4.06 (s, 1H), 3.32-3.29 (m, 2H), 2.42 (s, 3H), 1.71-1.57 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H) MS obsd. (ESI$^+$) [(M+H)$^+$]: 363.

Example 35

6-Amino-9-[(2-methyl-4-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



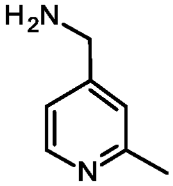
Step 1: Preparation of 2-methylpyridine-4-carbonitrile



35a

A mixture of 2-chloropyridine-4-carbonitrile (30.0 g, 216.0 mol), $AlMe_3$ (11 mL, 220 mmol, 2 *M* in toluene) and $Pd(PPh_3)_4$ (2.3 g, 2.0 mmol) in dioxane (400 mL) was heated to 130 °C for 10 hrs under N_2 atmosphere. The mixture was cooled to RT, then poured into ice water (1000 mL), extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluted with PE/EtOAc (2/1) to afford 2-methylpyridine-4-carbonitrile (compound **35a)** as a yellow crystal. (5.2 g). ^1H NMR (400 MHz, DMSO-d_6) ppm: 8.68 (d, J = 5.0 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 5.0 Hz, 1H), 2.63 (s, 3H). MS obsd. (ESI^+) [$(M+H)^+$]: 119.

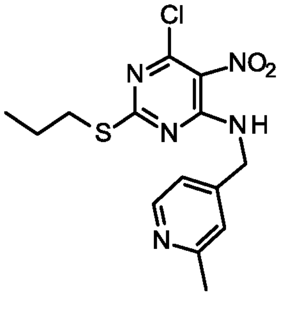
Step 2: Preparation of (2-methyl-4-pyridyl)methylanamine



35b

To a solution of 2-methylpyridine-4-carbonitrile (1.6 g, 13 mmol, compound **35a**) in MeOH (30 mL) and NH_3/MeOH (20 mL, 7 *M*) was added Raney-Ni (2.0 g) under N_2 atmosphere. The suspension was degassed *in vacuo* and purged with H_2 two times. The mixture was stirred under H_2 (50 psi) atmosphere at 40 °C for 12 hrs. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to give (2-methyl-4-pyridyl)methylanamine ((1.6 g, compound **35b**) as a brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.41 (J = 5.0 Hz, 1H), 7.12-7.04 (m, 2H), 3.86 (s, 2H), 2.54 (s, 3H). MS obsd. (ESI^+) [$(M+H)^+$]: 123.

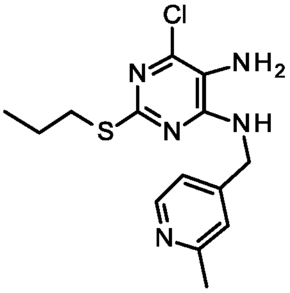
Step 3: Preparation of 6-chloro-*N*-[(2-methyl-4-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



35c

Compound **35c** was prepared in analogy to **Example 15**, **Step 1** by using (2-methyl-4-pyridyl)methylamine (compound **35b**) instead of (2-chlorophenyl)methanamine. 6-Chloro-*N*-[(2-methyl-4-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (4.3 g, compound **35c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 354.

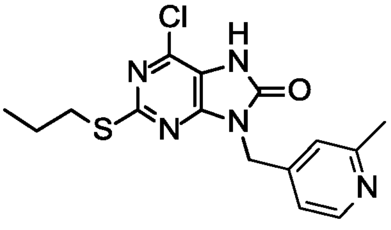
Step 4: Preparation of 6-chloro-*N*4-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



35d

Compound **35d** was prepared in analogy to **Example 15**, **Step 2** by 6-chloro-*N*-[(2-methyl-4-pyridyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **35c**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*-4-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (2.0 g, compound **35d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 324.

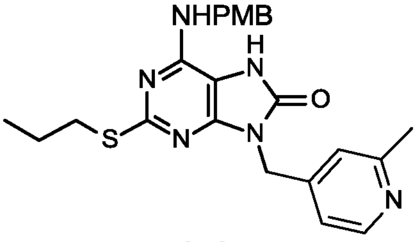
Step 5: Preparation of 6-chloro-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



35e

Compound **35e** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **35d**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (2.5 g, compound **35e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 350.

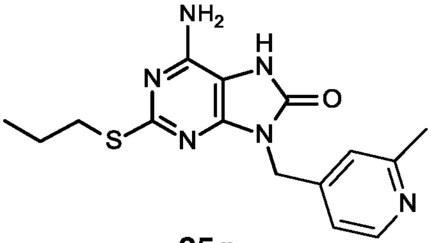
Step 6: Preparation of 6-[(4-methoxyphenyl)methylamino]-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



35f

Compound **35f** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **35e**) instead of 6-chloro-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (3.3 g, compound **35f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 450.

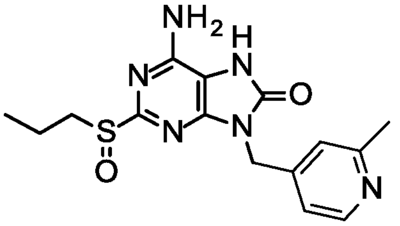
Step 7: Preparation of 6-amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



35g

Compound **35g** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **35f**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). 6-Amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **35g**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 331.

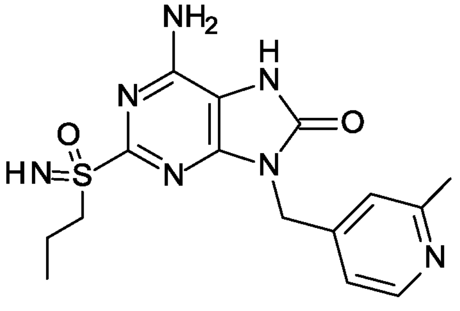
Step 8: Preparation of 6-amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



35h

Compound **35h** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **35g**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (180 mg, compound **35h**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 347.

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



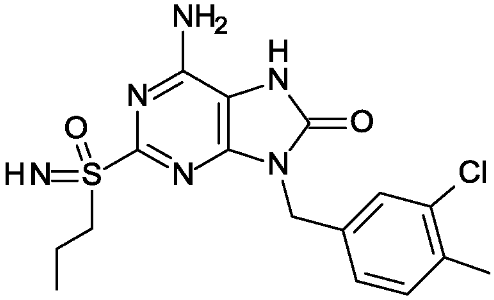
35

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(2-methyl-4-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **35h**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-

2-(propylsulfonimidoyl)-9-[[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one (21 mg, **Example 35**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.68 (br. s., 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.24-7.14 (m, 1H), 7.01 (br. s., 2H), 4.98 (s, 2H), 4.05 (s, 1H), 3.32-3.24 (m, 2H),2.45 (s, 3H), 1.71-1.52 (m, 2H), 0.90 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 362.

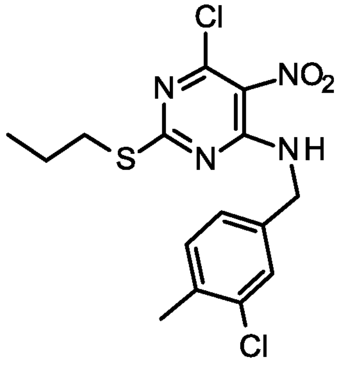
Example 36

6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



36

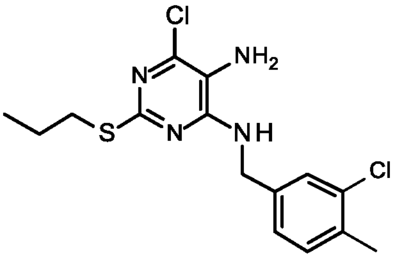
Step 1: Preparation of 6-chloro-*N*-[(2,4-difluorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



36a

Compound **36a** was prepared in analogy to **Example 15**, **Step 1** by using (3-chloro-4-methyl-phenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(3-chloro-4-methyl-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (5.0 g, compound 3**6a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

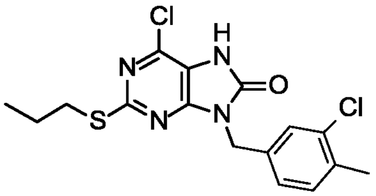
Step 2: Preparation of 6-chloro-*N*4-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



36b

Compound **36b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(3-chloro-4-methyl-phenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **36a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (4.0 g, compound **36b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 357.

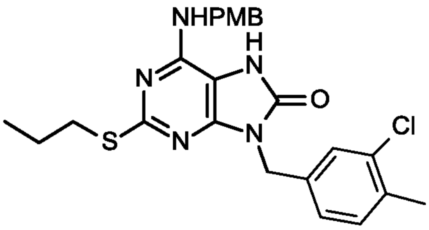
Step 3: Preparation of 6-chloro-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



36c

Compound **36c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **36b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **36c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 383.

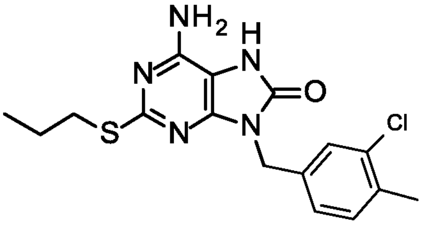
Step 4: Preparation of 9-[(3-chloro-4-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one



36d

Compound **36d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **36c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 9-[(3-Chloro-4-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (4.0 g, compound **36d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 484.

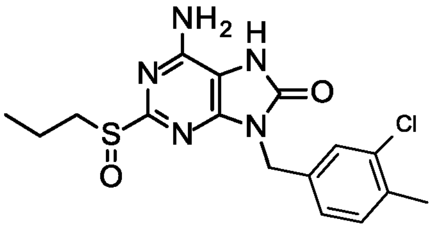
Step 5: Preparation of 6-amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



36e

Compound **36e** was prepared in analogy to **Example 15**, **Step 5** by using 9-[(3-chloro-4-methyl-phenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **36d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one. 6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (230 mg, compound **36e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 364.

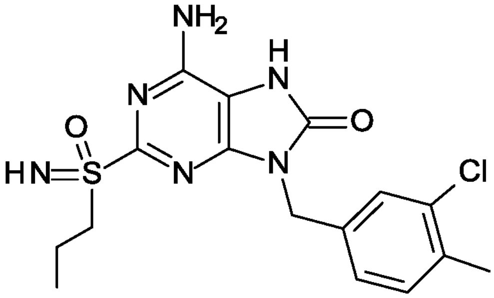
Step 6: Preparation of 6-amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



36f

Compound **36f** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **36e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (155 mg, compound **36f**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 380.

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

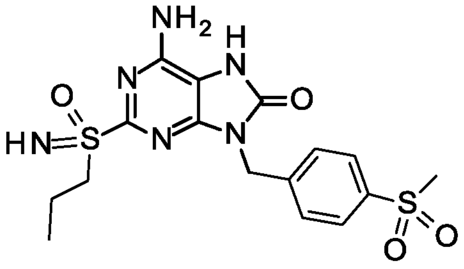


36

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (155 mg, compound **36f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (34 mg, **Example 36**) was obtained as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.39 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.03 (br. s., 2H), 4.93 (s, 2H), 4.02 (s, 1H), 3.30-3.27 (m, 2H), 1.72-1.54 (m, 2H), 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 395.

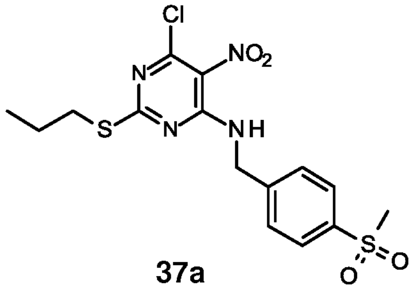
Example 37

6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



37

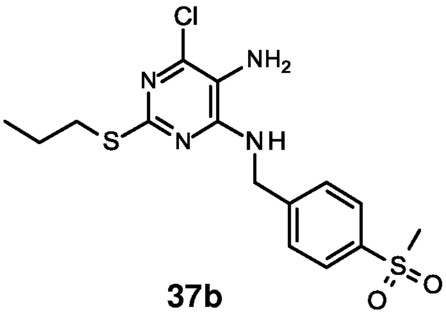
Step 1: Preparation of 6-chloro-*N*-[(4-methylsulfonylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



37a

Compound **37a** was prepared in analogy to **Example 15**, **Step 1** by using (4-methylsulfonylphenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-methylsulfonylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (3.6 g, compound **37a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 417.

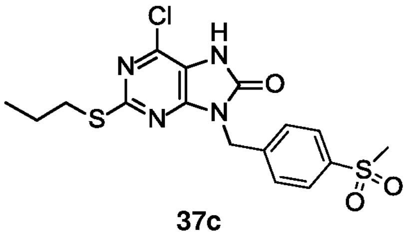
Step 2: Preparation of 6-chloro-*N*4-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



37b

Compound **37b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*-[(4-methylsulfonylphenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **37a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-*N*4-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (3.2 g, compound **37b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

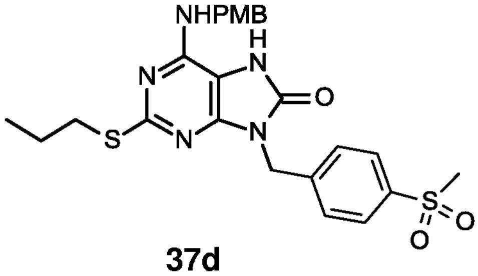
Step 3: Preparation of 6-chloro-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



37c

Compound **37c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **37b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (2.0 g, compound **37c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 413.

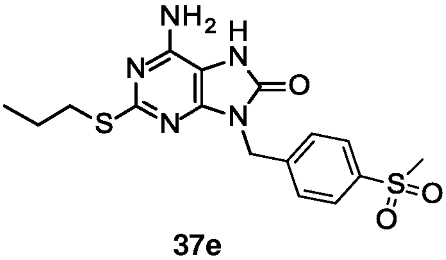
Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



37d

Compound **37d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **37c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (2.2 g, compound **37d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 514.

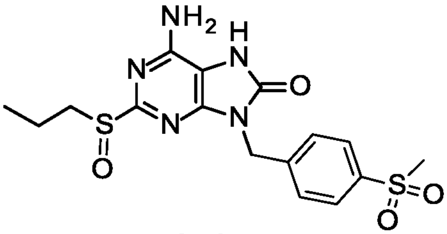
Step 5: Preparation of 6-amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



37e

Compound **37e** was prepared in analogy to **Example 15**, **Step 5** by using 6-[(4-methoxyphenyl)methylamino]-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **36d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one. 6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.2 g, compound **37e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 394.

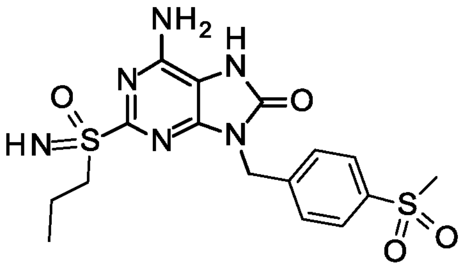
Step 6: Preparation of 6-amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



37d

Compound **37d** was prepared in analogy to **Example 15**, **Step 6** by using 6-amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **37e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (200 mg, compound **37f)** was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 410.

Step 7: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-[[(2,4-difluorophenyl)methyl]-7*H*-purin-8-one

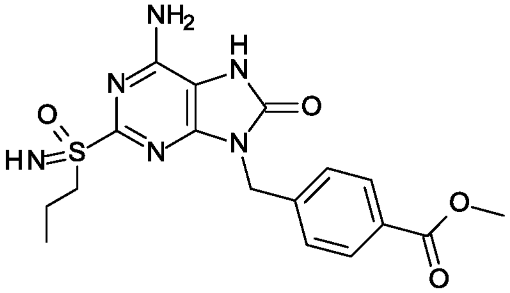


37

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-amino-9-[(4-methylsulfonylphenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **37f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (17 mg, **Example 37**) was obtained as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.89 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.11 (br. s., 2H), 5.08 (s, 2H), 4.07 (s, 1H), 3.34-3.28 (m, 2H), 3.18 (s, 3H), 1.65-1.57 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 425.

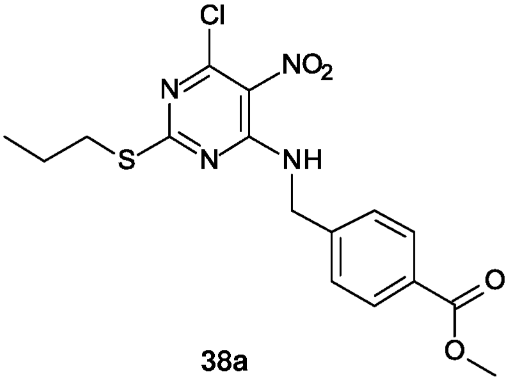
Example 38

Methyl 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoate



38

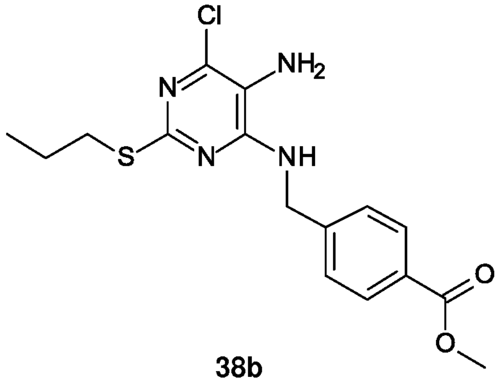
Step 1: Preparation of methyl 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate



38a

Compound **38a** was prepared in analogy to **Example 15**, **Step 1** by using methyl 4-(aminomethyl)benzoate instead of (2-chlorophenyl)methylamine. Methyl 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate (compound **38a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 397.

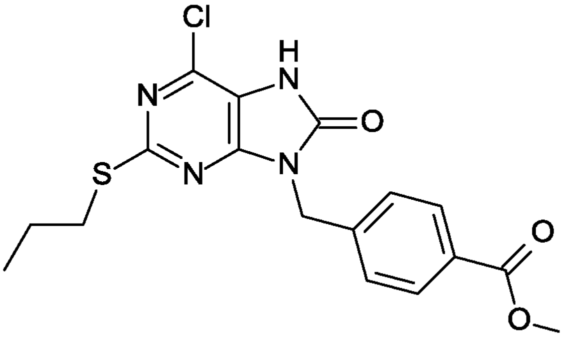
Step 2: Preparation of methyl 4-[[(6-chloro-5-methyl-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate



38b

Compound **38b** was prepared in analogy to **Example 15**, **Step 2** by using methyl 4-[[(6-chloro-5-nitro-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate (compound **38a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). Methyl 4-[[(6-chloro-5-methyl-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate (compound **38b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 366.

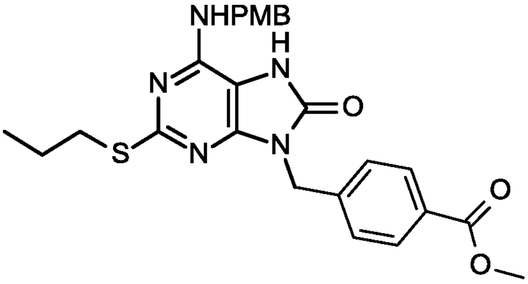
Step 3: Preparation of methyl 4-[(6-chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate



38c

Compound **38c** was prepared in analogy to **Example 15**, **Step 3** by using methyl 4-[[(6-chloro-5-methyl-2-propylsulfanyl-pyrimidin-4-yl)amino]methyl]benzoate (compound **38b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). Methyl 4-[(6-chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate (compound **38c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 39.

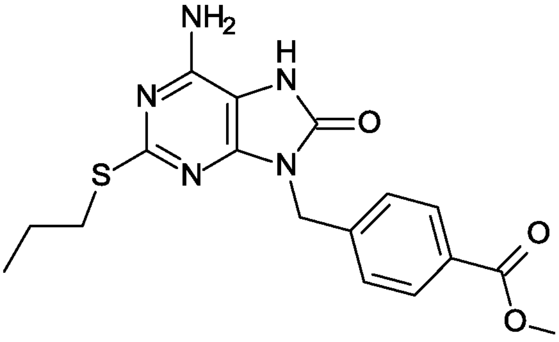
Step 4: Preparation of methyl 4-[[6-[(4-methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzoate



38d

Compound **38d** was prepared in analogy to **Example 15**, **Step 4** by using methyl 4-[(6-chloro-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate (compound **38c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). Methyl 4-[[6-[(4-methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzoate (compound **38d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 494.

