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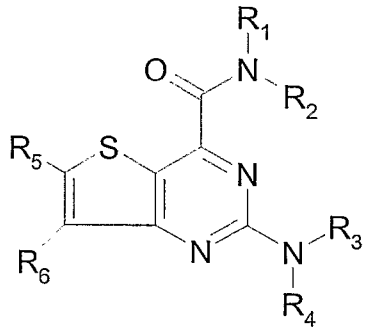

(I)

(57) Abstract: Compounds of formula (I) are A_{2B} wherein R1 and R2 are independently selected from hydrogen, or optionally substituted CrC6 alkyl, C_1-C_6alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl; or R_{-1} and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring; R_3 and R_4 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3- C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl- C_1-C_6)-alkyl; or R_3 and R_4 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring; R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl, - NHR_7 -N(-R_8)-R_9, -NH-(C=O)-R_{10}, -(C=O)-NH-R_{11}, -(C=O)-O-R_{12}, or halo; and R_7, R_8, R_9, R_{10}, R_{-11}, and R_{12} are independently selected from C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl and heteroaryl.

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THIENOPYRIMIDINE COMPOUNDS AND COMPOSITIONS

This invention relates to novel thienopyrimidine derivatives having A_{2B} receptor antagonistic activity, to the use of such compounds in medicine, in relation to the treatment of disorders which are responsive to antagonism of the A_{2B} receptor such as nociception, asthma, COPD, inflammatory disorders, diabetes, diabetic retinopathy and cancer, and to pharmaceutical compositions containing such compounds.

Background to the invention

Adenosine is a naturally occurring purine nucleoside, the effects of which include stimulation of nociception afferents, bronchconstriction, immunosupression, vasodilation, inhibition of platelet aggregation, cardiac depression and inhibition of neurotransmitter release.

Adenosine produces a wide range of pharmacological effects mediated by activation of specific cell surface receptors, which are members of the G-protein coupled receptor family. Four subtypes of adenosine receptors have been identified, designated A_1, A_{2A}, A_{2B} and A_3.

The A_{2B} adenosine receptor subtype is coupled to the G_s G-protein and stimulates adenylyl cyclase activity. Although significant advancement has been made in the understanding of the molecular pharmacology and physiology of A_{2B} adenosine receptors, due to the lack of highly potent and selective ligands for this receptor subtype, many questions about the patho-physiological role of A_{2B} receptors are yet to be resolved (Feoktistov and Biaggioni, Pharmacological Reviews (1997), 49(4), 381-402).

A_{2B} receptors have been implicated in:

(i) the regulation of mast cell secretion (Feoktistov and Biaggioni., Journal of Clinical Investigation (1995), 96(4), 1979-86).

(ii) pain (Abo-Salem et al., Journal of Pharmacology and Experimental Therapeutics (2004), 308(1), 358-366.).

(iii) inflammation (Yang et al., Journal of Clinical Investigation (2006), 116(7), 1913-1923).

(iv) cancer (Zeng et al., Drug Development Research (2003), 58(4), 405-411).

(v) diabetes (Harada et al., Journal of Medicinal Chemistry (2001), 44(2), 170-179).

(vi) gene expression (Boyle et al., Arthritis & Rheumatism (1996), 39(6), 923-930).

(vii) cell growth (Dubey et al., Hypertension (1996), 27(3 Pt 2), 786-93 Hypertension (1996), 27(3 Pt 2), 786-93, Dubey et al., Hypertension (1998), 31(1 Pt 2), 516-21).

(viii) intestinal functions (Murthy et al., Journal of Neurochemistry (1995), 64(1), 77-84).

(ix) neurosecretion (Mateo et al., 1995).

(x) vascular tone (Haynes et al., American Journal of Physiology (1995), 268(5, Pt. 2), H1862-H1868).

(xi) asthma (Feoktistov et al., Trends in pharmacological sciences (1998), 19(4), 148-153; Holgate, British Journal of Pharmacology (2005), 145(8), 1009-1015).

(xii) COPD (Van den Berge et al., Drugs in R&D (2007), 8(1), 13-23).

Thus, there remains a medical need for low molecular weight A_{2B} antagonists with pharmacokinetic and pharmacodynamic properties making them suitable for use as pharmaceutical agents. There also remains a medical need for new treatments of disorders mediated by the A_{2B} receptor, particularly nociception, asthma, COPD, inflammatory disorders, diabetes, diabetic retinopathy and cancer. The object of the present invention is to provide such pharmaceutical agents and treatments.

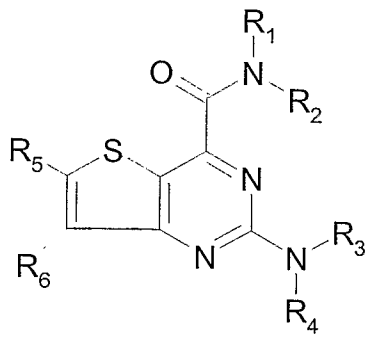
It has now been found that certain thienopyrimidine derivatives show efficacy as A_{2B} antagonists.

Brief description of the invention

The present invention relates to a class of substituted thienopyrimidine compounds useful as A_{2B} antagonists, for example, for the treatment of nociception, asthma, COPD, inflammatory disorders, diabetes, diabetic retinopathy and cancer. A core thieno-pyrimidine bicyclic ring, with substitution on the pyrimidine portion by an amido group in addition to an amino group are principle characterising features of the compounds with which the invention is concerned.

Detailed description of the invention

According to the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, hydrate or solvate thereof:



(I)

wherein

R_1 and R_2 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring;

R_3 and R_4 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl;

or R_3 and R_4 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring;

R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl, –NHR_7,–$N(-R_8)-R_9$, -NH-(C=O)-R_{10}, -(C=O)-NH-R_{11}, -(C=O)-O-R_{12}, or halo; and

R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are independently selected from C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl and heteroaryl.