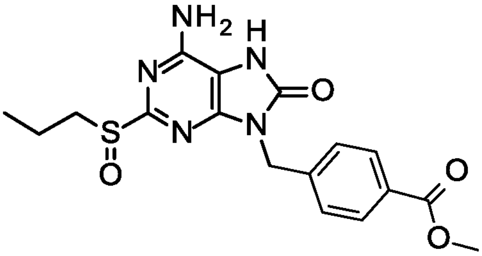
Step 5: Preparation of methyl 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate



38e

Compound **38e** was prepared in analogy to **Example 15**, **Step 5** by using methyl 4-[[6-[(4-methoxyphenyl)methylamino]-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl]methyl]benzoate (compound **38d**) instead of 9-[(2-chlorophenyl)methyl]-6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-7*H*-purin-8-one (compound **15d**). Methyl 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate (compound **38e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 374.

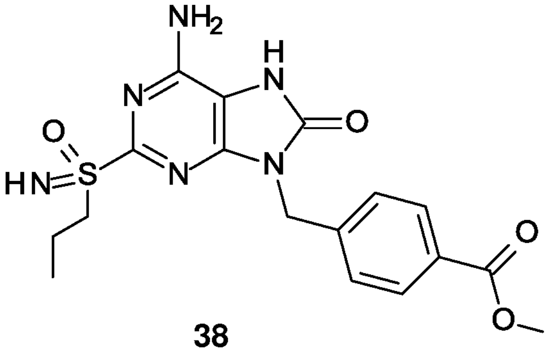
Step 6: Preparation of methyl 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzoate



38f

Compound **38f** was prepared in analogy to **Example 15**, **Step** 6 by using methyl 4-[(6-amino-8-*oxo*-2-propylsulfanyl-7*H*-purin-9-yl)methyl]benzoate (compound **38e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). Methyl 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzoate (compound **38f**) was obtained as a white solid MS obsd. (ESI$^+$) [(M+H)$^+$]: 390.

Step 7: Preparation of methyl 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoate

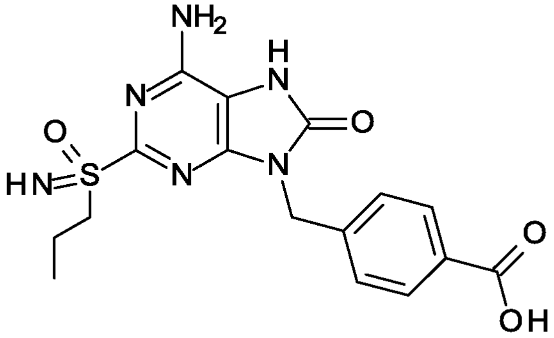


38

The title compound was prepared in analogy to **Example 15**, **Step 7** by using methyl 4-[(6-amino-8-*oxo*-2-propylsulfinyl-7*H*-purin-9-yl)methyl]benzoate (compound **38f**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one. Methyl 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoate (127 mg, **Example 38**) was obtained as a white solid. ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 10.75 (br. s., 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 6.99 (br. s., 2H), 5.05 (s, 2H), 4.00 (s, 1H), 3.84 (s, 3H), 3.32-3.27 (m, 2H), 1.64-1.56 (m, 2H), 0.88 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 405.

Example 39

4-[[6-Amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoic acid

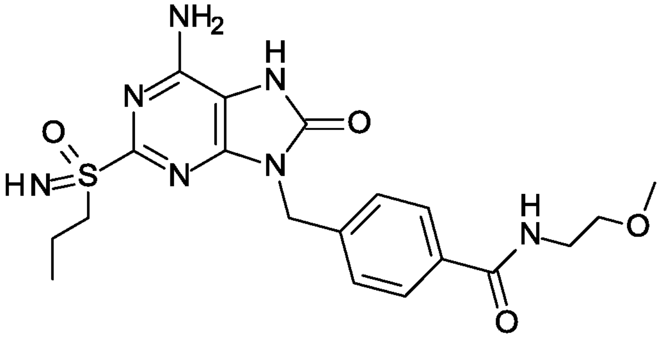


39

To a solution of methyl 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoate (70 mg, compound **38**) in THF/MeOH (2/1, V/V, 3 mL) was added aqueous LiOH (0.34 mL, 0.34 mmol, 1*M*) and the mixture was stirred at 25°C for 3 hrs. Then the reaction mixture was acidified by the addition of 1*N* HCl. The formed solid was collected by filtration and purified by prep-HPLC to give 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoic acid (38 mg, **Example 39**). ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 10.76 (br. s., 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.03 (br. s., 2H), 5.04 (s, 2H), 4.05 (s, 1H), 3.32-3.27 (m, 2H), 1.63-1.55 (m, 2H), 0.88 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 391.

Example 40

4-[[6-Amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]-*N*-(2-methoxyethyl)benzamide

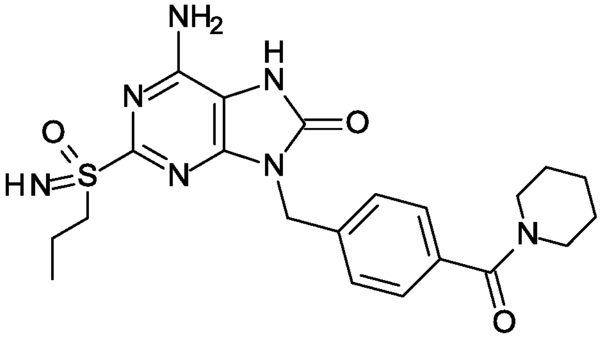


40

To a solution of 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]benzoic acid (100 mg, compound **39**), HATU (146 mg, 0.38 mmol) and anhydrous DIPEA (89 μL, 0.51 mmol) in anhydrous DMF (5 mL) was added 2-methoxyethanamine (44 μL, 0.51 mmol). The reaction mixture was stirred at rt overnight and then evaporated *in vacuo*. The residue was purified by Prep-HPLC to give 4-[[6-amino-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-9-yl]methyl]-*N*-(2-methoxyethyl)benzamide (18 mg, **Example 40**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.59 (s, 1H), 8.44-8.61 (m, 1H), 7.80 (d, J = 7.50 Hz, 2H), 7.40 (d, J = 7.49 Hz, 2H), 6.98 (br. s., 2H), 5.01 (s, 2H), 4.04 (br. s., 1H), 3.38-3.44 (m, 4H), 3.29-3.30 (m, 2H), 3.25 (s, 3H), 1.58-1.66 (m, 2H), 0.91 (t, J = 7.53 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 448

Example 41

6-Amino-9-[[4-(piperidine-1-carbonyl)phenyl]methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one

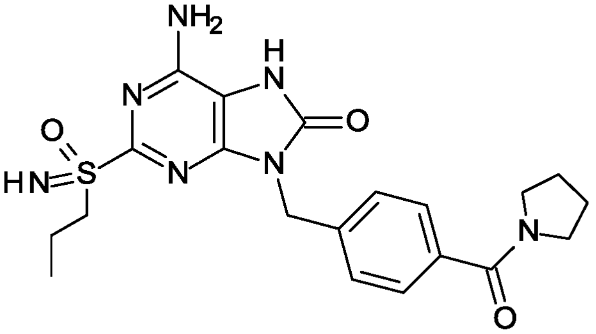


41

The title compound was prepared in analogy to **Example 40** by using piperidine instead of 2-methoxyethanamine. 6-Amino-9-[[4-(piperidine-1-carbonyl)phenyl]methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (6.5 mg, **Example 41**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.80 (s, 1H), 7.31-7.39 (m, 4H), 7.04 (br. s., 2H), 5.00 (s, 2H), 4.03 (s, 1H), 3.55 (br. s., 2H), 3.26-3.39 (m, 4H), 1.43-1.68 (m, 8H), 0.93 (t, *J* = 7.40 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 458.

Example 42

6-Amino-2-(propylsulfonimidoyl)-9-[[4-(pyrrolidine-1-carbonyl)phenyl]methyl]-7*H*-purin-8-one

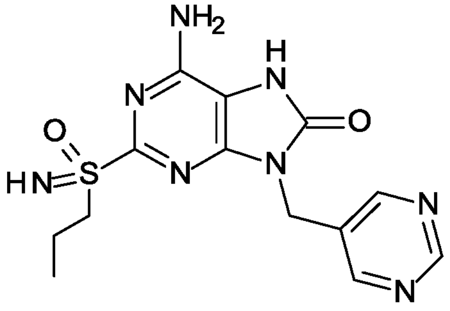


42

The title compound was prepared in analogy to **Example 40** by using pyrrolidine instead of 2-methoxyethanamine. 6-Amino-2-(propylsulfonimidoyl)-9-[[4-(pyrrolidine-1-carbonyl)phenyl]methyl]-7*H*-purin-8-one (8.0 mg, **Example 42**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.60 (s, 1H), 7.48 (d, *J* = 7.31 Hz, 2H), 7.37 (d, *J* = 8.03 Hz, 2H), 6.99 (br. s., 2H), 5.00 (s, 2H), 4.10 (s, 1H), 3.40-3.46 (m, 2H), 3.31-3.34 (m, 4H), 1.62-1.67 (m, 4H), 1.62-1.67 (m, 2H), 0.91 (t, *J* = 7.40 Hz, 3H). MS obsd. (ESI$^+$) [(M$^+$H)$^+$]: 444

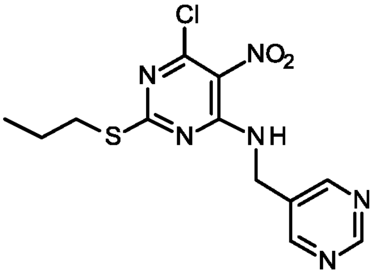
Example 43

6-Amino-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one



43

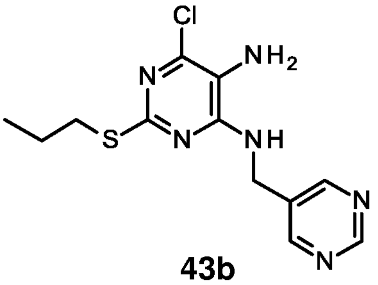
Step 1: Preparation of 6-chloro-5-nitro-2-propylsulfanyl-*N*-(pyrimidin-5-ylmethyl)pyrimidin-4-amine



43a

Compound **43a** was prepared in analogy to **Example 15**, **Step 1** by using 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine instead of (2-chlorophenyl)methylamine. 6-Chloro-5-nitro-2-(propylthio)-*N*-(pyrimidin-5-ylmethyl)-pyrimidin-4-amine (4.0 g, compound **43a**) was obtained as a light yellow oil. MS obsd. (ESI^+) $[(M+H)^+]$: 341.

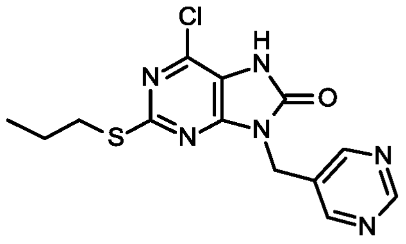
Step 2: Preparation of 6-chloro-2-propylsulfanyl-*N*4-(pyrimidin-5-ylmethyl)pyrimidine-4,5-diamine



43b

Compound **43b** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-5-nitro-2-(propylthio)-*N*-(pyrimidin-5-ylmethyl) pyrimidin-4-amine (compound **43a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-Chloro-2-propylsulfanyl-*N*4-(pyrimidin-5-ylmethyl)pyrimidine-4,5-diamine (1.0 g, compound **43b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 311.

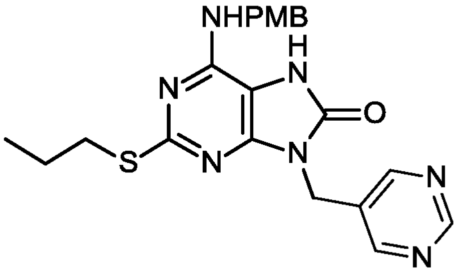
Step 3: Preparation of 6-chloro-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one



43c

Compound **43c** was prepared in analogy to **Example 15**, **Step 3** by using6-Chloro-2-propylsulfanyl-*N*4-(pyrimidin-5-ylmethyl)pyrimidine-4,5-diamine (compound **43b**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (0.5 g, compound **43c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 337.

Step 4: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7H-purin-8-one

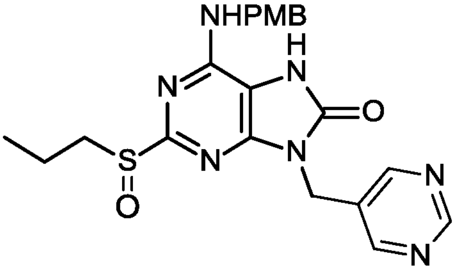


43d

Compound **43d** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (compound **43c**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (300 mg, compound **43d**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 438.

Step 5: Preparation of 6-[(4-methoxyphenyl)methylamino]-2-propylsulfinyl-9-(pyrimidin-5-

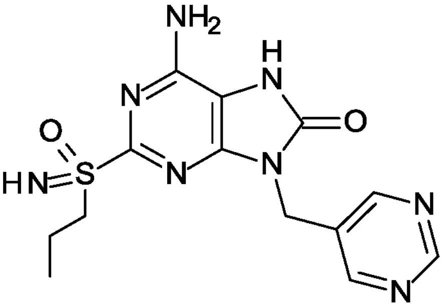
ylmethyl)-7*H*-purin-8-one



43e

Compound **43e** was prepared in analogy to **Example 15**, **Step 6** by using 6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (compound **43d**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-[(4-Methoxyphenyl)methylamino]-2-propylsulfinyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (280 mg, compound **43e**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 454.

Step 6: Preparation of 6-amino-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one

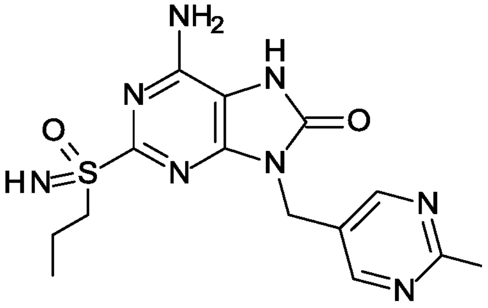


43

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-[(4-methoxyphenyl)methylamino]-2-propylsulfinyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (compound **43e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (70 mg, **Example 43**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.13 (s, 1 H), 8.83 (s, 2 H), 7.07 (br. s., 2 H), 5.04 (s, 2 H), 4.08 (s, 1 H), 3.27 - 3.34 (m, 2 H), 1.50 - 1.69 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 349.

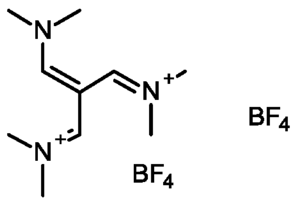
Example 44

6-Amino-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



44

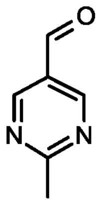
Step 1: Preparation of *N*,*N*'-[2-[1-(dimethylamino)methylidene]propane-1,3-diylidene]bis(*N*-methylmethanaminium) bis(tetrafluoroborate)



44a

To cooled DMF (400 mL) in a round-bottomed flask was added $POCl_3$ (165.5 g) at -10°C. The reaction mixture was stirred at 0°C for 3 hrs. To this reaction mixture was added 2-bromoacetic acid (50 g, 360 mmol) at 0°C. The resulting reaction mixture was stirred at 80°C for 16 hrs, then DMF was removed *in vacuo*. The dark red residue was cooled down to room temperature and sodium tetrafluoroborate (100 g, 911 mmol) was added into the residue. After the reaction mixture was cooled in ice bath, *N*,*N*'-[2-[1-(dimethylamino)methylidene]propane-1,3-diylidene]bis(*N*-methylmethanaminium) bis(tetrafluoroborate) (120g, compound **44a**) was obtained by filtration as a brown solid and used in next step without purification.

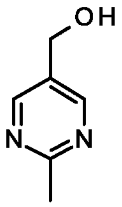
Step 2: Preparation of 2-methylpyrimidine-5-carbaldehyde



44b

To a mixture of *N*,*N*'-[2-[1-(dimethylamino)methylidene]propane-1,3-diylidene]bis(*N*-methylmethanaminium) bis(tetrafluoroborate) (70 g, 196 mmol, compound **44a**) and acetamidine HCl (37 g, 392 mmol) in $MeCN/H_2O$ (400 mL, V/V=1/1) was added NaOH (120 g, 3.0 mmol) at 15 °C, and the resulting reaction mixture was stirred at 15°C for 16 hrs. The reaction mixture was neutralized to pH 6-7 with AcOH, extracted by ethyl acetate (100 mL) three times. The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford 2-methylpyrimidine-5-carbaldehyde (10 g, compound **44b**) as a yellow solid.

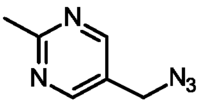
Step 3: Preparation of (2-methylpyrimidin-5-yl)methanol



44c

To a mixture of 2-methylpyrimidine-5-carbaldehyde (8 g, 66 mmol, compound **44b**) in MeOH (100 mL) was added $NaBH_4$ (7.5 g, 197 mmol) at 0 °C, and the resulting reaction mixture was stirred at 15°C for 3 hrs. Then the reaction mixture was quenched by saturated NH_4Cl solution (30 mL), extracted by ethyl acetate (20 mL) three times. The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford (2-methylpyrimidin-5-yl)methanol (4.1 g, 51%, compound **44c**) as a white solid.

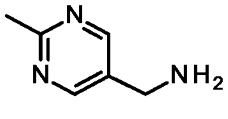
Step 4: Preparation of 5-(azidomethyl)-2-methylpyrimidine



44d

To a mixture of (2-methylpyrimidin-5-yl)methanol (4.1 g, 33 mmol, compound **44c**) in $CHCl_3$ (40 mL) and toluene (40 mL) was added DPPA (27 g, 83 mmol) and DBU (25 g, 164 mmol) at 0 °C and stirred at 15 °C for 16 hrs. The reaction mixture was diluted with DCM (100 mL) and washed with water (50 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column chromatography to afford crude 5-(azidomethyl)-2-methylpyrimidine (2.8 g, compound **44d**) as a light oil.

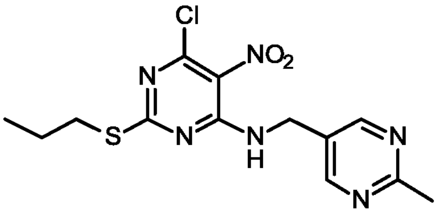
Step 5: Preparation of (2-methylpyrimidin-5-yl)methanamine.



44e

A mixture of 5-(azidomethyl)-2-methylpyrimidine (2.8 g, 18.8 mmol, compound **44d**) and Pd/C (500 mg) in MeOH (100 mL) was stirred under 1 atm of H_2 atmosphere at 15°C for 1 hour. Then the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to afford (2-methylpyrimidin-5-yl)methanamine (1.8 g, 78%, compound **44e**) as a white solid.

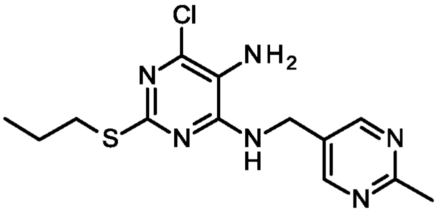
Step 6: 6-Chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



44f

Compound **44f** was prepared in analogy to **Example 15**, **Step 1** by using (2-methylpyrimidin-5-yl)methanamine (compound **44e**) instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (2.8 g, compound **44f**) was obtained as a light yellow oil. MS obsd. (ESI^+) $[(M+H)^+]$: 355.

Step 7: Preparation of 6-chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine

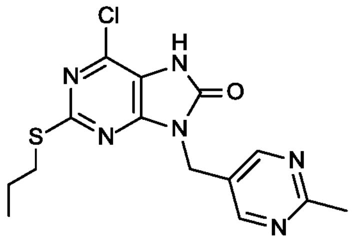


44g

Compound **44g** was prepared in analogy to **Example 15**, **Step 2** by using 6-chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **44f**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound

15a). 6-Chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (2.1 g, compound **44g**) was obtained and used in the next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 325.

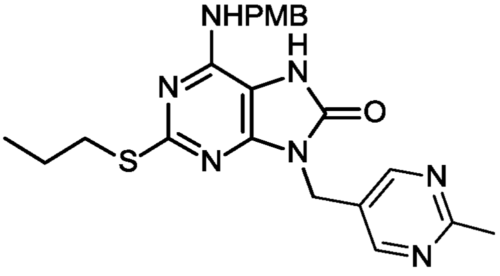
Step 8: Preparation of 6-chloro-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



44h

Compound **44h** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **44g**) instead of 6-chloro-*N*4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (1.8g, compound **44h**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 351.

Step 9: Preparation of 6-[(4-methoxyphenyl)methylamino]-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-7*H*-purin-8-one

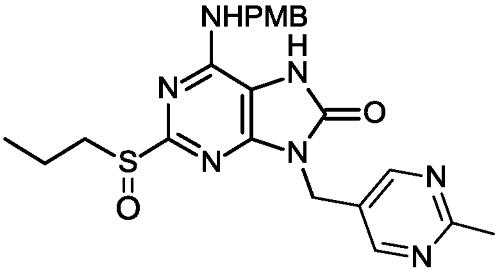


44i

Compound **44i** was prepared in analogy to **Example 15**, **Step 4** by using 6-chloro-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **44h**) instead of 6-chloro-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15c**). 6-[(4-Methoxyphenyl)methylamino]-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (500 mg, compound **44i**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 452.

Step 10: Preparation of 6-[(4-methoxyphenyl)methylamino]-9-[(2-methylpyrimidin-5-

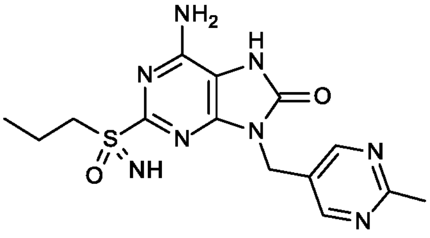
yl)methyl]-2-propylsulfinyl-7*H*-purin-8-one



44j

Compound **44j** was prepared in analogy to **Example 15**, **Step 6** by using 6-[(4-methoxyphenyl)methylamino]-2-propylsulfanyl-9-(pyrimidin-5-ylmethyl)-7*H*-purin-8-one (compound **43i**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). 6-[(4-Methoxyphenyl)methylamino]-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfinyl-7H-purin-8-one (420 mg, compound **44j**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 468.

Step 11: Preparation of 6-amino-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one

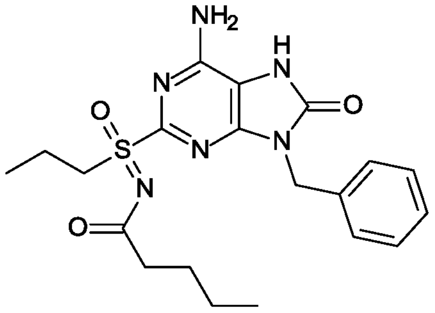


44

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-[(4-methoxyphenyl)methylamino]-9-[(2-methylpyrimidin-5-yl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **44j**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-Amino-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (16.5 mg, **Example 44**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.71 (s, 2 H), 6.98 (s, 2 H), 4.99 (s, 2 H), 4.10 (s, 1 H), 3.35 (m, 2 H), 2.59 (s, 3 H), 1.65-1.62 (m, 2H), 0.95-0.91 (t, J = 7.2 Hz, 3 H).MS obsd. (ESI$^+$) [(M+H)$^+$]: 363.

Example 46

N-[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]pentanamide

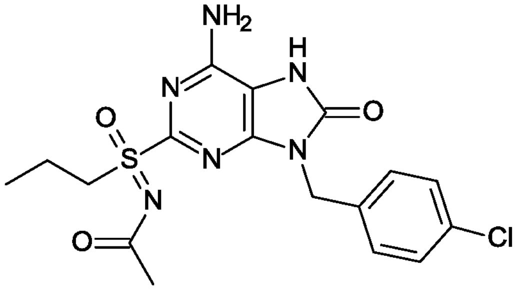


46

To the solution of 6-amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (70 mg, 0.21 mmol, compound **4**) in pyridine (2 mL) was added valeric acid anhydride (41 mg, 0.22 mmol). The reaction mixture was stirred at RT for 6 hrs. After reaction, the solvent was removed *in vacuo*. The residue was purified by prep-HPLC to give *N*-[(6-amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]pentanamide (13.7 mg, **Example 46**). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* ppm: 7.29-7.32 (m, 5H), 7.19 (br. s., 2H), 4.90 (m, 2H), 3.48-3.50 (m, 2H), 2.17 (t, *J* = 7.2Hz, 2H), 1.50-1.70 (m, 2H), 1.39-1.47 (m, 2H), 1.61-1.76 (m, 1H), 1.47-1.59 (m, 1H), 0.89 (t, *J* = 7.40Hz, 3H), 0.80 (t, *J* = 7.39 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 431.

Example 47

N-[[6-Amino-9-[(4-chlorophenyl)methyl]-8-*oxo*-7*H*-purin-2-yl]-*oxo*-propyl-λ^4-sulfanylidene]acetamide

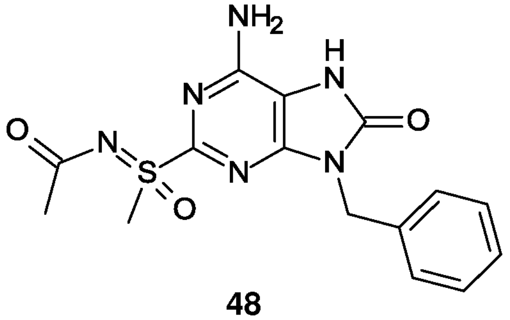


47

The title compound was prepared in analogy to **Example 46** by using acetic anhydride and 6-amino-9-(4-chlorobenzylmethyl)-2-(propylsulfonimidoyl)-7*H*-purin-8-one (compound **9**) instead of valeric acid anhydride and 6-amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (**Example 4**). N-[[6-Amino-9-[(4-chlorophenyl)methyl]-8-*oxo*-7*H*-purin-2-yl]-*oxo*-propyl-λ^4-sulfanylidene]acetamide (2 mg, **Example 47**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.31-7.40 (m, 4H), 7.29 (br. s., 2H), 4.95 (s, 2H), 3.42-3.57 (m, 2H), 1.90 (s, 3H), 1.61-1.76 (m, 1H), 1.47-1.59 (m, 1H), 0.89 (t, J = 7.40 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 423.

Example 48

N-[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-methyl-*oxo*-λ^4-sulfanylidene]acetamide

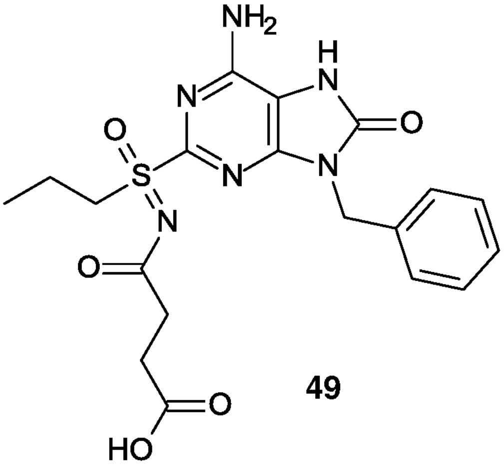


48

The title compound was prepared in analogy to **Example 46** by using acetic anhydride instead of valeric acid anhydride. *N*-[(6-amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-methyl-*oxo*-λ^4-sulfanylidene]acetamide (44 mg, **Example 48**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.80 (br. s., 1H), 7.26-7.36 (m, 5H), 7.18 (br. s., 2H), 4.96 (s, 2H), 3.39 (s, 3H), 1.91 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 361.

Example 49

4-[[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]amino]-4-*oxo*-butanoic acid



49

The title compound was prepared in analogy to **Example 46** by using succinic anhydride instead of valeric acid anhydride. 4-[[[6-Amino-9-[(4-chlorophenyl)methyl]-8-*oxo*-7*H*-purin-2-yl]-*oxo*-propyl-λ^4-sulfanylidene]amino]-4-*oxo*-butanoic acid (500 mg, **Example 49**) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.31-7.41 (m, 5H), 7.21 (br. s., 2H), 4.88-5.00 (m, 2H), 3.40-3.64 (m, 2H), 2.41-2.46 (m, 2H), 2.30-2.36 (m, 2H), 1.56-1.66 (m, 2H), 0.89 (t, J =7.4 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 481.

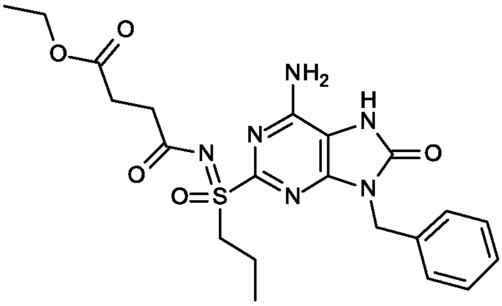
Separation of compound of **Example 49** by chiral HPLC afforded **Example 49-A** (faster eluting, 105 mg) and **Example 49-B** (slower eluting, 106.1 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak IC-3 column.)

Example 49-A: ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.40 (m, 2H), 7.27-7.30 (m, 5H), 4.95 (s, 2H), 3.44-3.55 (m, 2H), 2.42-2.45 (m, 2H), 2.28-2.32 (m, 2H), 1.55-1.69 (m, 2H), 0.87-0.910.87 (t, J = 7.8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 481

Example 49-B: ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 7.46 (s, 2H), 7.26-7.32 (m, 5H), 4.95 (s, 2H), 3.48-3.53 (m, 2H), 2.42-2.45 (m, 2H), 2.28-2.31 (m, 2H), 1.55-1.69 (m, 2H), 0.87-0.90 (t, J = 7.8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 481

Example 50

Ethyl 4-[[(6-amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]amino]-4-*oxo*-butanoate



The title compound was prepared in analogy to **Example 46** by using ethyl 4-chloro-4-*oxo*-butanoate instead of valeric acid anhydride. *N*-[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide (30 mg, **Example 50**) was obtained as a white solid.

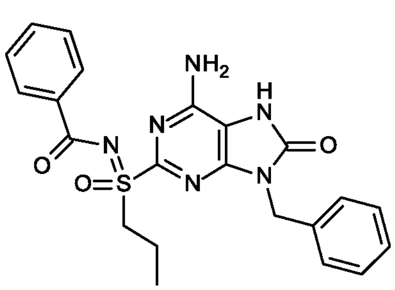
Separation of compound of **Example 50** by chiral HPLC afforded **Example 50-A** (faster eluting, 11 mg) and **Example 50-B** (slower eluting, 12 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak OD-3 column.)

Example 50-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.28-7.35 (m, 5H), 7.22 (br. s., 2H), 4.94 (s, 2H), 3.98-4.03 (m, 2H), 3.48-3.51 (m, 2H), 2.33-2.40 (m, 4H), 1.55-1.69 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 475.

Example 50-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.28-7.35 (m, 5H), 7.22 (br. s., 2H), 4.94 (s, 2H), 3.98-4.03 (m, 2H), 3.48-3.51 (m, 2H), 2.33-2.40 (m, 4H), 1.55-1.69 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 475.

Example 51

N-[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]benzamide



The title compound was prepared in analogy to **Example 46** by using benzoyl benzoate instead of valeric acid anhydride. *N*-[(6-Amino-9-benzyl-8-*oxo*-7*H*-purin-2-yl)-*oxo*-propyl-λ^4-sulfanylidene]benzamide (220 mg, **Example 51**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.77 (br.s., 1H), 8.08 - 7.89 (m, 2H), 7.61 -7.41 (m, 3H), 7.31 - 7.07 (m, 7H), 4.88 (d, J = 3.8 Hz, 2H), 3.72 - 3.56 (m, 2H), 1.84 - 1.61 (m, 2H), 0.97 (t, J =7.8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 451.

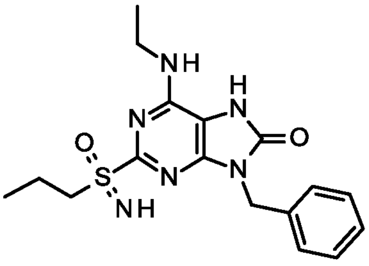
Separation of compound of **Example 51** by chiral HPLC afforded **Example 51-A** (faster eluting, 50 mg) and **Example 51-B** (slower eluting, 50.5 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak OD-3S column.)

Example 51-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.77 (br. s., 1H), 7.89-8.08 (m, 2H), 7.41-7.61 (m, 3H), 7.07-7.31 (m, 7H), 4.88 (d, J = 3.8 Hz, 2H), 3.56-3.72 (m, 2H), 1.61-1.84 (m, 2H), 0.97 (t, J =7.8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 451.

Example 51-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.78 (br. s., 1H), 7.94-8.05 (m, 2H), 7.42-7.62 (m, 3H), 7.07-7.31 (m, 7H), 4.88 (d, J = 3.8 Hz, 2H), 3.60-3.73 (m, 2H), 1.61-1.90 (m, 2H), 0.97 (t, J = 7.8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 451.

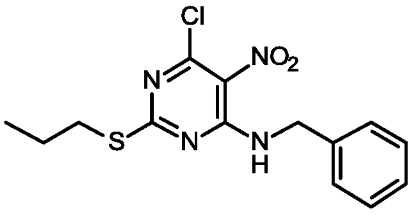
Example 52

9-Benzyl-6-(ethylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



52

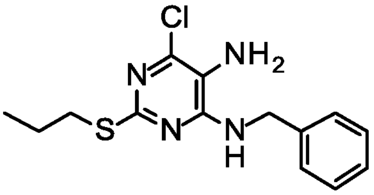
Step 1: Preparation of *N*-benzyl-6-chloro-5-nitro-2-(propylthio)pyrimidin-4-amine



52a

Compound **52a** was prepared in analogy to **Example 15**, **Step 1** by using benzylamine instead of (2-chlorophenyl)methylamine. *N*-Benzyl-6-chloro-5-nitro-2-(propylthio)pyrimidin-4-amine (35g, compound **52a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 339.

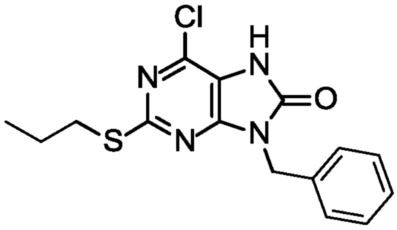
Step 2: Preparation of *N*4-benzyl-6-chloro-2-propylsulfanyl-pyrimidine-4,5-diamine



52b

Compound **52b** was prepared in analogy to **Example 15**, **Step 2** by using *N*-benzyl-6-chloro-5-nitro-2-(propylthio)pyrimidin-4-amine (compound **52a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). *N*4-benzyl-6-chloro-2-propylsulfanyl-pyrimidine-4,5-diamine (28.0 g, compound **52b**) was obtained as a brown solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 309.

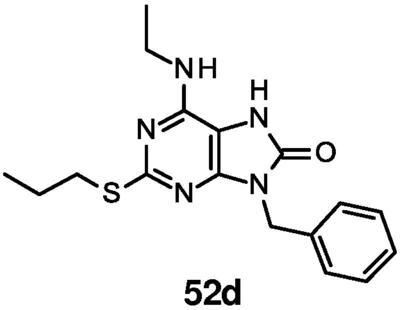
Step 3: Preparation of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one



52c

Compound **52c** was prepared in analogy to **Example 15**, **Step 3** by using *N*4-benzyl-6-chloro-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **52b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 9-Benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (24.0 g, compound **52c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 335.

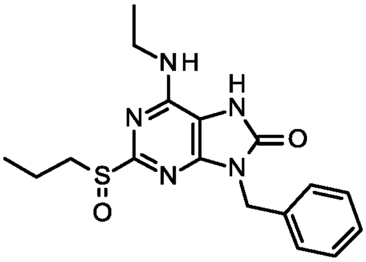
Step 4: Preparation of 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one



52d

To a solution of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (2.3 g, 6.9 mmol, compound **52c**) in *n*-BuOH (8 mL) was added $EtNH_2 \cdot HCl$ (1.7 g, 20.6 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (5.4 g, 41.4 mmol). The reaction vessel was sealed and heated in microwave at 130 °C for 2 hrs. The solvent was removed *in vacuo*. The residue was suspended in EtOAc (20 mL), washed with water (15 mL) two times and brine (30 mL). The separated organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (1.2 g, compound **52d**) as light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 344

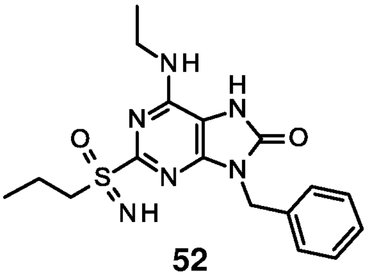
Step 5: Preparation of 9-benzyl-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one



52e

To a solution of 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (682 mg, 2.0 mmol, compound **51d**) in THF (8 mL) was added *m*-CPBA (415 mg, 2.4 mmol) in THF (2 mL) at 0 °C under N_2 atmosphere. After the addition, the mixture was stirred at this temperature for 30 min until a clear solution was formed. The reaction was quenched by the addition of saturated Na_2SO_3 (5 mL), extracted with *i*-PrOH/DCM (20 mL, V/V=1/3) two times. The combined organic layer was dried over Na_2SO_4 and concentrated to give 9-benzyl-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one (580 mg, compound **52e**) as light yellow solid. MS obsd. (ESI^+) $[(M+H)^+]$: 360.

Step 6: Preparation of 9-benzyl-6-(ethylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one

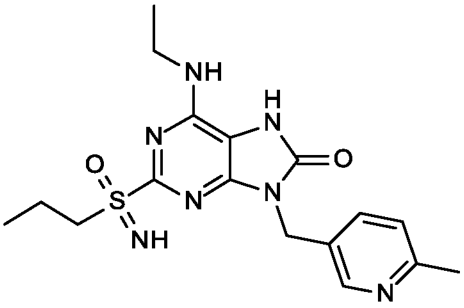


52

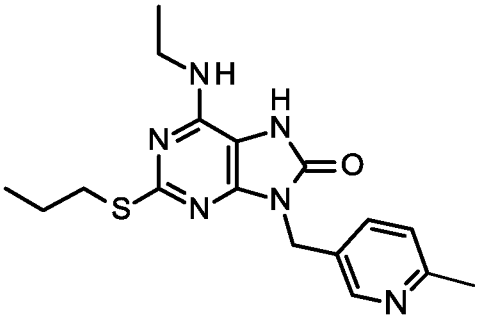
The title compound was prepared in analogy to **Example 15**, **Step 7** by using 9-benzyl-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one (280 mg, compound **52e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 9-Benzyl-6-(ethylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one (94 mg, **Example 52**) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 10.65 (s, 1H), 7.50-7. 22 (m, 5H), 7.14-6.97 (m, 1H), 4.97 (s, 2H), 4.07 (s, 1H), 3.58-3.44 (m, 2H), 3.36-3.28 (m, 2H), 1.78-1.54 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H). MS obsd. (ESI^+) $[(M+H)^+]$: 375.

Example 53

6-(Ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one



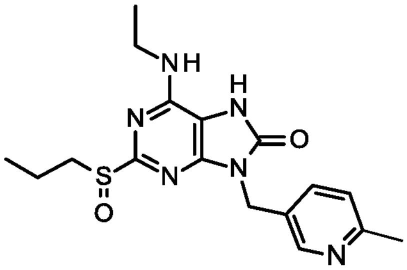
Step 1: Preparation of 6-(ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



53a

Compound **53a** was prepared in analogy to **Example 52**, **Step 4** by using 6-chloro-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **34e**) instead of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (compound **52c**). 6-(Ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (810 mg, compound **53a**) was obtained as light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 359.

Step 2: Preparation of 6-(ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one

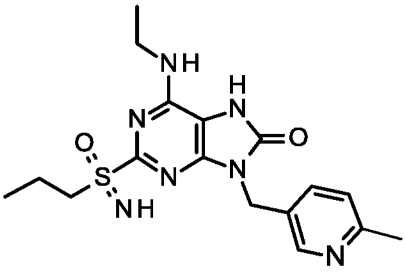


53b

Compound **53b** was prepared in analogy to **Example 52**, **Step 5** by using 6-chloro-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **53a**) instead of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (compound **52d**). 6-(Ethylamino)-9-[(6-

methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (380 mg, compound **53b**) was obtained as light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 375.

Step 3: Preparation of 6-(ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one

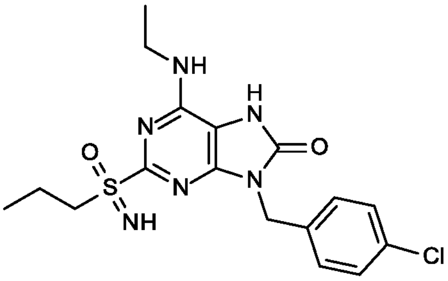


53

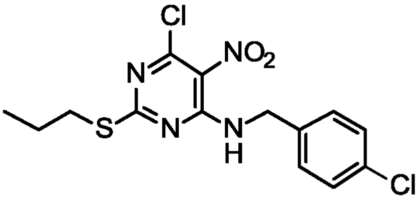
The title compound was prepared in analogy to **Example 15**, **Step 7** by using 6-(ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (280 mg, compound **53b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 6-(Ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7*H*-purin-8-one (78 mg, **Example 53**) was obtained as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.56 (s,1H), 8.47 (s, 1H), 7.62-7.64 (dd, J = 8.0, 2.4 Hz, 1H), 7.20-7.22 (d, J = 8.0 Hz, 1H), 7.00 (m, 1H), 4.95 (s, 2H), 4.21 (s, 1H), 3.50-3.45 (m, 2H), 3.39-3.35 (m, 2H), 2.42 (s, 3H), 1.61-1.71 (m, 2H), 1.18-1.21 (t, J = 7.2 Hz, 3H), 0.95-0.95 (t, J = 7.2 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 390.