The active compounds of formula (I) are antagonists of the A_{2B} receptor and are useful for the treatment, prevention and suppression of disorders mediated by the A_{2B} receptor. Such disorders include nociception; asthma; chronic obstructive pulmonary disease (COPD); inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, lupus, psoriasis and inflammatory bowel disease; diabetes mellitus or diabetes insipidus; diabetic retinopathy and cancer.

According to a further embodiment of the present invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, in the manufacture of a medicament for the treatment of disorders mediated by the adenosine A_{2B} receptor.

According to a further embodiment of the present invention there is provided a method of treatment of a disorder mediated by the A_{2B} receptor comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

According to a further embodiment of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and a pharmaceutically acceptable carrier.

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C_a-C_b)alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

As used herein the term "(C_a-C_b)alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C_a-C_b)alkenylene radical" refers to a hydrocarbon chain having from a to b carbon atoms, at least one double bond, and two unsatisfied valences.

As used herein the term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" refers to a carbocyclic radical having from 3-8 carbon atoms containing at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "carbocyclic" refers to a mono- or bi-cyclic radical whose ring atoms are all carbon, and includes monocyclic aryl, cycloalkyl, and

cycloalkenyl radicals, provided that no single ring present has more than 8 ring members. A "carbocyclic" group includes a mono-bridged or multiply-bridged cyclic alkyl group.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular refers to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical, and to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O which is mono-bridged or multiply-bridged. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent, for example selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-

C_6)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$, -$NR^BSO_2OR^A$, -$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group, or R^A and R^B when attached to the same nitrogen may form a cyclic amino ring such as a morpholinyl, piperidinyl or piperazinyl ring. An "optional substituent" or "susbtituent" may be one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

So-called 'pro-drugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof (-NR^1R^2 -> -NHR^1 or -NHR^2);

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof (-NHR^1 -> -NH_2);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof (-$CONH_2$ -> COOH).

The group –N(R_1)-R_2

In the compounds in accordance with the invention, R_1 and R_2 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

In a subclass of compounds with which the invention is concerned, R_1 and R_2 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

In a further subclass of compounds with which the invention is concerned, R_1 is hydrogen and R_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl. In such cases, R_2 may be hydrogen, methyl, ethyl, isopropyl, 2-methoxy-ethyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, 2-phenyl-ethyl, or pyrid-3-yl-methyl.

It is presently preferred that R_1 is hydrogen and R_2 is selected from C_1-C_6 alkyl, or C_3-C_8 cycloalkyl.

Particularly preferred are those compounds wherein R_1 is hydrogen and R_2 is methyl, ethyl, isopropyl, or cyclopropyl.

In another subclass of compounds with which the invention is concerned, R_1 and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring.

Preferred compounds are those wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidine or piperidine ring.

Particularly preferred are those compounds wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form pyrrolidin-1-yl or piperidin-1-yl.

The group $-N(R_3)-R_4$

In the compounds in accordance with the invention, R_3 and R_4 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

In a subclass of compounds with which the invention is concerned, R_3 and R_4 are independently selected from hydrogen or heteroaryl-(C_1-C_6)-alkyl.

In a further subclass of compounds with which the invention is concerned, R_3 is hydrogen and R_4 is heteroaryl-(C_1-C_6)-alkyl. In such cases, R_4 includes methyl- or ethyl- substituted by an optionally substituted 5- or 6-membered heteroaryl ring.

Preferred compounds include those wherein R_3 is hydrogen and R_4 is C_1-C_6 alkyl substituted by pyridyl.

Particularly preferred at present are those compounds wherein R_3 is hydrogen and R_4 is pyrid-3-ylmethyl or 1-(pyrid-3-yl)ethyl.

In another subclass of compounds with which the invention is concerned, R_3 and R_4 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring.

The groups R_5 and R_6

In the compounds in accordance with the invention, R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl, –NHR_7,–$N(-R_8)-R_9$, -NH-(C=O)-R_{10}, -(C=O)-NH-R_{11}, -(C=O)-O-R_{12}, or halo; wherein R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are independently selected from C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl and heteroaryl.

It is presently preferred that both R_5 and R_6 are hydrogen.

Specific compounds with which the invention is concerned include those of the Examples.

The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

As used herein, the term "treatment" as used herein includes prophylactic treatment.

The compound of formula (I) may be used in combination with one or more additional drugs useful in the treatment of the disorders mentioned above, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of

administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg, once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the

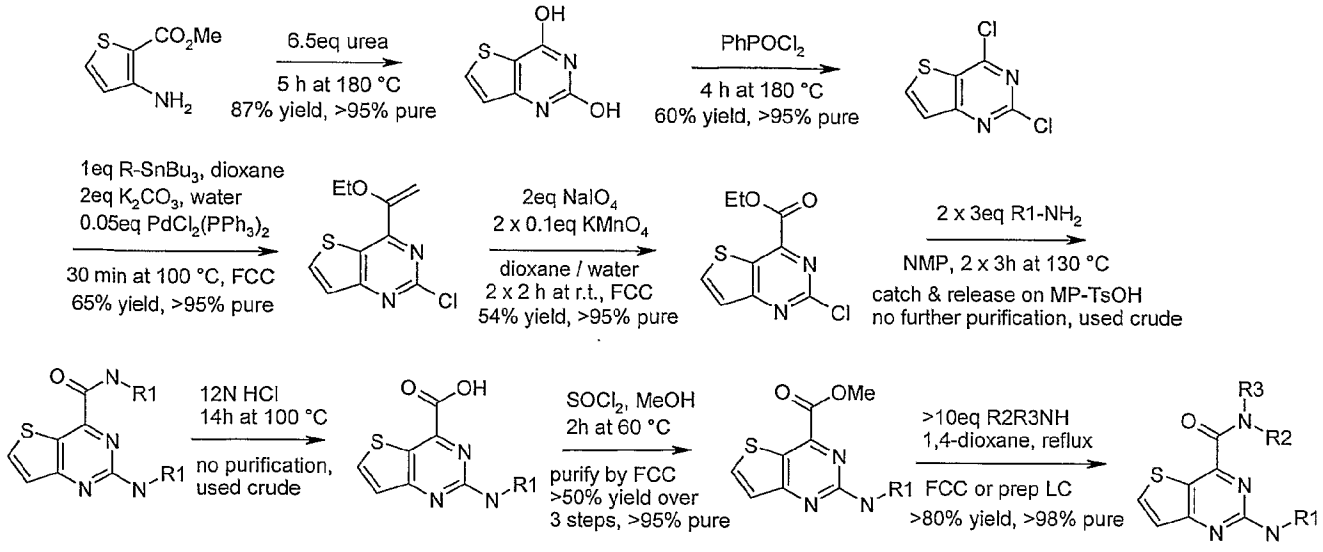
drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