Example 54

9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



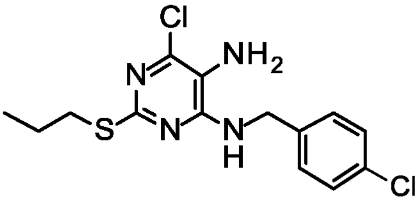
Step 1: Preparation of 6-chloro-*N*-[(4-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine



54a

Compound **54a** was prepared in analogy to **Example 15**, **Step 1** by using (4-Chlorophenyl)methylamine instead of (2-chlorophenyl)methylamine. 6-Chloro-*N*-[(4-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (11 g, compound **54a**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 373.

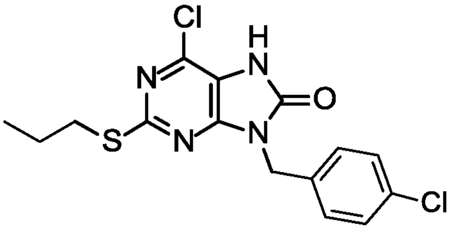
Step 2: Preparation of 6-chloro-*N*4-[(4-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine



54b

Compound **54b** was prepared in analogy to **Example 15**, **Step 2** by using *N-4-*chlorobenzyl-6-chloro-5-nitro-2-(propylthio)pyrimidin-4-amine (compound **54a**) instead of 6-chloro-*N*-[(2-chlorophenyl)methyl]-5-nitro-2-propylsulfanyl-pyrimidin-4-amine (compound **15a**). 6-chloro-*N*4-[(4-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (4.8 g, compound **54b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 343.

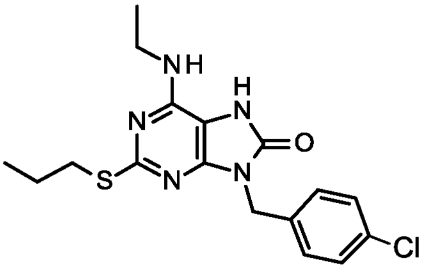
Step 3: Preparation of 6-chloro-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one



54c

Compound **54c** was prepared in analogy to **Example 15**, **Step 3** by using 6-chloro-*N*4-[(4-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **54b**) instead of 6-chloro-*N*-4-[(2-chlorophenyl)methyl]-2-propylsulfanyl-pyrimidine-4,5-diamine (compound **15b**). 6-Chloro-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (4.5 g, compound **54c**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 369.

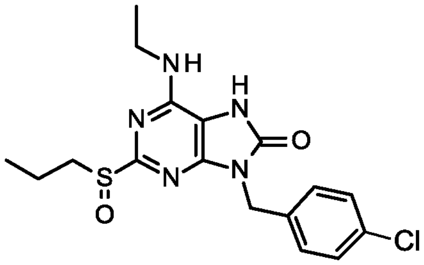
Step 4: Preparation of 9-[(4-chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one



54d

Compound **54d** was prepared in analogy to **Example 52**, **Step 4** by using 6-chloro-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **54c**) instead of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (compound **52c**). 9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (400 mg, compound **54d**) was obtained as light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 378.

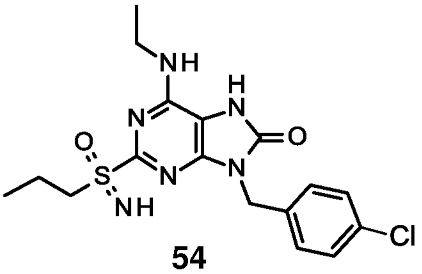
Step 5: Preparation of 9-[(4-chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one



54e

Compound **54e** was prepared in analogy to **Example 52**, **Step 5** by using 9-[(4-chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (compound **54d**) instead of 9-benzyl-6-chloro-2-propylsulfanyl-7*H*-purin-8-one (compound **52d**). 9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one (300 mg, compound **54e**) was obtained as light yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 394.

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

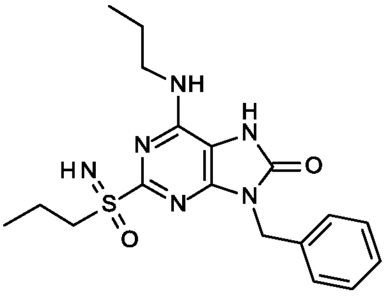


54

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 9-[(4-chlorophenyl)methyl]-6-(ethylamino)-2-propylsulfinyl-7*H*-purin-8-one (compound **54e**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15e**). 9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one (86 mg, **Example 54**) was obtained as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.50 (s, 1H), 7.31-7.42 (m, 3H), 6.97 (t, J = 5.4 Hz, 1H), 4.96 (s, 2H), 4.18 (s, 1H), 3.42-3.59 (m, 2H), 3.30-3.39 (m, 2H), 1.54-1.76 (m, 2H), 1.15-1.28 (m, 3H), 0.86-0.99 (m, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 409.

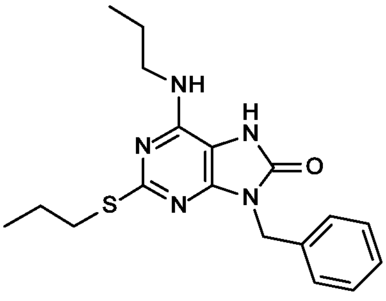
Example 55

9-Benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



55

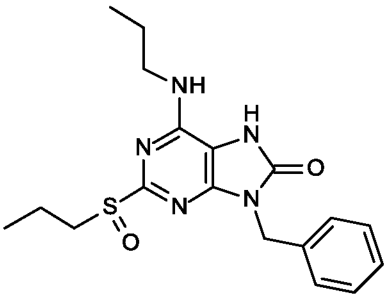
Step 1: Preparation of 9-benzyl-6-(propylamino)-2-propylsulfanyl-7*H*-purin-8-one



55a

Compound **55a** was prepared in analogy to **Example 52**, **Step 4** by using propan-1-amine instead of EtNH$_2$·HCl. 9-Benzyl-6-(propylamino)-2-propylsulfanyl-7*H*-purin-8-one (820 mg, compound **55a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 358.

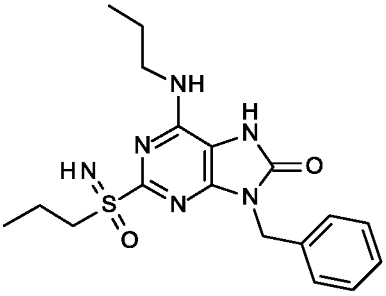
Step 2: Preparation of 9-benzyl-6-(propylamino)-2-propylsulfinyl-7H-purin-8-one



55b

Compound **55b** was prepared in analogy to **Example 52**, **Step 5** by using 9-benzyl-6-(propylamino)-2-propylsulfanyl-7*H*-purin-8-one (compound **55a**) instead of 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (compound **52d**). 9-Benzyl-6-(propylamino)-2-propylsulfanyl-7*H*-purin-8-one (400 mg, compound **55b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 374.

Step 3: Preparation of 9-benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one

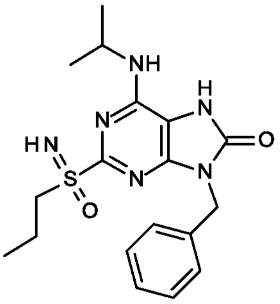


55

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 9-benzyl-6-(propylamino)-2-propylsulfinyl-7*H*-purin-8-one (compound **55b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 9-Benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one (113.5 mg, **Example 55**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.67 (s, 1H), 7.45-7.19 (m, 5H), 7.16-7.01 (m, 1H), 4.97 (s, 2H), 4.17 (s, 1H), 3.52-3.40 (m, 2H), 3.36-3.28 (m, 2H), 1.81-1.44 (m, 4H), 1.06-0.79 (m, 6H). MS obs. (ESI$^+$) [(M+H)$^+$]: 389.

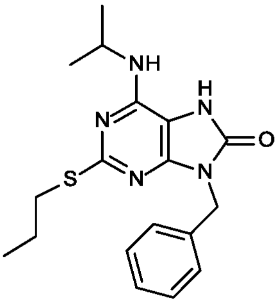
Example 56

9-Benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



56

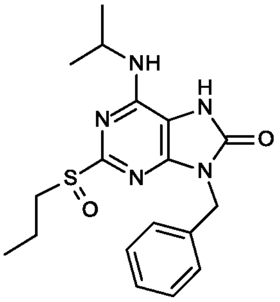
Step 1: Preparation of 9-benzyl-6-(isopropylamino)-2-propylsulfanyl-7*H*-purin-8-one



56a

Compound **56a** was prepared in analogy to **Example 52**, **Step 4** by using propan-2-amine instead of $EtNH_2 \cdot HCl$. 9-Benzyl-6-(isopropylamino)-2-propylsulfanyl-7*H*-purin-8-one (1.5 g, compound **56a**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 358.

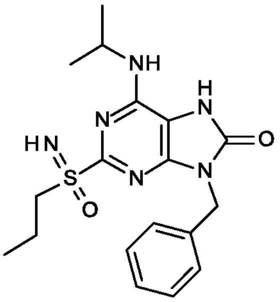
Step 2: Preparation of 9-benzyl-6-(isopropylamino)-2-propylsulfinyl-7*H*-purin-8-one



56b

Compound **56b** was prepared in analogy to **Example 52**, **Step 5** by using 9-benzyl-6-(isopropylamino)-2-propylsulfanyl-7*H*-purin-8-one (compound **56a**) instead of 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (compound **52d**). 9-Benzyl-6-(isopropylamino)-2-propylsulfinyl-7*H*-purin-8-one (1.35 g, compound **56b**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 373.

Step 3. Preparation of 9-benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one

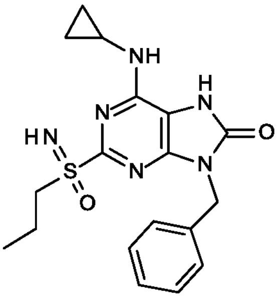


56

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 9-benzyl-6-(isopropylamino)-2-propylsulfinyl-7*H*-purin-8-one (compound **56b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 9-Benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one (100 mg, **Example 56**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.45 (br. s., 1H), 7.47-7.21 (m, 5H), 6.93-6.80 (m, 1H), 4.95 (s, 2H), 4.26-4.17 (m, 1H), 4.14 (s, 1H), 3.38-3.37 (m, 2H), 1.65-1.55 (m, 2H), 1.23 (dd, J = 6.4, 2.1 Hz, 6H), 0.92 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 389.

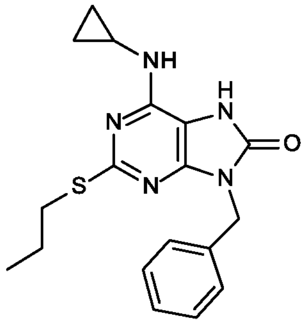
Example 57

9-Benzyl-6-(cyclopropylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one



57

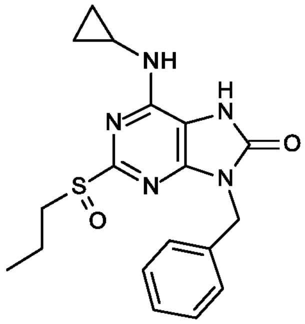
Step 1: Preparation of 9-benzyl-6-(cyclopropylamino)-2-propylsulfanyl-7*H*-purin-8-one



57a

Compound **57a** was prepared in analogy to **Example 52**, **Step 4** by using cyclopropanamine instead of $EtNH_2 \cdot HCl$. 9-Benzyl-6-(cyclopropylamino)-2-propylsulfanyl-7*H*-purin-8-one (1.35g, compound **57a**) was obtained as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 356.

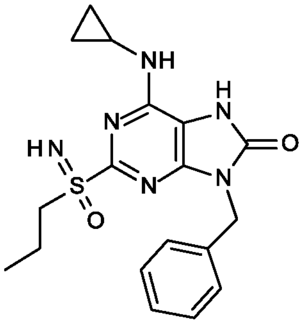
Step 2: Preparation of 9-benzyl-6-(cyclopropylamino)-2-propylsulfinyl-7*H*-purin-8-one



57b

Compound **57b** was prepared in analogy to **Example 52**, **Step 5** by using 9-benzyl-6-(cyclopropylamino)-2-propylsulfanyl-7*H*-purin-8-one instead of 9-benzyl-6-(ethylamino)-2-propylsulfanyl-7*H*-purin-8-one (**52d**). 9-Benzyl-6-(cyclopropylamino)-2-propylsulfinyl-7*H*-purin-8-one (1.35g, compound **57b**) was obtained as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 372

Step 3: Preparation of 9-benzyl-6-(cyclopropylamino)-2-(propylsulfonimidoyl)-7*H*-purin-8-one

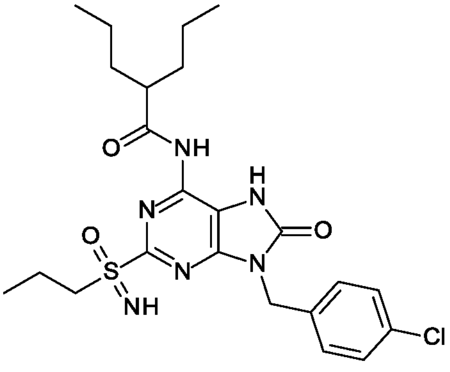


57

The title compound was prepared in analogy to **Example 15**, **Step 7** by using 9-benzyl-6-(cyclopropylamino)-2-propylsulfinyl-7*H*-purin-8-one (compound **57b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). 9-Benzyl-6-(cyclopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one (30.5 mg, **Example 57**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.40-7.57 (m, 1H), 7.28-7.34 (m, 5H),4.97 (s, 2H), 4.12 (s, 1H), 3.38-3.40 (m, 2H), 1.65-1.70 (m, 2H), 0.94 (t, J = 8.0 Hz, 3H), 0.80-0.81 (m, 2H), 0.52-0.59 (m, 2H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 387.

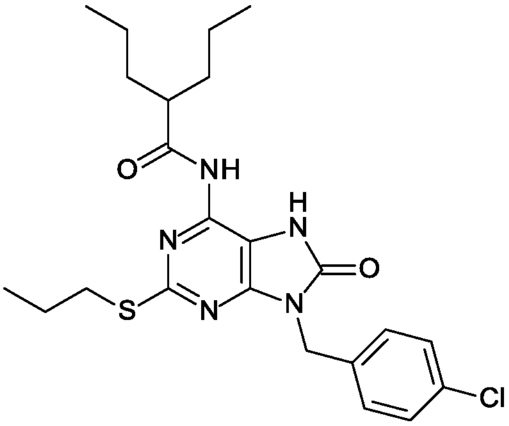
Example 58

N-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide



58

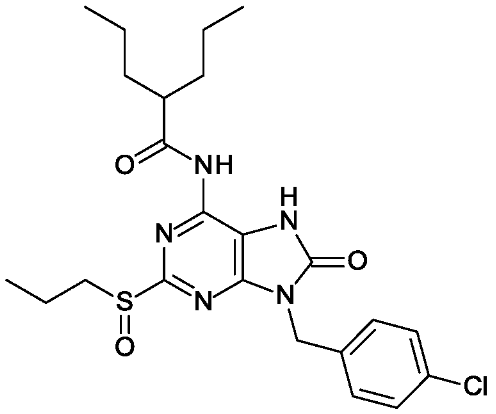
Step 1: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide



58a

To a 50 mL microwave vial was added 6-amino-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-8-one (2.2 g, 6.29 mmol, compound **9c**), 2-propylpentanoic anhydride (17 g, 62.9 mmol) and sulfuric acid (308 mg, 3.14 mmol). The vial was sealed and heated in the microwave at 70 °C for 10 min. Then the reaction mixture was diluted with H_2O (50 mL) and neutralized with saturated sodium bicarbonate solution. The mixture was extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 40 g, 100% DCM) to give *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (2.9 g, compound **58a**) as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 476.

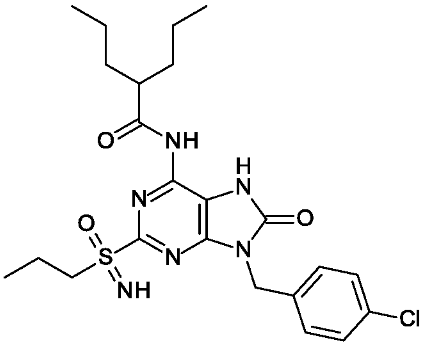
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide



58b

Compound **58b** was prepared in analogy to **Example 15**, **Step 6** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (2.9 g, compound **58a**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **15e**). *N*-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (2.8 g, compound **58b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 492.

Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide

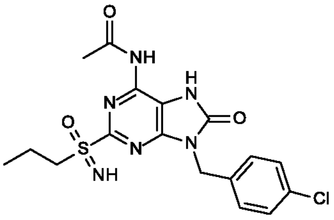


58

The title compound was prepared in analogy to **Example 15**, **Step 7** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**) instead of 6-amino-9-[(2-chlorophenyl)methyl]-2-propylsulfinyl-7*H*-purin-8-one (compound **15f**). *N*-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide (21 mg, **Example 58**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.15 (s, 1H), 10.45 (br. s, 1H), 7.39 (s, 4H), 5.04 (s, 2H), 4.27 (s, 1H), 3.37-3.44 (m, 2H), 2.68-2.73 (m, 1H), 1.56-1.65 (m, 4H), 1.24-1.42 (m, 6H), 0.90 (t, J = 8 Hz, 3H), 0.88 (t, J = 8 Hz, 6H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 507.

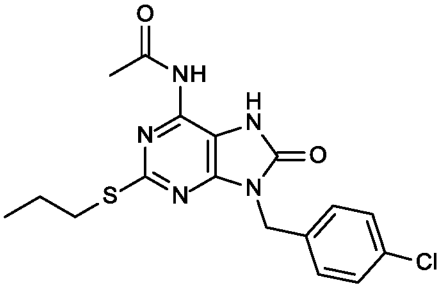
Example 59

N-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]acetamide



59

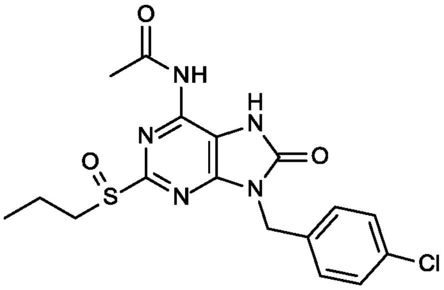
Step 1: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]acetamide



59a

Compound **59a** was prepared in analogy to **Example 58, Step 1** by using acetyl acetate instead of 2-propylpentanoic anhydride. *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]acetamide (300 mg, compound **59a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 392.

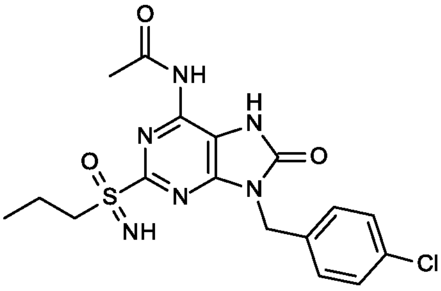
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]acetamide



59b

Compound **59b** was prepared in analogy to **Example 58, Step 2** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]acetamide (300 mg, 0.76 mmol, compound **59a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]acetamide (260 mg, compound **59b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 408.

Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]acetamide

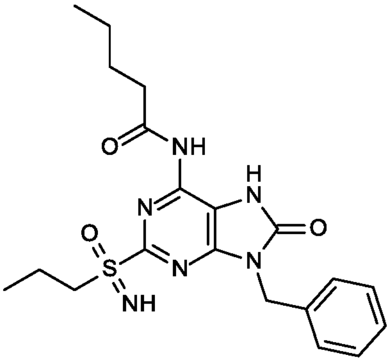


59

Compound **59** was prepared in analogy to **Example 50, Step 3** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]acetamide (250 mg, 0.61 mmol, compound **59b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]acetamide (47 mg, **Example 59**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.04 (br. s, 1H), 10.34 (s, 1H), 7.40 (s, 4H), 5.03 (s, 2H), 4.29 (s, 1H), 3.37-3.44 (m, 2H), 2.16 (s, 3H), 1.60-1.66 (m, 2H), 0.91 (t, J = 8 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 423.