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

There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to formula (I) can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "Advanced organic chemistry", 4th Edition (Wiley), J March, "Comprehensive Organic Transformation", 2nd Edition (Wiley), R.C. Larock , "Handbook of Heterocyclic Chemistry", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "Synthesis", "Acc. Chem. Res." , "Chem. Rev", or primary literature sources identified by standard literature searches online or from secondary sources such as "Chemical Abstracts" or "Beilstein". Such literature methods include those of the preparative Examples herein, and methods analogous thereto.

Scheme 1 represents a method known in the art of organic chemistry in general, by which the compounds of the present invention may be prepared:

Scheme 1



EXAMPLES

The following examples illustrate the preparation of specific compounds of the invention and are not intended to be limiting of the full scope of the invention.

Examples 1 to 6 relate to the method indicated in Scheme 1.

Preparative Example 1

Urea Cyclisation

Thieno[3,2-d]pyrimidine-2,4-diol

A solid mixture of methyl 3-aminothiophene-2-carboxylate (40.0 g, 254 mmol) and urea (99.4 g, 163 mmol) was stirred and heated to 180 °C for 5 h. The now semi-fluid mixture was cooled to 75-80 °C before water (800 ml) was added. After stirring at room temperature for 2 h the formed precipitate was filtered off, washed with further water and dried at 40 °C *i. vac.* Thieno[3,2-d]pyrimidine-2,4-diol was obtained as cream-coloured powder (37.15 g, 87% yield) of >95% purity.

LC-MS: *m/z* = 169 [M+H$^+$]; RT = 1.29 (LC-MS method 2)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 6.91 (1H, d, *J* 5.02 Hz), 8.04 (1H, d, *J* 5.02 Hz), 11.30 (2H, br s)

Preparative Example 2

Hydroxy-Chloro exchange

2,4-Dichloro-thieno[3,2-d]pyrimidine

A mixture of Example 1 (20 g, 119 mmol) in phenylphosphonic dichloride (120 ml, 850 mmol) was stirred and heated to 180 °C for 4 h. The resulting dark solution was cooled to 80 °C and transferred slowly by pipette onto stirred ice / water (800ml). After an hour of vigorous stirring, the yellow-orange precipitate was filtered off, washed and dried at 40 °C *i. vac.* The solid was dissolved in DCM (ca. 20 volumes). The solution was passed through a pad of silica and washed through with ethyl acetate : iso-hexane (1:1). The filtrate was reduced *i. vac.* to yield 2,4-dichloro-thieno[3,2-d]pyrimidine (14.56 g, 60% yield) as a yellow crystalline product.

LC-MS: *m/z* = 205 [M+H$^+$]; RT = 4.36 (LC-MS method 2)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 7.74 (1H, d, *J* 5.52 Hz), 8.70 (1H, d, *J* 5.52 Hz)

Preparative Example 3

Stille Coupling

2-Chloro-4-(1'-ethoxy-vinyl)-thieno[3,2-d]pyrimidine

To a solution of Example 2 (3.0 g, 14.6 mmol) in 1,4-dioxane (200 mL) was added a solution of K_2CO_3 (4.0 g, 29.3 mmol) in water (40 mL). The almost clear solution was placed under nitrogen atmosphere and (1-Ethoxyvinyl)-tributylstannane (5.0 mL, 14.6 mmol) and $PdCl_2(PPh_3)_2$ (500 mg, 0.731 mmol). The mixture was heated to 100 °C and stirred at 100 °C for 30 min under nitrogen atmosphere. After cooling to room temp. the 1,4-dioxane was removed *i. vac.* The residue was re-dissolved in DCM (100 mL) and water (50 mL) and transferred to a separating funnel. The aqueous layer was extracted with DCM (30 mL), the combined organic layers were washed with water (50 mL) and sat. brine (30 mL), dried over Na_2SO_4 and evaporated to dryness *i. vac.* The residue was purified by flash column chromatography (50 g SiO_2 Isolute® pre-wetted with 1CV DCM) eluting with neat DCM collecting 12 mL fractions. Desired product eluted in fractions 10 to 20 with R_f = 0.31 (DCM). By-products eluted in fractions 6 to 9 (R_f = 0.59 in DCM) and fractions 21-31 ((R_f = 0.14 in DCM). Fractions 10 to 20 were combined and evaporated to

dryness *i. vac.* providing 2.28 g (65% yield) 2-chloro-4-(1'-ethoxy-vinyl)-thieno[3,2-d]pyrimidine as yellow powder of 95% purity.

LC-MS: *m/z* = 241 [M+H$^+$]; RT = 3.38 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.49 (3H, t, *J* 7.03 Hz), 4.11 (2H, q, *J* 7.03 Hz), 4.88 (1H, d, *J* 2.51 Hz), 5.76 (1H, d, *J* 2.51 Hz), 7.59 (1H, d, *J* 5.52 Hz), 8.62 (1H, d, *J* 6.02 Hz)

Preparative Example 4

Ethyl 2-chloro-thieno[3,2-d]pyrimidine-4-carboxylate

$NaIO_4$ (1.07 g, 4.99 mmol) was suspended in water (13 mL) and sonicated until a clear solution (pH ~4) was obtained. This solution was added to a solution of Example 3 (600 mg, 2.49 mmol) in 1,4-dioxane (40 mL). $KMnO_4$ (40 mg, 0.249 mmol) was added and the reaction mixture was stirred at room temp for 2 h. Progress of the reaction was checked by TLC (DCM). If remaining starting material was detected, further $KMnO_4$ (40 mg, 0.249 mmol) was added and the reaction mixture was stirred at room temp for further 2 h. The mixture was adjusted to pH 7-8 with sat. aqueous K_2CO_3 solution (1-2 mL). The precipitate was filtered off and the residue was rinsed thoroughly with DCM (4 × 20 mL). The combined filtrates were washed with water, dried over Na_2SO_4 and evaporated to dryness *i. vac.* The residue was purified by flash column chromatography (10 g SiO_2 Isolute®, pre-wetted with 1CV DCM) eluting with neat DCM collecting 10 mL fractions. Ethyl 2-chloro-thieno[3,2-d]pyrimidine-4-carboxylate (325 mg, 54% yield) was isolated as colourless powder of 95% purity.

LC-MS: *m/z* = 243 [M+H$^+$]; RT = 2.92 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.41 (3H, t, *J* 7.03), 4.50 (2H, q, *J* 7.03 Hz), 7.72 (1H, d, *J* 5.52 Hz), 8.76 (1H, d, *J* 6.02 Hz)

General Procedure 1

To a solution of Example 4 (200 mg, 0.824 mmol) in NMP (4 mL) was added R1 amine (2.47 mmol). The reaction mixture was shaken at 130 °C for 3 h. Further R1 amine (2.47 mmol) was added and shaking at 130 °C was continued for further 3 h. After cooling to room temperature the mixture was

transferred to a separating funnel with DCM (20 mL) and washed with water (3 × 10 mL). The organic layer was loaded onto MP-TsOH (1g, Argonaut, pre-wetted with neat DCM). The resin was rinsed with DCM (30 mL) and 2-amino substituted thieno[3,2-d]pyrimidine-4-carboxamide eluted with 0.2 N NH_3 in DCM / MeOH (prepared from 2 mL 7N NH_3 in MeOH + 60 mL DCM + 8 mL MeOH) as intensively yellow fractions. Fractions were combined and evaporated to dryness *i. vac.*

The crude intermediate was dissolved in 12*N* aq HCl (10 mL) and evaporated to dryness *i. vac.* at a bath temperature of 80 °C. The residue was re-dissolved in 12*N* aq HCl (12 mL) and stirred at 100 °C for 14 h. The reaction mixture was evaporated to dryness *i. vac.* at a bath temperature of 80 °C, re-dissolved in MeOH and evaporated to dryness again to obtain 2-amino substituted thieno[3,2-d]pyrimidine-4-carboxylic acid as a yellow-brownish solid.

The crude acid was dissolved in MeOH (20 mL) and thionylchloride (360 µL, 4.94 mmol) was added dropwise at room temp. The mixture was stirred at 60 °C for 2.5 h and then evaporated to dryness *i. vac.* The residue was dissolved in DCM / MeOH (10:1, 100 mL), washed with sat aqueous $NaHCO_3$ (50 mL) and sat. brine (50 mL), dried over Na_2SO_4 and evaporated to dryness *i. vac.* The residue was purified by column chromatography (10 g SiO_2 Isolute® pre-wetted with 1CV DCM / MeOH 50:1) eluting with DCM / MeOH 50:1 collecting 5 mL fractions. Fractions were combined and evaporated to dryness *i. vac.* providing >50% yield of 2-amino substituted thieno[3,2-d]pyrimidine-4-methyl ester as a yellow solid of >95% purity.

The following analogues were prepared using general procedure 1.

Preparative Example 5

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid methyl ester

LC-MS: *m/z* = 301 [M+H$^+$]; RT = 2.44 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 3.97 (3H, s), 4.60 (2H, d, *J* 6.02 Hz), 7.28 (1H, d, *J* 5.52 Hz), 7.31 (1H, m), 7.77 (1H, m), 8.14 (1H, br s), 8.34 (1H, d, *J* 5.52 Hz), 8.42 (1H, m), 8.60 (1H, br s)

Preparative Example 6

2-(1-Pyridin-3-yl-ethylamino)-thieno[3,2-d]pyrimidine-4-carboxylic acid methyl ester

LC-MS: *m/z* = 315 [M+H$^+$]; RT = 2.47 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.51 (3H, d, *J* 7.03 Hz), 3.96 (3H, s), 5.21 (1H, m), 7.24 (1H, d, *J* 5.52 Hz), 7.31 (1H, m), 7.83 (1H, dt, *J* 7.53, 2.01 Hz), 8.19 (1H, br s), 8.31 (1H, d, *J* 5.52 Hz), 8.39 (1H, dd, *J* 5.02, 1.51 Hz), 8.66 (1H, d, *J* 2.01 Hz)

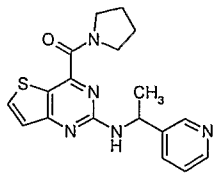
General Procedure 2

To a solution of the corresponding example 5 or 6 (0.50 mmol) in 1,4-dioxane (4 mL) was added the required amine (>10 eq). The mixture was stirred under reflux for 1 h. After cooling to room temp the mixture was evaporated to dryness *i. vac.* and the residue was purified by flash column chromatography (5 g SiO_2 Isolute® pre-wetted with EtOAc). Crude material was loaded as a solution in a minimum neat DCM and product was eluted with neat EtOAc collecting 6 mL fractions. Fractions were combined and evaporated to dryness *i. vac.* providing >80% yield 2-amino substituted thieno[3,2-d]pyrimidin-4-carboxamide as yellow powder of >95% purity.