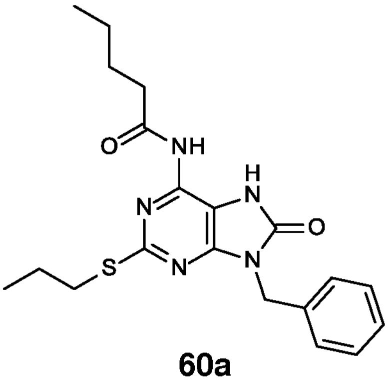
Example 60

N-[9-Benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]pentanamide



60

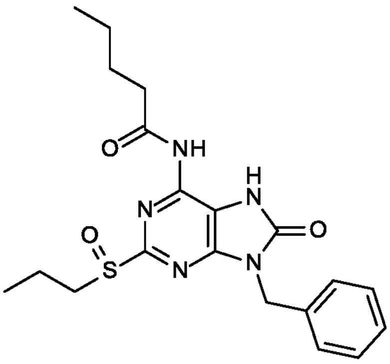
Step 1: Preparation of *N*-(9-benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)pentanamide



60a

Compound **60a** was prepared in analogy to **Example 58, Step 1** by using pentanoyl pentanoate (TCI, Catalog number: V0006-25ML) and 6-amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (**Example 50**) instead of 2-propylpentanoic anhydride and 6-amino-9-[(4-chlorophenyl)methyl]-2-propylsulfanyl-7*H*-purin-8-one (compound **9c**). *N*-(9-benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)pentanamide (320 mg, compound **60a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 400.

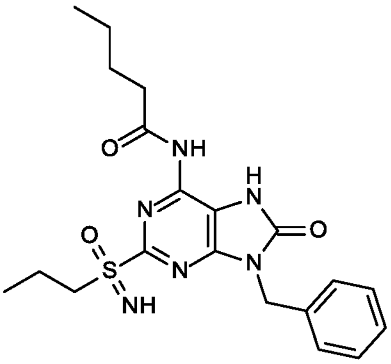
Step 2: Preparation of *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)pentanamide



60b

Compound **60b** was prepared in analogy to **Example 58, Step 2** by using *N*-(9-benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)pentanamide (310 mg, 0.77 mmol, compound **60a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)pentanamide (276 mg, compound **60b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 416.

Step 3: Preparation of *N*-[9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]pentanamide

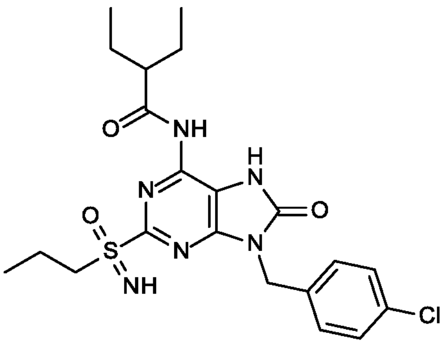


60

Compound **60** was prepared in analogy to **Example 58, Step 3** by using *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)pentanamide (200 mg, 0.48 mmol, compound **60b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]pentanamide (28 mg, **Example 60**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.98 (s, 1H), 7.27-7.39 (m, 5H), 5.04 (s, 2H), 4.27 (br. s., 1H), 3.24-3.44 (m, 2H), 2.46 (t, J = 8.0 Hz, 2H), 1.58-1.71 (m, 4H), 1.32-1.37 (m, 2H),0.90-0.93 (m, 6H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 431.

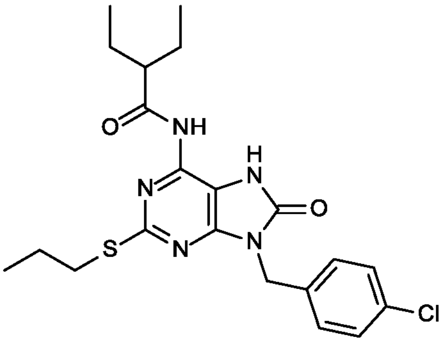
Example 61

N-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-ethyl-butanamide



61

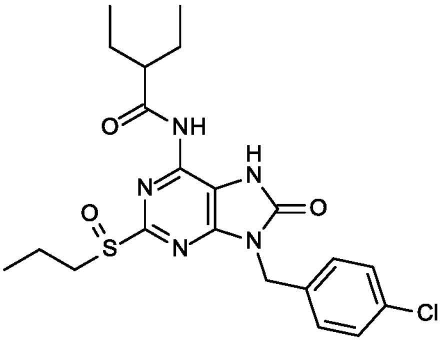
Step 1: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-ethyl-butanamide



61a

Compound **61a** was prepared in analogy to **Example 58, Step 1** by using 2-ethylbutanoyl 2-ethylbutanoate instead of 2-propylpentanoic anhydride. *N*-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-ethyl-butanamide (150 mg, compound **61a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 448.

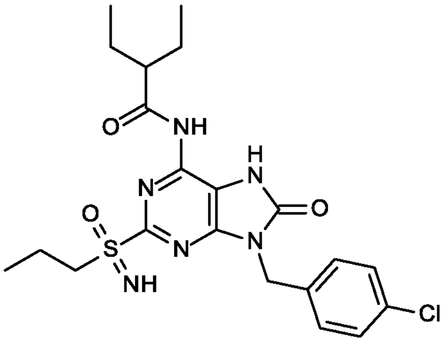
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-ethyl-butanamide



61b

Compound **61b** was prepared in analogy to **Example 58, Step 2** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-ethyl-butanamide (136 mg, 0.30 mmol, compound **61a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-ethyl-butanamide (126 mg, compound **61b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 464.

Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-ethyl-butanamide

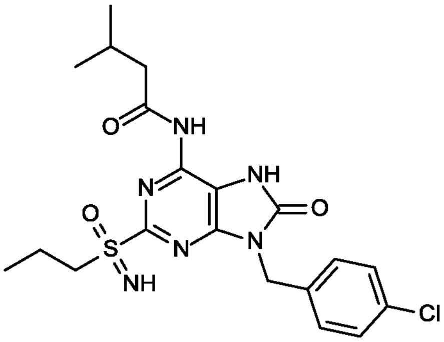


61

Compound **61**was prepared in analogy to **Example 58, Step 3** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-ethyl-butanamide (200 mg, 0.43 mmol, compound **61b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-ethyl-butanamide (39 mg, **Example 61**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.15 (br. s., 1H), 10.50 (br. s., 1H), 7.36-7.41 (m, 4H), 5.05 (s, 2H), 4.22-4.36 (m, 1H), 3.29-3.40 (m, 2H), 2.67 (d, J = 1.8 Hz, 1H), 1.43-1.69 (m, 4H), 1.15-1.38 (m, 2H), 0.86-0.94 (m, 9H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 479.

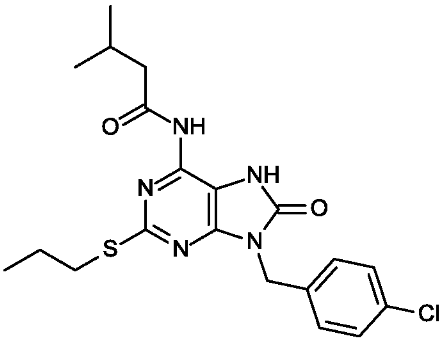
Example 62

N-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-3-methyl-butanamide



62

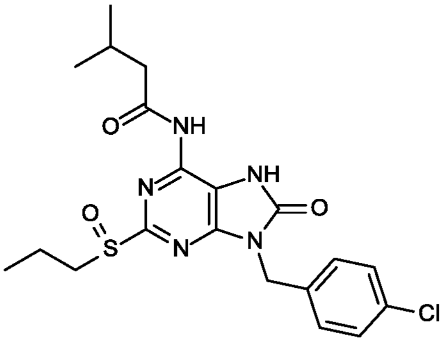
Step 1: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-3-methyl-butanamide



62a

Compound **62a** was prepared in analogy to **Example 58, Step 1** by using 2-methylbutanoyl 2-methylbutanoate (J&K, Catalog number: j20-038361-25g) instead of 2-propylpentanoic anhydride. *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-methyl-butanamide (390 mg, compound **62a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 434.

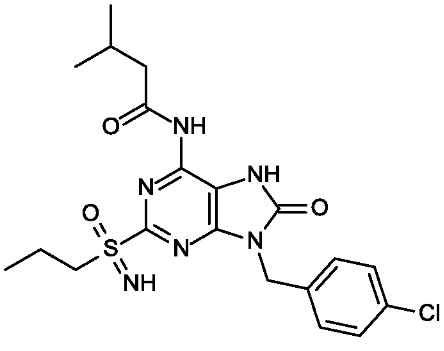
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-3-methyl-butanamide



62b

Compound **62b** was prepared in analogy to **Example 58, Step 2** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-methyl-butanamide (390 mg, 0.90 mmol, compound **62a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-methyl-butanamide (390 mg, compound **62b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 450.

Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-3-methyl-butanamide

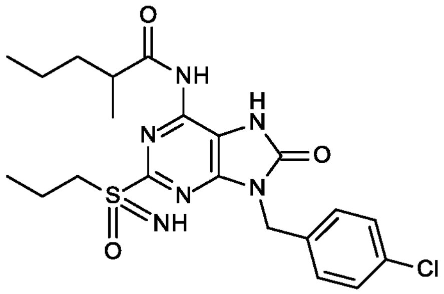


62

Example 62 was prepared in analogy to **Example 58, Step 3** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-methyl-butanamide (390 mg, 0.87 mmol, compound **62b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-methyl-butanamide (89 mg, **Example 62**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.07 (br. s., 1H), 10.58 (br. s., 1H), 7.36-7.43 (m, 4H), 5.05 (s, 2H), 4.29 (s, 1H), 3.30-3.37 (m, 2H), 2.36 (d, J = 7.0 Hz, 2H), 2.05-2.19 (m, 1H), 1.63 (sxt, J = 7.6 Hz, 2H), 0.89-0.99 (m, 9H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 465.

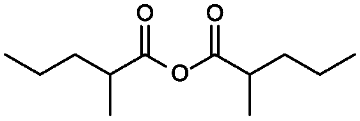
Example 63

N-[9-[(4-Chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-methyl-pentanamide



63

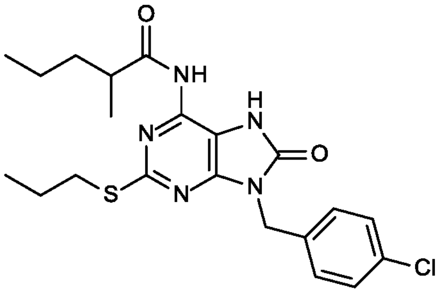
Step 1: Preparation of 2-methylpentanoyl 2-methylpentanoate



63a

In a 250 mL three-necked flask, 2-methylpentanoic acid (116.g, 99.9 mmol). Di-*tert*-butyl dicarbonate (10.9 g, 49.9 mmol) and magnesium chloride (951mg, 9.99 mmol) were dissolved in THF (100 mL) to give a colorless solution. The reaction mixture was stirred at 25 °C for 20 hrs. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (50 mL) three times. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 2-methylpentanoyl-2-methylpentanoate (19 g, compound **63a**) as a light yellow oil which was used in the next step without further purification.

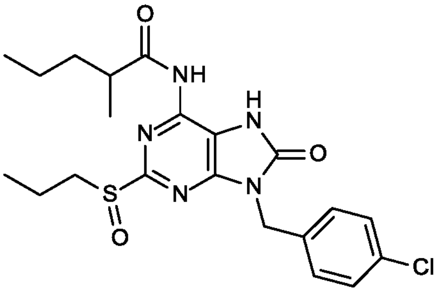
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-methyl-pentanamide



63b

Compound **63b** was prepared in analogy to **Example 58, Step 1** by using **2-**methylpentanoyl 2-methylpentanoate (compound **63b**) instead of 2-propylpentanoic anhydride. *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-methyl-pentanamide (330 mg, compound **63b**) was obtained as a white solid. MS obsd. (ESI^+) $[(M+H)^+]$: 448.

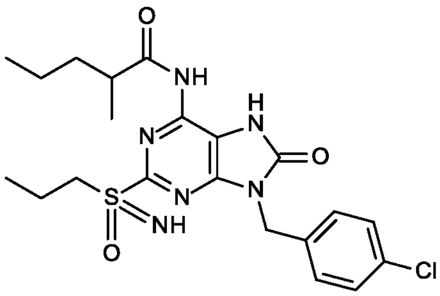
Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-methyl-pentanamide



63c

Compound **63c** was prepared in analogy to **Example 58, Step 2** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-methyl-pentanamide (compound **63b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-methyl-pentanamide (250 mg, compound **63c**) as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 464.

Step 4: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-methyl-pentanamide

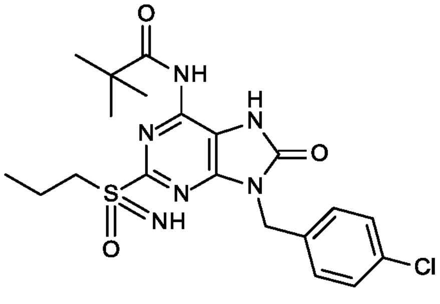


63

Example 63 was prepared in analogy to **Example 58, Step 3** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-methyl-pentanamide (250 mg, 0.87 mmol, compound **63c**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-methyl-pentanamide (122 mg, **Example 63**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.1 (s, 1H), 10.6 (s, 1H), 7.40 (m, 4H), 5.05 (s, 2H), 4.30 (s, 1H),3.32-3.42 (m, 2H), 2.68-2.82 (m, 1H), 1.54-1.74 (m, 2H), 1.23-1.43 (m, 4H), 1.13 (d, J = 8.0 Hz, 3H), 0.91 (t, J = 7.2 Hz, 6H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 479.

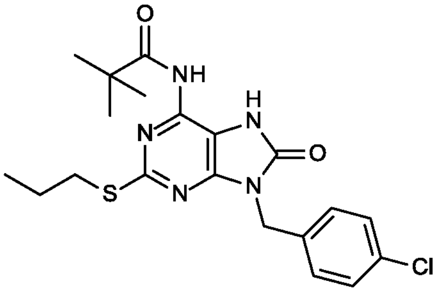
Example 64

N-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2,2-dimethyl-propanamide



64

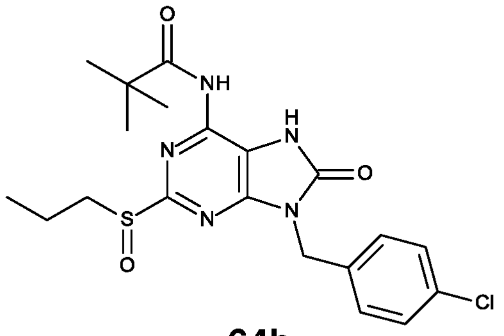
Step 1: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide



64a

Compound **64a** was prepared in analogy to **Example 58, Step 1** by using 2,2-dimethylpropanoyl 2,2-dimethylpropanoate (TCI, Catalog number: P1414-25ML) instead of 2-propylpentanoic anhydride. *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (400 mg, compound **64a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 434.

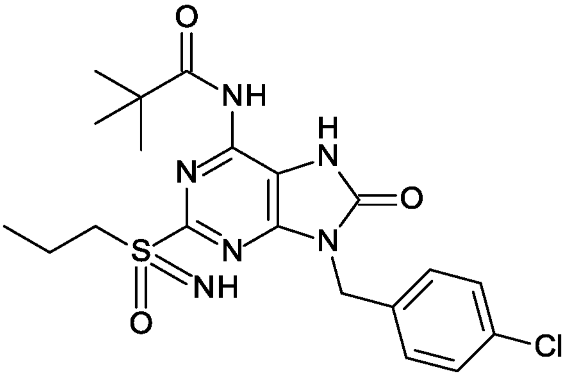
Step 2: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide



64b

Compound **64b** was prepared in analogy to **Example 58, Step 2** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (compound **64a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58a**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (250 mg, compound **64b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 450.

Step 3: Preparation of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (64)

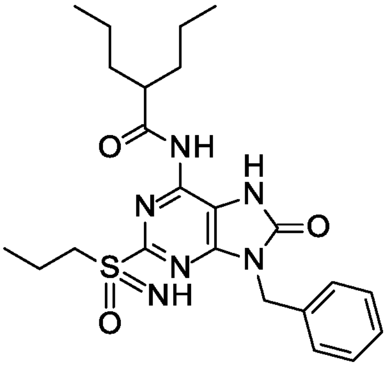


64

Example 64 was prepared in analogy to **Example 58, Step 3** by using *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (compound **64b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2,2-dimethyl-propanamide (33.5 mg, **Example 64**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.96 (s, 1H), 10.60 (s, 1H), 7.41 (m, 4H), 5.06 (s, 2H), 4.31 (s, 1H), 3.35-3.47 (m, 2H), 1.57-1.65 (m, 2H), 1.26 (m, 9H, 0.91 (t, J = 8.0 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 465.

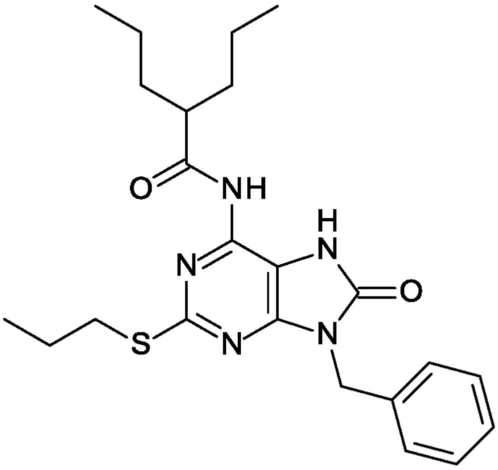
Example 65

N-[9-Benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide



65

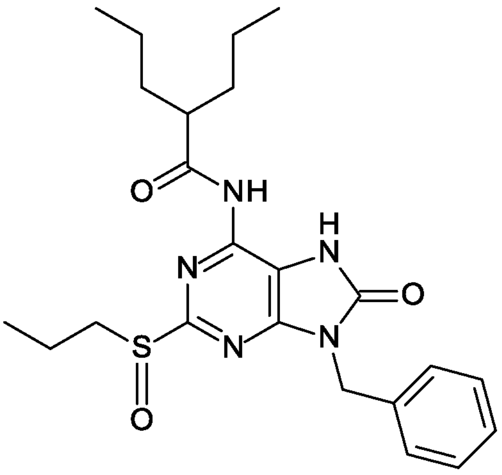
Step 1: Preparation of *N*-(9-benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)-2-propyl-pentanamide (65a)



65a

Compound **65a** was prepared in analogy to **Example 58, Step 1** by using 6-amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (compound **4a**) instead of 6-amino-9-benzyl-2-propylsulfanyl-7*H*-purin-8-one (compound **9c**). *N*-(9-Benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)-2-propyl-pentanamide (500 mg, compound **65a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 442.

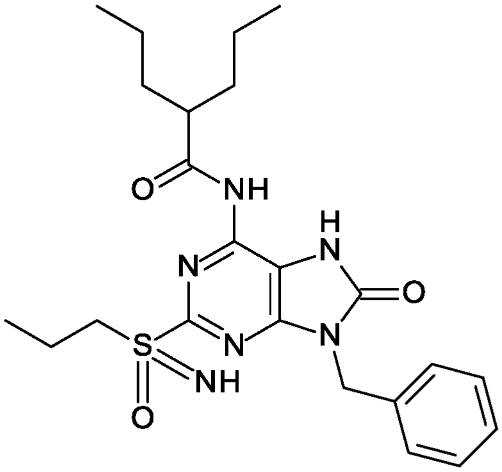
Step 2: Preparation of *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)-2-propyl-pentanamide



65b

Compound **65b** was prepared in analogy to **Example 58, Step 2** by using *N*-(9-benzyl-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl)-2-propyl-pentanamide (compound **65a**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfanyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **50a**). *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)-2-propyl-pentanamide (400 mg, compound **65b**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 458.