The following analogues were prepared using general procedure 2.

Example 7

[2-(1-Pyridin-3-yl-ethylamino)-thieno[3,2-d]pyrimidin-4-yl]-pyrrolidin-1-yl-methanone

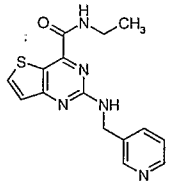


LC-MS: *m/z* = 345 [M+H$^+$]; RT = 2.52 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.52 (3H, d, *J* 7.03 Hz), 1.81 (4H, m), 3.52 (2H, m), 3.82 (2H, m), 5.17 (1H, m), 7.19 (1H, d, *J* 5.52 Hz), 7.31 (1H, m), 7.80 (1H, dt, *J* 8.03, 2.01 Hz), 7.84 (1H, d, *J* 7.53 Hz), 8.24 (1H, d, *J* 5.52 Hz), 8.40 (1H, dd, *J* 5.02, 1.51 Hz), 8.63 (1H, d, *J* 2.51 Hz)

Example 8

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid ethylamide

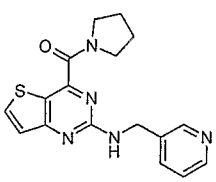


LC-MS: *m/z* = 314 [M+H$^+$]; RT = 1.59 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.15 (3H, t, *J* 7.07 Hz), 3.38 (2H, q, *J* 7.07 Hz), 4.70 (2H, br s), 7.22 (1H, d, *J* 5.56 Hz), 7.34 (1H, dd, *J* 7.83, 4.80 Hz), 7.80 (2H, m), 8.32 (1H, d, *J* 5.56 Hz), 8.43 (1H, d, *J* 4.55 Hz), 8.64 (1H, s), 8.81 (1H, br s)

Example 9

{2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidin-4-yl}-pyrrolidin-1-yl-methanone

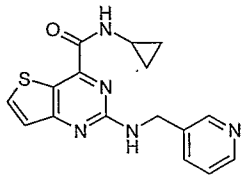


LC-MS: *m/z* = 340 [M+H$^+$]; RT = 2.42 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.81 (4H, m), 3.54 (2H, t, *J* 6.53 Hz), 3.78 (2H, br s), 4.60 (2H, d, *J* 6.02 Hz), 7.23 (1H, d, *J* 5.52 Hz), 7.32 (1H, m), 7.74 (1H, d, *J* 7.53 Hz), 7.88 (1H, t, *J* 6.02 Hz), 8.27 (1H, d, *J* 6.02 Hz), 8.43 (1H, dd, *J* 4.52, 1.51 Hz), 8.57 (1H, s)

Example 10

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid cyclopropylamide

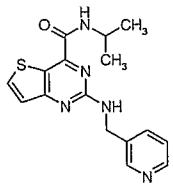


LC-MS: *m/z* = 326 [M+H$^+$]; RT = 2.39 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 0.68 (2H, m), 0.77 (2H, m), 2.90 (1H, m), 4.67 (2H, d, *J* 6.02 Hz), 7.22 (1H, d, *J* 5.52 Hz), 7.31 (1H, m), 7.76 (2H, m), 8.32 (1H, d, *J* 5.52 Hz), 8.42 (1H, br d, *J* 4.52 Hz), 8.61 (2H, m)

Example 11

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid isopropylamide



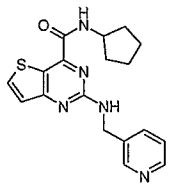
LC-MS: *m/z* = 328 [M+H$^+$]; RT = 1.74 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.22 (6H, d, *J* 6.57 Hz), 4.10 (1H, m), 4.65 (2H, br d, *J* 5.56 Hz), 7.23 (1H, d *J* 5.31 Hz), 7.34 (1H, m), 7.80 (1H, dm, *J*

7.83 Hz), 7.89 (1H, m), 8.32 (1H, d, *J* 8.34 Hz), 8.33 (1H, d, *J* 5.56 Hz), 8.43 (1H, dd, *J* 4.55, 1.26 Hz), 8.64 (1H, s)

Example 12

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid cyclopentylamide

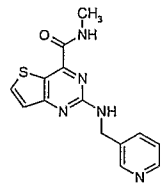


LC-MS: *m/z* = 354 [M+H$^+$]; RT = 1.95 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.58 (4H, m), 1.71 (2H, m), 1.93 (2H, m), 4.23 (1H, m), 4.64 (2H, d, *J* 5.56 Hz), 7.23 (1H, d, *J* 5.56 Hz), 7.32 (1H, dd, *J* 7.83, 4.80 Hz), 7.77 (1H, dt, *J* 7.83, 1.90 Hz), 7.89 (1H, br s), 8.33 (1H, d, *J* 5.56 Hz), 8.35 (1H, m), 8.42 (1H, dd, *J* 4.55, 1.52 Hz), 8.62 (1H, s)

Example 13

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid methylamide

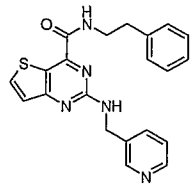


LC-MS: *m/z* = 300 [M+H$^+$]; RT = 1.46 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 2.88 (3H, d, *J* 5.05 Hz), 4.72 (2H, m), 7.21 (1H, d, *J* 5.56 Hz), 7.34 (1H, dd, *J* 7.83, 4.80 Hz), 7.79 (2H, dm, *J* 7.83 Hz), 832 (1H, d, *J* 5.56 Hz), 8.43 (1H, dd, *J* 4.55, 1.01 Hz), 8.63 (1H, s), 8.84 (1H, br s)