Step 3: Preparation of *N*-[9-Benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide



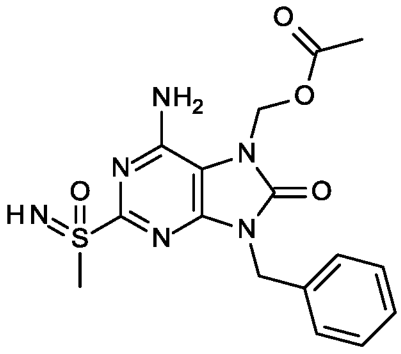
65

Example 65 was prepared in analogy to **Example 58, Step 3** by using *N*-(9-benzyl-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl)-2-propyl-pentanamide (compound **65b**) instead of *N*-[9-[(4-chlorophenyl)methyl]-8-*oxo*-2-propylsulfinyl-7*H*-purin-6-yl]-2-propyl-pentanamide (compound **58b**). *N*-[9-Benzyl-8-*oxo*-2-(propylsulfonimidoyl)-7*H*-purin-6-yl]-2-propyl-pentanamide (25 mg,

Example 65) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.15 (br. s., 1H), 10.45 (br. s., 1H), 7.27-7.39 (m, 5H), 5.06 (s, 2H), 4.29 (s, 1H), 3.31-3.37 (m, 2H), 2.61-2.87 (m, 1H), 1.50-1.75 (m, 4H), 1.23-1.43 (m, 6H), 0.81-0.97 (m, 9H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 473.

Example 66

[6-Amino-9-benzyl-2-(methylsulfonimidoyl)-8-*oxo*-purin-7-yl]methyl acetate

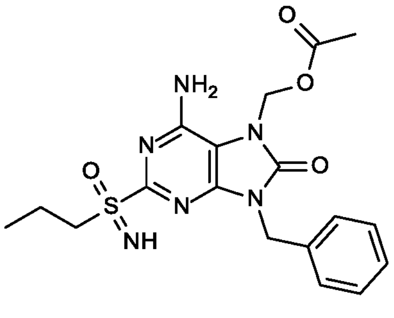


66

To a solution of 6-amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one (300 mg, 0.94 mmol, **Example 1**) in DMF (5 mL) was added NaH (45 mg, 1.13 mmol). The reaction was stirred for 10 min, then chloromethyl acetate (123 mg, 1.13 mmol) was added. The reaction mixture was stirred at RT for 0.5 hr, then quenched with sat. NH_4Cl and concentrated *in vacuo*. The residue was purified by prep-HPLC to give [6-amino-9-benzyl-2-(methylsulfonimidoyl)-8-*oxo*-purin-7-yl]methyl acetate (8.3 mg, **Example 66**) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.48-7.35 (m, 2H), 7.33-7.26 (m, 3H), 6.01 (s, 2H), 5.12 (s, 2H), 3.35-3.33 (m, 3H), 2.11 (s, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 391.

Example 67

[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]methyl acetate

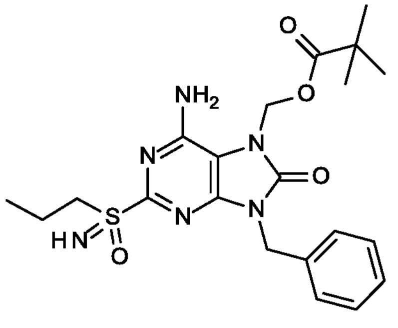


67

The title compound was prepared in analogy to **Example 66** by using 6-amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (**Example 4**) instead of 6-amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one (**Example 1**). [6-Amino-9-benzyl-2-(propylsulfonimidoyl)purin-8-yl] *N*-ethyl-*N*-methyl-carbamate (15 mg, **Example 67**) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.45-7.43 (m, 2H), 7.35-7.28 (m, 3H), 6.01 (s, 2H), 5.12 (s, 2H), 3.55-3.44 (m, 2H), 2.12 (s, 3H), 1.81-1.74 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 419.

Example 68

[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]methyl 2,2-dimethylpropanoate

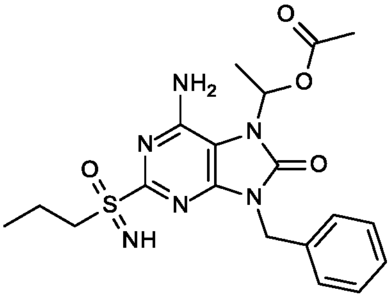


68

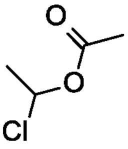
The title compound was prepared in analogy to **Example 66** by using 6-amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (**Example 4**) and chloromethyl 2,2-dimethylpropanoate instead of 6-amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one (**Example 1**) and chloromethyl acetate. [6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]methyl 2,2-dimethylpropanoate (15.8 mg, **Example 68**) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.48-7.50 (m, 2H), 7.31-7.36 (m, 3H), 6.01 (s, 2H), 5.95 (s, 2H), 5.12 (s, 2H), 3.58-3.44 (m, 2H), 1.85-1.94 (m, 2H), 1.24 (s, 9H), 1.07 (t, J = 7.12 Hz, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 461.

Example 69

1-[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]ethyl acetate

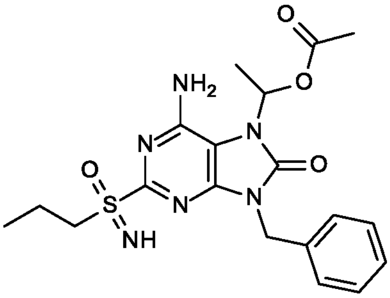


Step1: Preparation of 1-chloroethyl acetate



To a flask containing freshly dried catalytic amount of $ZnCl_2$ (680 mg, 5 mmol) under nitrogen was added acetyl chloride (3.9 g, 50 mmol) and the mixture was cooled to -5 °C to -10 °C. Acetaldehyde (2.4 g, 55 mmol) was added dropwise and the resulting reaction mixture stirred at 22-33 °C for 1 hr. The mixture was concentrated *in vacuo* to afford 1-chloroethyl acetate which was used in the next step without further purification.

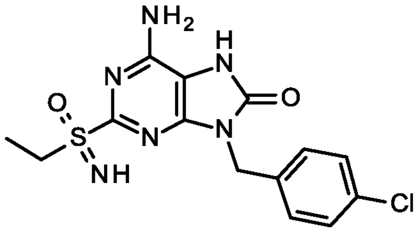
Step 2: Preparation of 1-[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]ethyl acetate



The title compound was prepared in analogy to **Example 66** by using 6-amino-9-benzyl-2-(propylsulfonimidoyl)-7*H*-purin-8-one (**Example 4**) and 1-chloroethyl acetate instead of 6-amino-9-benzyl-2-(methylsulfonimidoyl)-7*H*-purin-8-one (**Example 1**) and chloromethyl acetate. 1-[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purin-7-yl]ethyl acetate (9.3 mg, **Example 69**) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.44-7.30 (m, 5H), 7.05-7.03 (m, 1H), 5.12 (s, 2H), 3.33 (br. s., 2H), 2.14 (s, 3H), 1.74 (m, 2H), 1.72 (d, J = 6.8 Hz, 3H), 1.04-1.00 (m, 3H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 433.

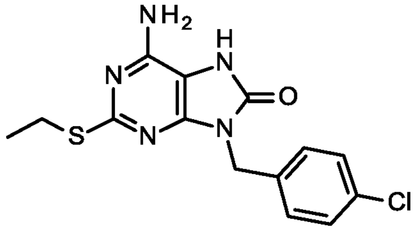
Example 70

6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7*H*-purin-8-one



70

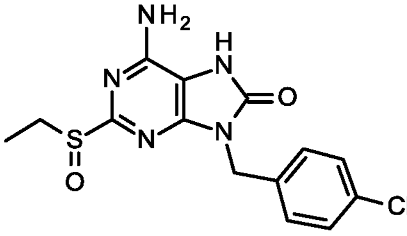
Step 1: Preparation of 6-amino-9-[(4-chlorophenyl)methyl]-2-ethylsulfanyl-7*H*-purin-8-one



70a

Compound **70a** was prepared in analogy to **Example 1**, **Step 3** by using iodoethane and 6-amino-9-[(4-chlorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **9b**) instead of methyl iodide and 6-amino-9-phenylmethyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-ethylsulfanyl-7*H*-purin-8-one (2.5g, compound **70a**) was obtained as a white solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 336.

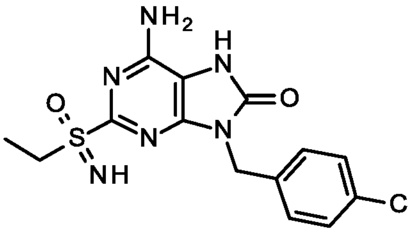
Step 2: Preparation of 6-amino-9-(4-chlorobenzyl)-2-ethylsulfinyl-7*H*-purin-8-one



70b

Compound **70b** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-9-[(4-chlorophenyl)methyl]-2-ethylsulfanyl-7*H*-purin-8-one (compound **70a**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-9-(4-chlorobenzyl)-2-ethylsulfinyl-7*H*-purin-8-one (1.94 g, compound**70b**) was obtained as a white solid. MS obsd. (ESI^+) [$(M+H)^+$]: 352.

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



70

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-9-(4-chlorobenzyl)-2-ethylsulfinyl-7*H*-purin-8-one (compound **70b**) instead of 6-amino-9-benzyl-2-(2-methylsulfinyl)-7*H*-purin-8-one (compound **1d**). 6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7*H*-purin-8-one (217 mg, **Example 70**) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.61 (s, 1 H), 7.42 - 7.35 (m, 4 H), 6.98 (s, 2 H), 4.96 (s, 2 H), 4.05 (s, 1 H), 3.42 - 3.37 (m, 2 H), 1.16 (t, $J = 7.4$ Hz, 3 H). MS obsd. (ESI^+) [$(M+H)^+$]: 367.

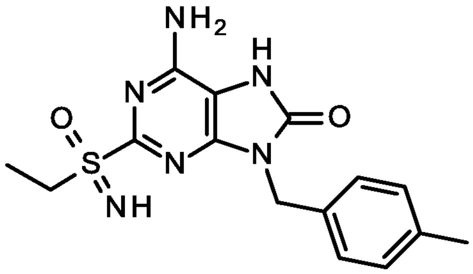
Separation of compound of **Example 70** by chiral HPLC afforded **Example 70-A** (faster eluting, 31.8 mg) and **Example 70-B** (slower eluting, 10 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak IC-3 column.)

Example 70-A: ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 10.76 (s, 1 H), 7.45 - 7.33 (m, 4 H), 7.01 (s, 2 H), 4.96 (s, 2 H), 4.03 (s, 1 H), 3.40 - 3.34 (m, 2 H), 1.17 (t, J = 7.4 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 367.

Example 70-B: ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 10.70 (s, 1 H), 7.46 -7.28 (m, 4 H), 7.01 (s, 2 H), 4.96 (s, 2 H), 4.03 (s, 1 H), 3.44 - 3.36 (m, 2 H), 1.17 (t, J = 7.4 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 367.

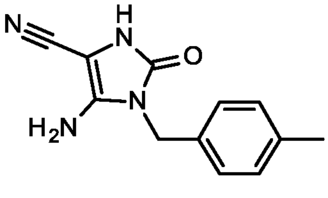
Example 71

6-Amino-2-(ethylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one



71

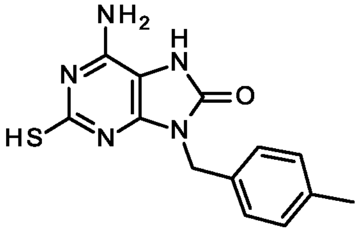
Step 1: Preparation of 4-amino-2-*oxo*-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile



71a

Compound **71a** was prepared in analogy to **Example 9**, **Step 1** by using *p*-tolylmethanamine instead of 4-chloropenylmethylamine. 4-Amino-2-*oxo*-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile (26.6 g, compound **71a**) was obtained as a grey solid and used directly in next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 229.

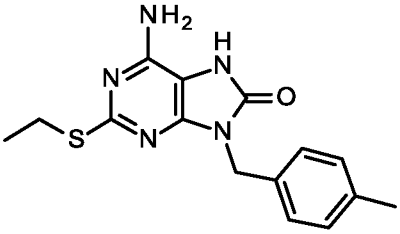
Step 2: Preparation of 6-amino-9-(*p*-tolylmethyl)-2-sulfanyl-7*H*-purin-8-one



71b

Compound **71b** was prepared in analogy to **Example 9**, **Step 2** by using of 4-amino-2-*oxo*-3-(*p*-tolylmethyl)-1*H*-imidazole-5-carbonitrile (compound **71a**) instead of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **9a**). 6-Amino-9-(*p*-tolylmethyl)-2-sulfanyl-7*H*-purin-8-one (20.0 g, compound **71b**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 288.

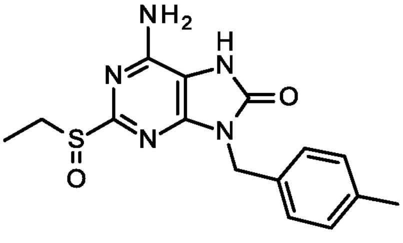
Step 3: Preparation of 6-amino-2-ethylsulfanyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one



71c

Compound **71c** was prepared in analogy to **Example 1, Step 3** by using 6-amino-9-(*p*-tolylmethyl)-2-sulfanyl-7*H*-purin-8-one (compound **71b**) and iodoethane instead of 6-amino-9-benzyl-2-ethylsulfanyl-7*H*-purin-8-one (compound **2a**) and methyl iodide. 6-Amino-2-ethylsulfanyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one (13 g, compound **71c**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 316.

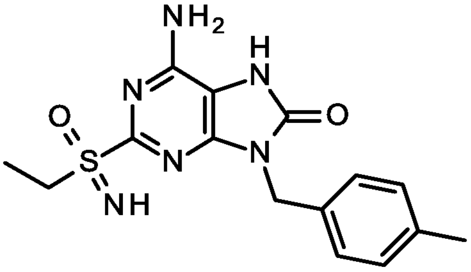
Step 4: Preparation of 6-amino-2-ethylsulfinyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one



71d

Compound **71d** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-2-ethylsulfanyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one (compound **71c**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**). 6-Amino-2-ethylsulfinyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one6 (3.5 g, compound **71d**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 332.

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



71

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-2-ethylsulfinyl-9-(*p*-tolylmethyl)-7*H*-purin-8-one (compound **71d**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(ethylsulfonimidoyl)-9-(*p*-tolylmethyl)-7*H*-purin-8-one (530 mg, **Example 71**) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (s, 1 H), 7.24 (d, J = 8.03 Hz, 2 H), 7.13 (d, J = 8.03 Hz, 2 H), 6.94 (br. s., 2 H), 4.91 (s, 2 H), 4.03 (s, 1 H), 3.36 - 3.41 (m, 2 H), 2.26 (s, 3 H), 1.18 (t, J = 7.28 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 347.

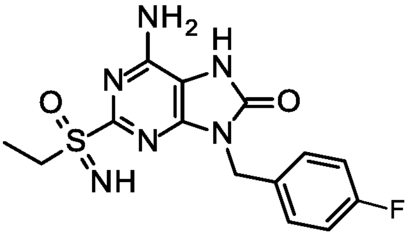
Separation of compound of **Example 71** by chiral HPLC afforded **Example 71-A** (faster eluting, 56.8 mg) and **Example 71-B** (slower eluting, 56.7 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak AD-3 column.)

Example 71-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.52 (br. s., 1 H), 7.24 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 7.9 Hz, 2 H), 6.94 (br. s., 2 H), 4.91 (s, 2 H), 4.02 (s, 1 H), 3.43 - 3.33 (m, 2 H), 2.26 (s, 3 H), 1.18 (t, J = 7.3 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 347.

Example 71-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.52 (br. s., 1 H), 7.24 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 2 H), 6.94 (br. s., 2 H), 4.91 (s, 2 H) 4.02 (s, 1 H), 3.42 - 3.33 (m, 2 H), 2.26 (s, 3 H), 1.18 (t, J = 7.3 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 347.

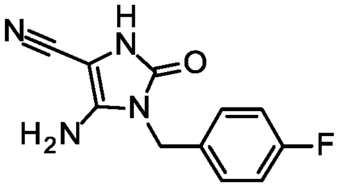
Example 72

6-Amino-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one



72

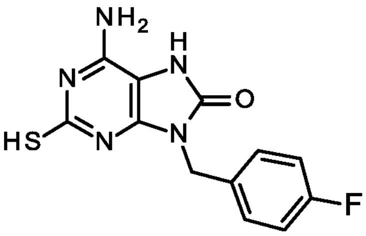
Step 1: Preparation of 4-amino-3-[(4-fluorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile



72a

Compound **72a** was prepared in analogy to **Example 9**, **Step 1** by using (4-fluorophenyl)methylamine instead of 4-chloropenylmethylamine. 4-Amino-3-[(4-fluorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (48 g, compound **72a**) was obtained as a light yellow solid and used directly in next step without further purification. MS obsd. (ESI$^+$) [(M+H)$^+$]: 233.

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

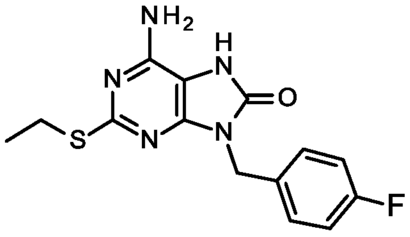


72b

Compound **72b** was prepared in analogy to **Example 9**, **Step 2** by using of 4-amino-3-[(4-fluorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **72a**) instead of 4-amino-3-[(4-chlorophenyl)methyl]-2-*oxo*-1*H*-imidazole-5-carbonitrile (compound **9a**). 6-Amino-9-[(4-

fluorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (32.0 g, compound **72b**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 292.

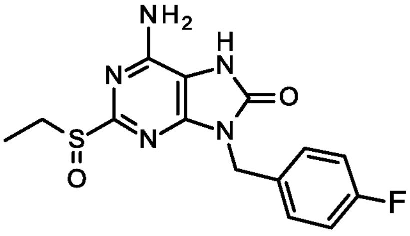
Step 3: Preparation of 6-amino-2-ethylsulfanyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one



72c

Compound **72c** was prepared in analogy to **Example 1, Step 3** by using 6-amino-9-[(4-fluorophenyl)methyl]-2-sulfanyl-7*H*-purin-8-one (compound **72b**) and iodoethane instead of 6-amino-9-benzyl-2-sulfanyl-7*H*-purin-8-one (compound **1b**) and methyl iodide. 6-Amino-2-ethylsulfanyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (5.6 g, compound **72c**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 320.

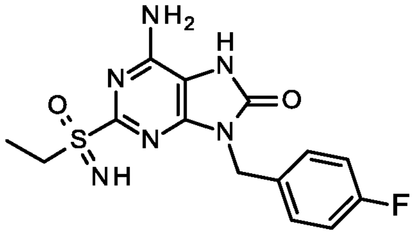
Step 4: Preparation of 6-amino-2-ethylsulfinyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one



72d

Compound **72d** was prepared in analogy to **Example 1**, **Step 4** by using 6-amino-2-ethylsulfanyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (compound **72c**) instead of 6-amino-9-benzyl-2-methylsulfanyl-7*H*-purin-8-one (compound **1c**)**.** 6-Amino-2-ethylsulfinyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (4.8 g, compound **72d**) was obtained as a yellow solid. MS obsd. (ESI$^+$) [(M+H)$^+$]: 332.

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



72

The title compound was prepared in analogy to **Example 1**, **Step 5** by using 6-amino-2-ethylsulfinyl-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (compound **72d**) instead of 6-amino-9-benzyl-2-methylsulfinyl-7*H*-purin-8-one (compound **1d**). 6-Amino-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7*H*-purin-8-one (2.9 g, **Example 72**) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.57 (br. s., 1 H), 7.40 (dd, J = 8.5, 5.5 Hz, 2 H), 7.16 (t, J = 8.9 Hz, 2 H), 6.97 (br. s., 2 H), 4.94 (s, 2 H), 4.07 (s, 1 H), 3.43 - 3.36 (m, 2 H), 1.17 (t, J = 7.4 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 351.

Separation of compound of **Example 72** by chiral HPLC afforded **Example 72-A** (faster eluting, 85.4 mg) and **Example 72-B** (slower eluting, 36.4 mg) as white solid. (Separation condition: methanol 5%-40% (0.05%DEA)/CO_2 on ChiralPak AD-3 column.)

Example 72-A: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (br. s., 1 H), 7.41 (dd, J = 8.5, 5.5 Hz, 2 H), 7.17 (t, J = 8.9 Hz, 2 H), 6.98 (br. s., 2 H), 4.95 (s, 2 H), 4.07 (s, 1 H), 3.45 - 3.36 (m, 2 H), 1.17 (t, J = 7.3 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 351.