Example 14

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid phenethyl-amide

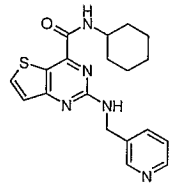


LC-MS: *m/z* = 390 [M+H$^+$]; RT = 2.07 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 2.88 (2H, t, *J* 7.33), 3.58 (2H, m), 4.69 (2H, m), 7.17-7.34 (7H, m), 7.75 (1H, dm, *J* 7.83 Hz), 7.82 (1H, br s), 8.33 (1H, d, *J* 5.56 Hz), 8.43 (1H, dd, *J* 4.80, 1.26 Hz), 8.61 (1H, m), 8.85 (1H, br s)

Example 15

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid cyclohexylamide

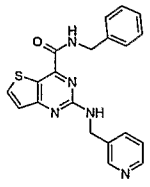


LC-MS: *m/z* = 368 [M+H$^+$]; RT = 2.10 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.13-1.45 (5H, m), 1.60 (1H, m), 1.72 (2H, m), 1.82 (2H, m), 3.78 (1H, m), 4.64 (2H, m), 7.23 (1H, d, *J* 5.05 Hz), 7.32 (1H, m), 7.78 (1H, d, *J* 7.33 Hz), 7.90 (1H, br s), 8.32 (2H, m), 8.42 (1H, br d, *J* 4.04 Hz), 8.62 (1H, s)

Example 16

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid benzylamide

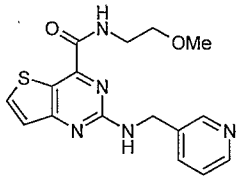


LC-MS: *m/z* = 376 [M+H$^+$]; RT = 1.99 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 4.56 (2H, d, *J* 6.32 Hz), 4.71 (2H, br s), 7.21-7.31 (3H, m), 7.32-7.35 (4H, m), 7.78 (1H, dm, *J* 7.83 Hz), 7.84 (1H, br s), 8.33 (1H, d, *J* 5.56 Hz), 8.41 (1H, m), 8.63 (1H, s), 9.37 (1H, br s)

Example 17

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid (2-methoxy-ethyl)-amide

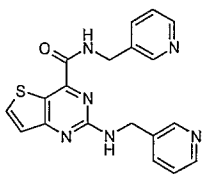


LC-MS: *m/z* = 344 [M+H$^+$]; RT = 2.35 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 3.30 (2H, m, under DMSO·H_2O), 3.51 (5H, m), 4.67 (2H, br d, *J* 6.02 Hz), 7.23 (1H, d, *J* 5.52 Hz), 7.32 (1H, m), 7.78 (1H, dt, *J* 7.53, 2.01Hz), 7.85 (1H, t, *J* 6.53 Hz), 8.33 (1H, d, *J* 5.52 Hz), 8.42 (1H, dd, *J* 5.02, 1.51 Hz), 8.63 (2H, br m)

Example 18

2-[(Pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidine-4-carboxylic acid (pyridin-3-ylmethyl)-amide

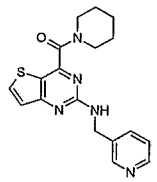


LC-MS: *m/z* = 377 [M+H$^+$]; RT = 2.46 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 4.58 (2H, d, *J* 6.02 Hz), 4.71 (2H, d, *J* 5.52 Hz), 7.22 (1H, d *J* 5.52 Hz), 7.29 (1H, m), 7.37 (1H, m), 7.76 (3H, m), 8.33 (1H, d, *J* 5.52 Hz), 8.42 (1H, dd, *J* 5.02, 1.51 Hz), 8.48 (1H, dd, *J* 5.02, 1.51 Hz), 8.58 (1H, m), 8.63 (1H, m), 9.41 (1H, br s)

Example 19

Piperidin-1-yl-{2-[(pyridin-3-ylmethyl)-amino]-thieno[3,2-d]pyrimidin-4-yl}-methanone



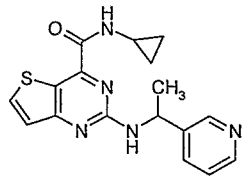
LC-MS: *m/z* = 354 [M+H$^+$]; RT = 1.66 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 1.31-1.48 (2H, m), 1.58 (4H, m), 3.41 (2H, m), 3.61 (2H, m), 4.57 (2H, d, *J* 6.06 Hz), 7.25 (1H, d, *J* 5.56 Hz), 7.32 (1H, m), 7.73 (1H, br d, *J* 7.33 Hz), 7.96 (1H, m), 8.28 (1H, d, *J* 5.56 Hz), 8.42 (1H, m), 8.56 (1H, s)

Crude 2-amino substituted thieno[3,2-d]pyrimidine-4-methyl ester, before purification by column chromatography, could also be used as starting material for the amide formation, however, this left a more difficult final purification. Using this procedure the following product was isolated together with the 2-NH_2 analogue as by-product.

Example 20

2-(1-Pyridin-3-yl-ethylamino)-thieno[3,2-d]pyrimidine-4-carboxylic acid cyclopropylamide

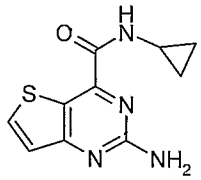


LC-MS: *m/z* = 340 [M+H$^+$]; RT = 2.46 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 0.67 (2H, m), 0.78 (2H, m), 1.51 (3H, d, *J* 7.03 Hz), 2.90 (1H, m), 5.33 (1H, br m), 7.19 (1H, d, *J* 5.52 Hz), 7.31 (1H, m), 7.78 (1H, br m), 7.84 (1H, dt, *J* 8.03, 2.01 Hz), 8.30 (1H, d, *J* 5.52 Hz), 8.39 (1H, dd, *J* 4.52, 1.51 Hz), 8.49 (1H, br d, *J* 4.52 Hz), 8.69 (1H, br d, *J* 2.01 Hz)