Example 72-B: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.53 (br. s., 1 H), 7.41 (dd, J = 8.5, 5.5 Hz, 2 H), 7.17 (t, J = 8.9 Hz, 2 H), 6.98 (br. s., 2 H), 4.95 (s, 2 H), 4.07 (s, 1 H), 3.44 - 3.37 (m, 2 H) 1.17 (t, J = 7.3 Hz, 3 H). MS obsd. (ESI$^+$) [(M+H)$^+$]: 351.

Example 73: HEK-Blue-hTLR 7 cells assay:

A stable HEK-Blue-hTLR7 cell line was purchased from InvivoGen (Cat.#: hkb-htlr7, San Diego, California, USA). These cells were designed for studying the stimulation of human TLR7 by monitoring the activation of NF-κB. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. The SEAP was induced by activating NF-κB and AP-1 via stimulating HEK-Blue-hTLR7 cells with TLR7 ligands. Therefore the reporter expression was regulated by the NF-κB promoter upon stimulation of human TLR7 for 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qb1, 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.

HEK-Blue-hTLR7 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 180 μL 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 HEK-Blue-hTLR-7 cells were incubated with addition of 20 μL test compound in a serial dilution in the presence of final DMSO at 1% and perform incubation under 37 ºC in a CO_2 incubator for 20 hrs. Then 20 μL of the supernatant from each well was incubated with 180 μL 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 NF-κB 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 of the present invention were tested in HEK-Blue- hTLR7 assay for their TLR7 agonism activity as described herein and results are listed in Table 1. The Examples were found to have EC_{50} of about 0.01 μM to about 0.7 μM. Particular compounds of the present invention were found to have EC_{50} of about 0.01 μM to about 0.1 μM.

Table 1: Activity of Compounds in HEK-Blue-hTLR7 assay in vitro

Example No.	**HEK-Blue-hTLR7 (EC_{50} (μM))**	**Example No.**	**HEK-Blue-hTLR7 (EC_{50} (μM))**
GS-9620	0.80	**22**	0.042
S-1	0.37	**23**	0.016
P-2	0.27	**24**	0.037
P-5	3.14	**25**	0.0096
1	0.30	**26**	0.021
1-B	0.18	**27**	0.036
2	0.20	**28**	0.021
3	0.33	**29**	0.027
3-A	0.27	**29-A**	0.019

3-B	0.55	**29-B**	0.022
4	0.065	**30**	0.018
4-A	0.067	**31**	0.040
4-B	0.086	**32**	0.054
5	0.32	**33**	0.066
6	0.43	**34**	0.030
7	0.18	**35**	0.12
9	0.012	**36**	0.022
9-A	0.014	**37**	0.023
9-B	0.011	**38**	0.075
10	0.074	**39**	0.17
11	0.066	**40**	0.15
13	0.043	**41**	0.084
14	0.017	**42**	0.09
15	0.19	**43**	0.24
16	0.22	**44**	0.136
16-A	0.76	**70**	0.057
16-B	0.15	**70-A**	0.054
17	0.068	**70-B**	0.077
18	0.047	**71**	0.098
19	0.67	**71-A**	0.134
20	0.26	**71-B**	0.087

Example 74: HEK-Blue-hTLR8 cells assay and selectivity index (EC$_{50(TLR8)}$/EC$_{50(TLR7)}$):

A stable HEK-Blue-hTLR8 cell line was purchased from InvivoGen (Cat.#: HEK-Blue-htlr8, San Diego, California, USA). These cells were designed for studying the stimulation of human TLR8 by monitoring the activation of NF-κB. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. The SEAP was induced by activating NF-κB and AP-1 via stimulating HEK-Blue-hTLR8 cells with TLR8 ligands. Therefore the reporter expression was regulated by the NF-κB promoter upon stimulation of human TLR8 for 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qb1, 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.

HEK-Blue-hTLR8 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 180 µL 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 HEK-Blue-hTLR8 cells were incubated with addition of 20 µL test compound in a serial dilution in the presence of final DMSO at 1% and perform incubation under 37 °C in a CO_2 incubator for 20 hrs. Then 20 µL of the supernatant from each well was incubated with 180 µL Quanti-blue substrate solution at 37°C for 2 hours and the absorbance was read at 620~655 nm using a spectrophotometer. The signalling pathway that TLR8 activation leads to downstream NF-κB activation has been widely accepted, and therefore similar reporter assay was also widely used for evaluating TLR8 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 of the present invention were tested in HEK-Blue-hTLR8 assay for their TLR8 agonism activity as described herein and results are listed in Table 2. The ratio of TLR8 agonism activity compared to TLR7 agonism activity was defined as the selectivity index ($EC_{50\,(TLR8)}$ value/$EC_{50(TLR7)}$ value) and calculated accordingly. Since TLR7 and TLR8 agonists differ in their target cell selectivity and cytokine induction profile, and TLR7-specific agonists activate plasmacytoid DCs (pDCs) and B cells and induce mainly IFN-α and IFN-regulated cytokines, which may be potentially beneficial as the HBV therapy. The higher selectivity index the compound shows, the more TLR7 specific the compound is. The compounds of present invention showed comparable or better selectivity index over reference compounds.

Table 2: Activity of Compounds in HEK Blue-hTLR-8 assay in vitro and selective index

Example No.	**HEK Blue hTLR-8 EC50 (µM)**	**Selective index**
GS-9620	11.6	14
S-1	>1000	>2703
P-2	>1000	>3707
P-5	>1000	> 318

1	652.4	2175
1-B	535.7	2976
13	300	6977
16	>1000	> 4546
20	>1000	> 3846
70	90.0	1579
70-A	>1000	>18518

Example 75: Lysa solubility

LYSA solubility assay is used to determine the aqueous solubility of a compound.

Samples were prepared in duplicate from 10 mM DMSO stock solution. After evaporation of DMSO with a centrifugal vacuum evaporator, the compounds were dissolved in 0.05 M phosphate buffer (pH 6.5), stirred for one hour and shaken for two hours. After one night, the solutions were filtered using a microtiter filter plate. Then the filtrate and its 1/10 dilution were analyzed by HPLC-UV. In addition a four-point calibration curve was prepared from the 10 mM stock solutions and used for the solubility determination of the compounds. The results are in µg/mL and summarized in Table 3. Compounds with higher solubility could broaden its suitability for different dosage forms and increase the chance to achieve desired concentration in systemic circulation, which in turn can potentially lower the required dose. The exemplified compounds of present invention showed much improved solubility compared to S-1, P-2 and P-5.

Table 3: Solubility data of compounds of present invention

Example No.	**LYSA (µg/mL)**	**Example No.**	**LYSA (µg/mL)**
S-1	0.5	**24**	12
P-2	1	**27**	7
P-5	1	**29-A**	6
1-A	85	**29-B**	11
1-B	98	**32**	18
2	29	**33**	79
3	300	**39**	>520
4	21	**40**	168
4-A	56	**43**	>465
4-B	50	**44**	357

5	40	**70**	7
6	89	**70-B**	5
7	18	**71**	12
11	18	**71-A**	13
13	10	**71-B**	13
18	166	**72**	152
19	>428	**72-A**	90
21	121	**72-B**	115

Example 76: Metabolic stability in human liver microsomes

The human microsomal stability assay is used for early assessment of metabolic stability of a test compound in human liver microsomes.

Human liver microsomes (Cat.NO.: 452117, Corning, USA; Cat.NO.:H2610, Xenotech, USA) were preincubated with test compound for 10 minutes at 37°C in 100 mM potassium phosphate buffer, pH 7.4. The reactions were initiated by adding NADPH regenerating system. The final incubation mixtures contained 1 μM test compound, 0.5 mg/mL liver microsomal protein, 1 mM $MgCL_2$, 1 mM NADP, 1 unit/mL isocitric dehydrogenase and 6 mM isocitric acid in 100 mM potassium phosphate buffer, pH 7.4. After incubation times of 0, 3, 6, 9, 15 and 30 minutes at 37°C, 300 μL of cold ACN (including internal standard) was added to 100 μL incubation mixture to terminate the reaction. Following precipitation and centrifugation, the amount of compound remaining in the samples were determined by LC-MS/MS. Controls of no NADPH regenerating system at zero and 30 minutes were also prepared and analyzed. The results were categorized as: low (<7.0 mL/min/kg), medium (7.0-16.2 mL/min/kg) and high (16.2-23.2 mL/min/kg). Results of metabolic stability study in human liver microsomes are given in Table 4. Exemplified compounds of this invention showed low clearance in human liver microsomes, while reference compounds GS-9620 and P-2 were categorized as high and medium respectively.

Table 4. Metabolic stability in human liver microsomes of compounds of this invention.

Example No.	**Human Liver Microsome Clearance (mL/min/kg)**
GS-9620	17.8
P-2	7.3

1	< 6.15[*]
1-A	< 6.15
1-B	< 6.15
2	< 6.15
3	< 6.15
3-A	< 6.15
4	< 6.15
5	< 6.15
29-A	< 6.15
31	< 6.15
32	< 6.15
33	< 6.15
34	< 6.15
35	< 6.15
37	<6.15
39	< 6.15
40	< 6.15
43	< 6.15
44	< 6.15
70-A	< 6.15
70-B	< 6.15
71-A	< 6.15
71-B	< 6.15
72	< 6.15
72-A	< 6.15
72-B	< 6.15

[*] 6.15 mL/min/kg is the limitation of assay sensitivity.

Example 77: Cytochrome P450 (Cyp450) induction screening assay mRNA induction

Induction of cytochrome P450 enzymes is associated with an increased prevalence of clinical drug-drug interactions. The clinical consequences of induction may be therapeutic failure caused by a decreased systemic exposure of the drug itself or a co-administered therapy, or toxicity as a result of increased bioactivation. Cytochrome P450 (CYP450) induction assay has been used to understand the potential drug-drug interaction liabilities in drug discovery stage.

Cell culture

Human cryopreserved hepatocytes (Life Technologies, Carlsbad, USA) were thawed and cultured in collagen I coated 96-well plates with a density of 52,000 cells/well. After attachment, hepatocyte maintenance medium (HMM; Lonza, Switzerland) was changed after cells were pre-cultured overnight.

Test compounds were dosed to the cells next morning at an indicated concentration (up to 10 µM) in HMM culture medium containing gentamycin and a constant 0.1 % DMSO. Similarly, dilutions of the positive inducer compounds omeprazole (prototypical inducer of human CYP1A2; final concentrations: 1 and 10 µM), phenobarbital (prototypical inducer of human CYP2B6; final concentrations: 100 and 1000 µM) and rifampicin (prototypical inducer of human CYP3A4; final concentrations: 1 and 10 µM) were prepared from 1000 fold DMSO stock solutions in HMM containing gentamycin. Medium change was then performed and cells were exposed for 24 hours to test compounds, positive inducer compounds, or vehicle (0.1 % DMSO), respectively.

At the end of the compound exposure period, medium was removed and cells lysed using 100 µL/well MagNA Pure LC RNA isolation tissue lysis buffer (Roche Diagnostics AG, Rotkreuz, Switzerland). Plates were then sealed and frozen at -80°C until further workup.

mRNA isolation, processing and qRT-PCR

mRNA isolation was performed using the MagNA Pure 96 system (Roche Diagnostics AG, Rotkreuz, Switzerland) and the respective cellular RNA large volume kit (Roche Diagnostics AG, Rotkreuz, Switzerland) from thawed samples diluted 1:1 with PBS. The volume of the cell lysis and an elution volume of 100 µL were used. 20 µL of the resulting mRNA suspension was then used for reverse transcription using 20 µL of the transcript or first stand cDNA synthesis kit (Roche prime Supply, Mannheim, Germany). The resulting cDNA was diluted with 40 µL of H_2O before using for qRT-PCR. qRT-PCR was performed by using the forward and the reverse primer, the corresponding Universal Probe Library (all from Microsynth, Balgach, Switzerland) and the Taqman Fast advanced master mix (Applied Biosystems), on an ABI 7900 machine (Applied Biosystems).

Calculations

qRT-PCR Ct-values for the respective P450s were put into relation to the Ct-value of RN18S1 (microsynth, Balgach, Switzerland) of the same sample. Doing so, a respective Δct-value was calculated. Using the average of all Δct-values for the vehicle control samples, a ΔΔct-value was calculated for each sample (ΔΔct-value(sample) = Δct-value(sample) - average of Δct-value of all vehicle controls). The fold induction of the respective sample was calculated as 2^(-ΔΔct). The individual fold induction values were then averaged per treatment condition (usually n=3 biological replicates).

Relative induction values to the respective positive inducer compound condition (10 µM omeprazole for CYP1A2; 1000 µM Phenobarbital for CYP2B6; 10 µM Rifampicin for CYP3A4) were then calculated from the fold induction values as follows:

Relative induction (%) = 100×(T-V)/(P-V)

T: fold induction of test compound condition

P: fold induction of positive inducer compound

V: fold induction of vehicle controls

Results of CYP3A4 induction are given in Table 5. Exemplified compounds of present invention did not cause a significant change in CYP 3A4 mRNA at any concentration. The results indicated that exemplified compounds had no CYP induction liability, which can avoid potential drug drug interaction in clinical application.

Table 5. Relative induction values of compounds of present invention to 10 µM Rifampicin

Example No.	**Relative induction of Positive control (10 µM Rifampicin) (%)**
4-A	-0.63
4-B	-0.90
24	-0.72
70-A	0.42
70-B	-0.42
71-A	-0.10

Example 78: Ames microsuspension assay

The Ames microsuspension assay examines if a compound causes DNA mutations. The method was based on a modified pre-incubation version described by Kado et al (see references: B.N. Ames, J. McCann, E. Yamasaki, Mutation Res. 1975, 31, 347-364 N.Y. Kado, D. Langley, and E. Eisenstadt, Mutation Res. 1983, 121, 25-32). Five *Salmonella typhimurium* tester strains (TA1535, TA97, TA98, TA100, and TA102) were treated with the test compound in absence and in presence of an exogenous metabolic activation system (S9). The bacteria were pre-incubated for 1 h, the pre-incubation volume is 210 µL (100 µL of overnight culture, 100 µL of S9 mix

(10% S9) or 100 µL phosphate buffer, and 10 µL test compound solution). The overnight cultures were resuspended for the test in cold phosphate buffer. The S9 mix contains potassium chloride, magnesium chloride, sodium phosphate buffered saline, NADP$^+$ and glucose-6-phosphate. The test tubes are incubated and shaken for 60 minutes at 37°C. 2.2 mL soft agar supplemented with L-histidine and biotin was added afterwards and the content of the tubes were mixed and poured on Vogel-Bonner minimal agar plates.

Three replicate plates for the test compound and negative control or two replicate plates for the positive controls were incubated at 37°C, upside down, for 2 days. Colonies were counted electronically using an automatic image analysis system after having inspected the background lawn for signs of toxicity. Plates exhibiting precipitate or contamination were counted manually.

S9 is an in vitro metabolic system which is obtained from liver homogenates by centrifuging them at 9000 g for 20 minutes. It contains CYP450 isoforms, phase-II metabolic enzymes, etc. In the Ames microsuspension assay test, S9 is used to assess mutagenicity of compounds, some of which require metabolic activation to become mutagenic.

Criteria of the Ames microsuspension assay: a positive result is defined as a reproducible, dose-related increase in the number of revertant colonies in at least one of the strains. For TA1535 and TA98, the positive threshold is a 2-fold increase over control. For TA97, TA100 and TA102, the threshold is a 1.5-fold increase.

Results of Ames microsuspension assay are given in Table 6. Exemplified compounds of present invention showed negative results suggesting that there was no indication of mutagenicity of the compounds tested in the Ames microsuspension assay.

Table 6: Ames microsuspension assay results

Compound NO.	**Ames result**
1-B	negative
4	negative
4-A	negative
4-B	negative
9	negative
27	negative
29-A	negative
29-B	negative
34	negative
39	negative

70-A	negative
70-B	negative
71-A	negative

Example 79: hERG channel inhibition assay

The hERG channel inhibition assay is a highly sensitive measurement that identifies compounds exhibiting hERG inhibition related to cardiotoxicity in vivo. The hERG K^+ channels were cloned in humans and stably expressed in a CHO (Chinese hamster ovary) cell line. CHO_{hERG} cells were used for patch-clamp (voltage-clamp, whole-cell) experiments. Cells were stimulated by a voltage pattern to activate hERG channels and conduct I_{KhERG} currents (rapid delayed outward rectifier potassium current of the hERG channel). After the cells were stabilized for a few minutes, the amplitude and kinetics of I_{KhERG} were recorded at a stimulation frequency of 0.1 Hz (6 bpm). Thereafter, the test compound was added to the preparation at increasing concentrations. For each concentration, an attempt was made to reach a steady-state effect, usually, this was achieved within 3-10 min at which time the next highest concentration was applied. The amplitude and kinetics of I_{KhERG} are recorded in each concentration of the drug which were compared to the control values (taken as 100%). (references: Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG. 2003; Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc. Res. 58:32-45, Sanguinetti MC, Tristani-Firouzi M. 2006; hERG potassium channels and cardiac arrhythmia. Nature 440:463-469, Webster R, Leishman D, Walker D. 2002; Towards a drug concentration effect relationship for QT prolongation and torsades de pointes. Curr. Opin. Drug Discov. Devel. 5:116-26).

Results of hERG are given in Table 7. A safety ratio (hERG IC_{20} /EC_{50}) > 30 suggests a low potential of hERG related cardiotoxicity.

Table 7: hERG results and safety ratio.

Compound NO.	hERG IC_{20} (µM)	hERG IC_{50} (µM)	Safety ratio (hERG IC_{20} /EC_{50})
1-B	>10	>20	> 56
4	>10	>20	> 154
4-A	>10	>20	>149

4-B	>10	>20	>116
9	>10	>20	>833
27	>10	>20	>278
29-A	>10	>20	>526
29-B	>10	>20	>546
34	>10	>20	>333
39	>10	>20	>59
71-A	>10	>20	>75

Example 80: GSH adduct screening assay

The formation of reactive metabolites is an unwanted drug property because of the idiosyncratic clinical adverse effect. GSH adduct formation is used to evaluate the formation of reactive metabolites in vitro. Positive controls were Diclofenac, Troglitazone, Nefazodone and mGluR5. Solvent control was DMSO.

Incubation

All compounds including positive and solvent control were incubated using a 96-deep-well plate (Eppendorf) at 20 µM (addition of 1 µL of 10 mM DMSO stock solution) in 450 µL of 0.1 M sodium phosphate buffer at pH 7.4 containing rat liver microsomes (RLM) and human liver microsomes (HLM). Microsomal protein concentration is 1 mg/mL. Pipetting was performed using a TECAN pipetting robot. The buffer was prepared at room temperature by combining 2.62 g $NaH_2PO_4 \cdot 1H_2O$ and 14.43 g $Na_2HPO_4 \cdot 2H_2O$ dissolved in H_2O (Millipore, >18 MΩ) to a weight of 1000 g (pH 7.4). After 5 minutes of pre-incubation at 37°C the reaction was started by adding 50 µL of buffer containing GSH (100 mM) and NADPH (20 mM). Fresh stock solutions of GSH and NADPH were prepared straight before each experiment. The final concentrations were 5 mM for GSH and 1 mM for NADPH. After 60 minutes of incubation at 37°C (shaking at 800 rpm) the reaction is quenched with 500 µL of cold acetonitrile and centrifuged at 5000 × g at 25°C for 11 minutes. Before LC-MS/MS analysis the supernatant was split to two fractions, 450 µL and 400 µL each followed by evaporation using a N_2 stream at 35°C to a volume of approximately 150 µL.

Liquid chromatography

Sample clean-up and chromatography of analytes were performed on-line by a column-switching set-up of two HPLC columns. From each sample 50 µL were injected (Shimadzu

SilHTC) and loaded with water containing 0.1% formic acid onto a trapping column (Waters Oasis HLB 2.1 × 10 mm, 25 μm) with a flow rate of 0.3 mL/min. After 1.5 min the trapped analytes were then flushed (included a change in flow direction on the trapping column) onto an analytical column (Waters Atlantis T3 2.1 × 100 mm, 3 μm) with a total flow of 0.2 mL/min starting with 95/5% water containing 0.1% formic acid/acetonitrile. The fraction of acetonitrile was increased to 20% acetonitrile between 2 and 2.5 minutes, to 70% at 10 minutes and to 98% at 11 minutes. After 12 minutes the analytical column was equilibrated to start conditions (5% acetonitrile). The trapping column was washed with acetonitrile for 1 minute at a flow rate of 1.5 mL/min and equilibrated for 1.25 minutes with water containing 0.1% formic acid at a flow rate of 1.5 mL/min. The total running time was 14 min per sample.