Example 21

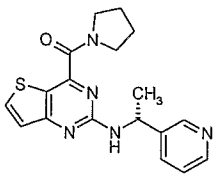
2-Amino-thieno[3,2-d]pyrimidine-4-carboxylic acid cyclopropylamide



LC-MS: *m/z* = 235 [M+H$^+$]; RT = 2.34 (LC-MS method 1)

^{1}H-NMR: δ_H (400 MHz, d_6-DMSO) 0.69 (2H, m), 0.76 (2H, m), 2.91 (1H, m), 6.61 (2H, s), 7.19 (1H, d, *J* 5.52 Hz), 8.31 (1H, d, *J* 5.52 Hz), 8.59 (1H, d, *J* 4.52 Hz)

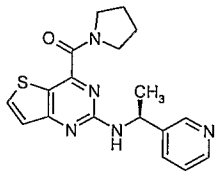
Example 22. (R)-[2-(1-Pyridin-3-yl-ethylamino)-thieno[3,2-d]pyrimidin-4-yl]-pyrrolidin-1-yl-methanone



Prepared as per example 7, using (R)-1-Pyridin-3-yl-ethylamine, which was itself obtained *via* the resolution protocol described in Smith *et. al.*, Journal of

the American Chemical Society, 1973, 95, pp 811–818. Example 22 had spectroscopic properties identical to the racemic example 7. Chiral LC RT = 45.40 min

Example 23. (S)-[2-(1-Pyridin-3-yl-ethylamino)-thieno[3,2-d]pyrimidin-4-yl]-pyrrolidin-1-yl-methanone



Prepared as per example 7, using (S)-1-Pyridin-3-yl-ethylamine, which was itself obtained *via* the resolution protocol described in Smith *et. al.*, Journal of the American Chemical Society, 1973, 95, pp 811–818. Example 23 had spectroscopic properties identical to the racemic example 7. Chiral LC RT = 30.40 min

General Procedures

All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying. Flash chromatography was performed with pre-packed silica-gel cartridges (Strata Si-1; 61 Å, Phenomenex, Cheshire, UK or IST Flash II, 54 Å, Argonaut, Hengoed, UK). Thin layer chromatography was conducted with 5 x 10 cm plates coated with Merck Type 60 F_{254} silica-gel. Microwave heating was performed with a Biotage Initiator™ 2.0 instrument.

The compounds of the present invention were characterized by liquid chromatography-mass spectroscopy (LC-MS) using the following methods.

LC-MS Method 1

Instrument: Waters 2695 pump and 2700 sample manager

Waters ZQ2000, M/z range 100 to 900 amu

Column: Gemini 5µm, C18 110A, 30 mm x 2mm from Phenomenex. Pt no 00A-4435-B0

Temperature: Ambient

Mobile Phase: A - Water + 10 mMol / ammonium formate + 0.04% (v/v) formic acid at pH ca 3.5

B - 100% Acetonitrile + 0.04% (v/v) formic acid

Injection Volume 10uL

Gradient:

Time (min)	Solvent A (%)	Solvent B (%)	Flow (cm^3min^{-1})
- 0.8 (Equil)	95	5	1.0
0	95	5	0.8
0.25	95	5	0.8
2.50	5	95	0.8
4.0	5	95	0.8
5	5	95	1.0
5.2	95	5	1.0

Detection: UV detection from 220 to 400nm (1:3 split MS to UV)

LC-MS Method 2

Instrument: Waters 2695 pump and 2700 sample manager
Waters ZQ2000, M/z range 100 to 900 amu

Column: Gemini 5µm, C18 110A, 30 mm x 2mm from Phenomenex. Pt no 00A-4435-B0

Temperature: Ambient

Mobile Phase: A - Water + 10 mMol / ammonium formate + 0.04% (v/v) formic acid at pH ca 3.5

B - 100% Acetonitrile + 0.04% (v/v) formic acid

Injection Volume 5 uL

Gradient:

Time (min)	Solvent A (%)	Solvent B (%)	Flow (cm^3min^{-1})
0	95	5	0.4
0.5	95	5	0.4
3	5	95	0.4
6	5	95	0.4
6.5	95	5	0.4

Detection: UV detection from 220 to 400nm

Nuclear magnetic resonance (NMR) analysis was performed with a Bruker DPX400 spectrometer and proton NMR spectra were measured at 400 MHz. The spectral reference was the known chemical shift of the solvent. Proton NMR data is reported as follows: chemical shift (δ) in ppm, followed by the integration, the multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets and br = broad), and the coupling constant rounded to the nearest 0.1 Hz.

Some compounds of the invention were purified by preparative HPLC. These were performed on a Waters FractionLynx MS autopurification system, with a Gemini® 5 µm C18(2), 100 mm × 20 mm i.d. column from Phenomenex, running at a flow rate of 20 cm^3min^{-1} with UV diode array detection (210–400 nm) and mass-directed collection. Gradients used for each compound are shown in Table 1.

At pH 4: solvent A = 10 mM ammonium acetate in HPLC grade water + 0.08% v/v formic acid. Solvent B = 95% v/v HPLC grade acetonitrile + 5% v/v solvent A + 0.08% v/v formic acid.

At pH 9: solvent A = 10 mM ammonium acetate in HPLC grade water + 0.08% v/v ammonia solution. Solvent B = 95% v/v HPLC grade acetonitrile + 5% v/v solvent A + 0.08% v/v ammonia solution.

The mass spectrometer was a Waters Micromass ZQ2000 spectrometer, operating in positive or negative ion electrospray ionisation modes, with a molecular weight scan range of 150 to 1000.