Mass spectrometry

A triple quadrupole-linear ion trap mass spectrometer 4000 Qtrap equipped with an electrospray ionization source (Turbo V) was used, both from Applied Biosystems/MDS Sciex. Based on a published method of Dieckhaus et al. (2005) a precursor ion survey scan (PreIS) method was used to detect GSH-conjugates in negative ion mode. Briefly, as survey scan ions (400 to 900 amu within 2 seconds) are scanned for precursors of m/z 272 amu, the ion spray voltage was -4200 V, the source temperature 500°C, nitrogen was used as curtain and collision gas. If the parent molecule exceeds a molecular mass of 500 the scan range was changed to 500 amu to 1000 amu within 2 seconds. For signals in the survey scan exceeding 7500 cts (that was approximately 5 times of the background signal), enhanced resolution scan and enhanced product ion scan were triggered which allowed isotope determination and confirmation of a positive GSH adduct by the presence of diagnostic fragment ions. Further instrument settings were as following: Curtain gas: 30 psi, CAD gas: 10 psi Gas 1: 30 psi, Gas 2: 50 psi, declustering potential: -70 V, entrance potential: -10 V, collision energy: -24 V, and cell exit potential -15 V. Data acquisition was performed using Analyst 1.4.2, data analysis, i.e. sample control (solvent) comparisons were performed with Metabolite ID 1.3 (Applied Biosystems/MDS Sciex).(reference: Dieckhaus, C.M., Fernandez-Metzler, C.L., King, R., Krolikowski, P.H., and Baillie, T.A. (2005). Negative ion tandem mass spectrometry for the detection of glutathione conjugates. Chem Res Toxicol *18*, 630-638).

Results of GSH are given in Table 8. Exemplified compounds of present invention showed no flag in GSH assay indicating that no potential reactive metabolite formation which might lead to idiosyncratic hepatotoxicity.

Table 8: GSH results

Compound NO.	GSH results*
4	No flag
4-A	No flag
4-B	No flag
9	No flag
27	No flag
29-A	No flag
34	No flag
39	No flag
70-A	No flag
70-B	No flag
71-A	No flag

* No Flag: no GSH adduct formation observed when compared to control (DMSO).

Example 81: Comparison of the mean plasma concentration and PK parameters after 1 mg/kg intravenous dosing to Rat

The single dose PK in Male Wister-Han Rats was performed to assess pharmacokinetic properties of tested compounds. Two groups of animals were dosed via bolus intravenous (IV) of the respective compound. Blood samples (approximately 20 μL) were collected via Jugular vein or an alternate site at 5 min, 15 min, 30 min, 1hr, 2hr, 4hr, 7hr and 24 hr post-dose for IV group. Blood samples were placed into tubes containing EDTA-K2 anticoagulant and centrifuged at 5000 rpm for 6 min at 4°C to separate plasma from the samples. Following centrifugation, the resulting plasma was transferred to clean tubes for bioanalysis on LC/MS/MS. The pharmacokinetic parameters were calculated using non-compartmental module of WinNonlin® Professional 6.2.

Results of PK parameters are given in Table 9. Exemplified compounds of present invention clearly showed unexpected superior PK profile on C0, CL and AUC compared to GS-9620 and S-1 in rat PK study with 5-10 folds higher C0, 3-5 folds lower systemic clearance (CL) and 5-10 folds higher exposure (AUC). Therefore, compounds of present invention potentially could lead to less dose frequency and lower dose in clinical application.

Table 9: the mean plasma concentration and PK parameters

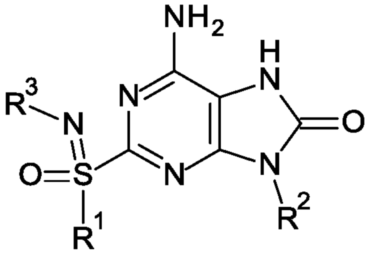
	Mean plasma concentration (nM)				
Dose compound	GS-9620*	S-1	Example 70-A	Example 70-B	Example 71-A
Test Compound	GS-9620	S-1	Example 70-A	Example 70-B	Example 71-A
Time (h)	IV (1mpk)	IV (1mpk)	IV (1mpk)	IV (1mpk)	IV (1mpk)
0.083	170	534	3052	2782	1848
0.25	102	236	1342	1434	1003
0.5	65.4	125	718	862	537
1	48.1	38	354	461	292
2	21.6	9	110	173	115
4	13	ND	20.5	29.1	18.2
8**	4.17	ND	6.28	16.7	ND
24	ND	ND	ND	ND	ND
C0 (nM)	220	534	3052	2782	1848
CL (mL/min/kg)	205	261	56	48.7	84.6
AUC0-inf (nM.hr)	201	201	1627	1894	1182

*GS-9620 data were available from WO2016023511.

**7 hrs for Example 70-A, Example 70-B and Example 71-A.

Claims

1. A compound of formula (I),



(I),

wherein

R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cylcoalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or pyrrolidinylC_{1-6}alkyl;

R^2 is C_{1-6}alkyl, phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl or pyrimidinylC_{1-6}alkyl, said phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl and pyrimidinylC_{1-6}alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

2. A compound according to claim 1, wherein

R^1 is methyl, ethyl, propyl, butyl, chloropropyl, cyclohexylmethyl, methoxyethyl, methoxypropyl, pyrrolidinylpropyl or trifluoroethyl;

R^2 is isobutyl, benzyl, chlorobenzyl, fluorobenzyl, bromobenzyl, chlorofluorobenzyl, chloromethylbenzyl, dichlorobenzyl, difluorobenzyl, methylbenzyl, methoxybenzyl, cyanobenzyl, carbamoylbenzyl, trifluoromethylbenzyl, methylsulfonylbenzyl, methoxycarbonylbenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, piperidinylcarbonylbenzyl, pyrrolidinylcarbonylbenzyl, pyridinylmethyl, chloropyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl;

R^3 is H;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

3. A compound according to claim 1, wherein R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl.

4. A compound according to claim 3, wherein R^1 is methyl, ethyl, propyl, butyl, chloropropyl, trifluoroethyl, methoxyethyl or methoxypropyl.

5. A compound according to claim 3, wherein R^1 is C_{1-6}alkyl.

6. A compound according to claim 2 or 5, wherein R^1 is methyl, ethyl or propyl.

7. A compound according to claim 6, wherein R^1 is ethyl.

8. A compound according to any one of claims 1 to 7, wherein R^2 is

phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen, carbamoyl, C_{1-6}alkyl, carboxy, cyano, C_{1-6}alkoxy, C_{1-6}alkylsulfonyl and C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl;

pyridinylC_{1-6}alkyl, said pyridinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl; or

pyrimidinylC_{1-6}alkyl, said pyrimidinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl.

9. A compound according to claim 8, wherein R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, difluorobenzyl, cyanobenzyl, carboxybenzyl, methoxybenzyl, methylsulfonylbenzyl, methoxyethylaminocarbonylbenzyl, pyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl.

10. A compound according to claim 9, wherein R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, difluorobenzyl, carboxybenzyl or methylpyridinylmethyl.

11. A compound according to any one of claims 10, wherein R^2 is methylbenzyl or chlorobenzyl.

12. A compound according to claim 1, wherein

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

R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen, carbamoyl, C_{1-6}alkyl, carboxy, cyano and C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl; or

pyrimidinylC_{1-6}alkyl, said pyrimidinylC_{1-6}alkyl is unsubstituted or substituted by C_{1-6}alkyl;
R^3 is H.

13. A compound according to claim 12, wherein
R^1 is methyl, ethyl, propyl, butyl or methoxyethyl;
R^2 is benzyl, methylbenzyl, chlorobenzyl, fluorobenzyl, cyanobenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, pyrimidinylmethyl or methylpyrimidinylmethyl;
R^3 is H.

14. A compound according to claim 1, wherein
R^1 is C_{1-6}alkyl;
R^2 is phenylC_{1-6}alkyl, said phenylC_{1-6}alkyl is unsubstituted or substituted by halogen or C_{1-6}alkyl;
R^3 is H.

15. A compound according to claim 14, wherein
R^1 is ethyl or propyl;
R^2 is benzyl, chlorobenzyl or methylbenzyl;
R^3 is H.

16. A compound according to claim 1 or 2 selected from:
6-Amino-9-benzyl-2-(methylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(ethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(2-methoxyethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(butylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(3-methoxypropylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(2,2,2-trifluoroethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-benzyl-2-(cyclohexylmethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-methoxyphenyl)methyl]-2-(methylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(3-chloropropylsulfonimidoyl)-9-[(4-methoxyphenyl)methyl]-7H-purin-8-one;
6-Amino-9-[(4-methoxyphenyl)methyl]-2-(3-pyrrolidin-1-ylpropylsulfonimidoyl)-7H-purin-8-one;

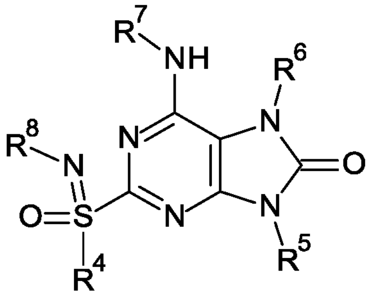
6-Amino-9-[(4-chlorophenyl)methyl]-2-(methylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(methylsulfonimidoyl)-9-(3-pyridylmethyl)-7H-purin-8-one;
3-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzonitrile;
3-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzamide;
6-Amino-2-(methylsulfonimidoyl)-9-(2-pyridylmethyl)-7H-purin-8-one;
6-Amino-2-(methylsulfonimidoyl)-9-(4-pyridylmethyl)-7H-purin-8-one;
6-Amino-9-isobutyl-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-[[4-(trifluoromethyl)phenyl]methyl]-7H-purin-8-one;
6-Amino-9-[(4-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-bromophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3,4-dichlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-(3,4-difluorophenylmethyl)-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chloro-3-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
6-Amino-9-[(4-chloro-3-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2,4-difluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzonitrile;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzamide;
6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(2-methyl-4-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(3-chloro-4-methyl-phenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-methylsulfonylphenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
Methyl 4-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoate;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoic acid;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]-N-(2-methoxyethyl)benzamide;
6-Amino-9-[[4-(piperidine-1-carbonyl)phenyl]methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(S-propylsulfonimidoyl)-9-[[4-(pyrrolidine-1-carbonyl)phenyl]methyl]-7H-purin-8-one;
6-Methyl-2-(propylsulfonimidoyl)-9-(pyrimidin-5-ylmethyl)-7H-purin-8-one;

6-Methyl-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-7H-purin-8-one.

17. A compound according to any one of claims 1, 2 or 16 selected from:
6-Amino-9-benzyl-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(6-chloro-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-fluorophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-bromophenyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-2-(propylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one;
6-Amino-9-[(6-methyl-3-pyridyl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
Methyl 4-[[6-amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoate;
4-[[6-Amino-8-oxo-2-(propylsulfonimidoyl)-7H-purin-9-yl]methyl]benzoic acid;
6-Methyl-9-[(2-methylpyrimidin-5-yl)methyl]-2-(propylsulfonimidoyl)-7H-purin-8-one;
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one.

18. A compound according to any one of claims 1 to17 selected from:
6-Amino-9-[(4-chlorophenyl)methyl]-2-(ethylsulfonimidoyl)-7H-purin-8-one; and
6-Amino-2-(ethylsulfonimidoyl)-9-(p-tolylmethyl)-7H-purin-8-one.

19. A compound of formula (Ia),



(Ia),

wherein

R^4 is $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, $C_{3\text{-}7}$cylcoalkyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl or pyrrolidinyl$C_{1\text{-}6}$alkyl;

R^5 is C_{1-6}alkyl, phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl or pyrimidinylC_{1-6}alkyl, said phenylC_{1-6}alkyl, pyridinylC_{1-6}alkyl and pyrimidinylC_{1-6}alkyl are unsubstituted or substituted by one, two or three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, carboxy, carbamoyl, haloC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, pyrrolidinylcarbonyl and piperidinylcarbonyl;

R^6 is H or C_{1-6}alkyl-C(O)O-C_{1-6}alkyl-;

R^7 is H, C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-10}alkylcarbonyl;

R^8 is H, C_{1-6}alkylcarbonyl, carboxyC_{1-6}alkylcarbonyl, C_{1-6}alkyoxycarbonylC_{1-6}alkylcarbonyl or benzoyl;

provided that R^6, R^7 and R^8 are not H simultaneously;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20. A compound according to claim 19, wherein

R^4 is methyl, ethyl, propyl, butyl, chloropropyl, cyclohexylmethyl, methoxyethyl, methoxypropyl, pyrrolidinylpropyl or trifluoroethyl;

R^5 is isobutyl, benzyl, chlorobenzyl, fluorobenzyl, bromobenzyl, chlorofluorobenzyl, chloromethylbenzyl, dichlorobenzyl, difluorobenzyl, methylbenzyl, methoxybenzyl, cyanobenzyl, carbamoylbenzyl, trifluoromethylbenzyl, methylsulfonylbenzyl, methoxycarbonylbenzyl, carboxybenzyl, methoxyethylaminocarbonylbenzyl, piperidinylcarbonylbenzyl, pyrrolidinylcarbonylbenzyl, pyridinylmethyl, chloropyridinylmethyl, methylpyridinylmethyl, pyrimidinylmethyl or methylpyrimidinylmethyl;

R^6 is H, acetoxymethyl, acetoxyethyl or dimethylpropanoyloxymethyl;

R^7 is H, ethyl, propyl, isopropyl, cyclopropyl, acetyl, pentanoyl, methylpentanoyl, propylpentanoyl, ethylbutanoyl, methylbutanoyl or dimethylpropanoyl;

R^8 is H, acetyl, pentanoyl, carboxypropanoyl, ethoxycarbonylpropanoyl or benzoyl;

provided that R^6, R^7 and R^8 are not H simultaneously;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

21. A compound according to claim 19, wherein R^4 is C_{1-6}alkyl.

22. A compound according to claim 19, wherein R^4 is methyl or propyl.

23. A compound according to any one of claims 19 to 22, wherein R^5 is phenylC_{1-6}alkyl or pyridinylC_{1-6}alkyl, said phenylC_{1-6}alkyl and pyridinylC_{1-6}alkyl are unsubstituted or substituted by one to three substituents independently selected from halogen or C_{1-6}alkyl.

24. A compound according to claim 23, wherein R^5 is benzyl, chlorobenzyl or methylpyridinylmethyl.

25. A compound according to any one of claims 19 to 24, wherein R^7 is H, C_{1-6}alkyl or C_{1-10}alkylcarbonyl.

26. A compound according to claim 25, wherein R^7 is H, ethyl, propyl, methylpentanoyl or propylpentanoyl.

27. A compound according to any one of claims 19 to 26, wherein R^8 is H, C_{1-6}alkylcarbonyl or carboxyC_{1-6}alkylcarbonyl.

28. A compound according to claim 27, wherein R^8 is H, pentanoyl or carboxypropanoyl.

29. A compound according to any one of claims 19 to 28 selected from:
N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]pentanamide;
N-[[6-Amino-9-[(4-chlorophenyl)methyl]-8-oxo-7H-purin-2-yl]-oxo-propyl-λ^4-sulfanylidene]acetamide;
N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-methyl-oxo-λ^4-sulfanylidene]acetamide;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl- λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
4-[[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoic acid;
Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-3-oxo-butanoate;
Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoate;

Ethyl 4-[[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]amino]-4-oxo-butanoate;

N-[(6-amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;

N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;

N-[(6-Amino-9-benzyl-8-oxo-7H-purin-2-yl)-oxo-propyl-λ^4-sulfanylidene]benzamide;

9-Benzyl-6-(ethylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;

6-(Ethylamino)-9-[(6-methyl-3-pyridyl)methyl]-2-(S-propylsulfonimidoyl)-7H-purin-8-one;

9-[(4-Chlorophenyl)methyl]-6-(ethylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;

9-Benzyl-6-(propylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;

9-Benzyl-6-(isopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;

9-Benzyl-6-(cyclopropylamino)-2-(propylsulfonimidoyl)-7H-purin-8-one;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]acetamide;

N-[9-Benzyl-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]pentanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-ethyl-butanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-3-methyl-butanamide;

N-[9-[(4-Chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-methyl-pentanamide;

N-[9-[(4-chlorophenyl)methyl]-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2,2-dimethyl-propanamide;

N-[9-Benzyl-8-oxo-2-(propylsulfonimidoyl)-7H-purin-6-yl]-2-propyl-pentanamide;

[6-Amino-9-benzyl-2-(methylsulfonimidoyl)-8-oxo-purin-7-yl]methyl acetate;

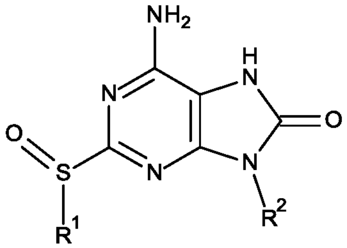
[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]methyl acetate;

[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]methyl 2,2-dimethylpropanoate; and

1-[6-Amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purin-7-yl]ethyl acetate.

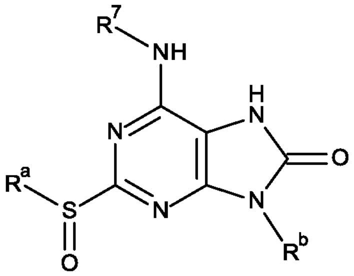
30. A process for the preparation of a compound according to any one of claims 1 to 29 comprising the following steps:

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


(IIa),

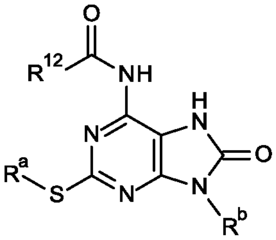
with an imination reagent;

(b) the reaction of a compound of formula (IIb),


(IIb),

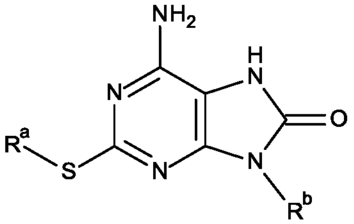
with an imination reagent; wherein R^a is R^1 or R^4, R^b is R^2 or R^5, R^7 is $C_{1\text{-}6}$alkyl or $C_{3\text{-}7}$cycloalkyl;

(c) the reaction of a compound of formula (IIIc),


(IIIc),

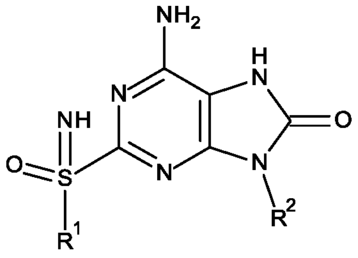
with an oxidant followed by an imination reagent, wherein R^a is R^1 or R^4, R^b is R^2 or R^5, R^{12} is $C_{1\text{-}10}$alkyl;

(d) the reaction of a compound of formula (IIIa),


(IIIa),

with an oxidant followed by an imination reagent, wherein R^a is R^1 or R^4, R^b is R^2 or R^5;

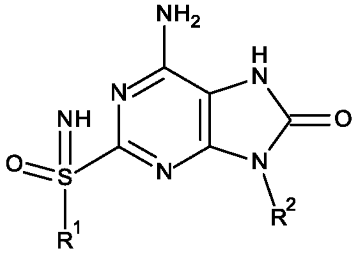
(e) the reaction of a compound of formula (Ie),



(Ie),

with haloester;

(f) the reaction of a compound of formula (Ie),



(Ie),

with carboxylic anhydride or acylchloride;

wherein R^1, R^2, R^4 and R^5 are defined as in any one of claims 1 to 29.

31. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 29 for use as therapeutically active substance.

32. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 29 and a therapeutically inert carrier.

33. The use of a compound according to any one of claims 1 to 29 for the treatment or prophylaxis of hepatitis B virus infection.

34. The use of a compound according to any one of claims 1 to 29 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

35. The use of a compound according to any one of claims 1 to 29 as the TLR7 agonist.

36. The use of a compound according to any one of claims 1 to 29 to induce production of interferon-α.

37. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 29 for the treatment or prophylaxis of hepatitis B virus infection.

38. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 29, when manufactured according to a process of claim 30.

39. A method for the treatment or prophylaxis of hepatitis B virus infection, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 29.

40. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/059961

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/24 A61K31/435 A61P31/12
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 A61K A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 2010/143301 A1 (DESAI MANOJ C [US] ET AL) 10 June 2010 (2010-06-10) cited in the application compound in claim 23;; claims 1, 23 -----	1-39

☐ 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 6 June 2016	Date of mailing of the international search report 20/06/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Wolf, Claudia

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/059961

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