Table 1. Preparative HPLC gradients

Time (min)	% Solvent B for Example No.					
	4, 5 and 14	**6, 8, 11, 12, 15–18, 21 and 26**	**19, 20 and 23**	**2, 3, 9,10 and 13**	**24**	**27**
0.0	5	5	5	5	5	5
0.5	6	15	15	30	10	25
7.0	25	30	40	40	20	50
7.5	95	95	95	95	95	95
9.5	95	95	95	95	95	95
10	5	5	5	5	5	5

Those compounds of the invention were analyded by chiral HPLC using the method detailed below.

Instrument:	Perkin Elmer Series 250 HPLC, equipped with a Perkin Elmer 785A UV/Visible detector
Column:	ChiralPak AD-H column, 250 x 4.6 mm
Temperature:	30 °C
Mobile Phase:	80% isohexane, 20% iso-propyl alcohol, 0.1% Diethylamine, 1 mL/min, 60 min run time
Detection:	UV detection at 265 nM
Injection Volume	10μL

IUPAC chemical names were generated using AutoNom Standard.

Assay Description

The use of a Fluorometric Imaging Plate Reader (FLIPR) to measure calcium flux in Adenosine-receptor expressing cells is a well-established technique. In this assay calcium flux is triggered by receptor activation and measured through the fluorescence of an incorporated calcium-sensitive dye. The potencies shown were determined using expressed human adenosine A_{2B} receptors in mammalian cell lines. Selectivity values were obtained by using mammalian cell lines expressing the human adenosine A_1, A_{2A} and A_3 receptors. Compound potency was determined from dose response curves and are reported as IC_{50} values.

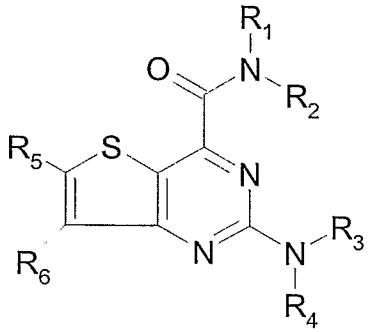
The compounds tested in the above assay were assigned to one of two activity ranges, namely A = IC_{50} <500 nM, or B = IC_{50} >500 nM, as indicated in Table 2 below.

Table 2

Example	Activity
7	B
8	B
9	A
10	B
11	A
12	B
13	B
14	A
15	A
16	A
17	B
18	B
19	B
20	A
21	B
22	B
23	A

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt, hydrate or solvate thereof:



(I)

wherein

R_1 and R_2 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring;

R_3 and R_4 are independently selected from hydrogen, or optionally substituted C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl;

or R_3 and R_4 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring;

R_5 and R_6 are independently selected from hydrogen, C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl, –NHR_7,–$N(-R_8)-R_9$, -NH-(C=O)-R_{10}, -(C=O)-NH-R_{11}, -(C=O)-O-R_{12}, or halo; and

R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are independently selected from C_1-C_6 alkyl, aryl, aryl-(C_1-C_6)-alkyl and heteroaryl.

2. A compound as claimed in claim 1 wherein R_1 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

3. A compound as claimed in claim 1 or claim 2 wherein R_1 is hydrogen, methyl, ethyl, isopropyl, 2-methoxy-ethyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, 2-phenyl-ethyl, or pyrid-3-yl-methyl.

4. A compound as claimed in any of the preceding claims wherein R_1 is methyl or ethyl.

5. A compound as claimed in any of the preceding claims wherein R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

6. A compound as claimed in claim 5 wherein R_2 is hydrogen, methyl, ethyl, isopropyl, 2-methoxy-ethyl, cyclopropyl, cyclopentyl, cyclohexyl, benzyl, 2-phenyl-ethyl, or pyrid-3-yl-methyl.

7. A compound as claimed in claim 5 or claim 6 wherein R_2 is methyl or ethyl.

8. A compound as claimed in claim 1 wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form an optionally substituted 5- or 6-membered ring.

9. A compound as claimed in claim 8 wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring optionally substituted by fluoro, chloro, bromo, cyano, methyl, trifluoromethyl, ethyl, hydroxyl, hydroxymethyl, or hydroxyethyl.

10. A compound as claimed in claim 8 or claim 9 wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form pyrrolidin-1-yl or piperidin-1-yl.

11. A compound as claimed in any of the preceding claims wherein R_3 is hydrogen or heteroaryl-(C_1-C_6)-alkyl.

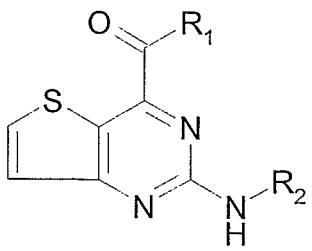
12. A compound as claimed in any of the preceding claims wherein R_4 is hydrogen or heteroaryl-(C_1-C_6)-alkyl.

13. A compound as claimed in any of claims 1 to 10 wherein R_3 is hydrogen and R_4 is heteroaryl-(C_1-C_6)-alkyl.

14. A compound as claimed in any of the preceding claims wherein R_5 is hydrogen.

15. A compound as claimed in any of the preceding claims wherein R_6 is hydrogen.

16. A compound of formula (II) or a pharmaceutically acceptable salt, hydrate or solvate thereof:



(II)

wherein

R_1 is –NH-R_3 or an optionally substituted monocyclic 5- or 6-membered nitrogen-containing ring coupled via a nitrogen atom;

R_2 is C_1-C_6 alkyl substituted by an optionally substituted 5- or 6-membered heteroaryl ring; and

R_3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy-(C_1-C_6)-alkyl, C_3-C_8 cycloalkyl, aryl-(C_1-C_6)-alkyl, or heteroaryl-(C_1-C_6)-alkyl.

17. A compound as claimed in claim 16 wherein R_1 is an optionally substituted monocyclic 5- or 6-membered nitrogen-containing ring coupled via a nitrogen atom.

18. A compound as claimed in claim 16 or claim 17 wherein R_1 is a pyrrolidine or piperidine ring optionally substituted by fluoro, chloro, bromo, cyano, methyl, trifluoromethyl, ethyl, hydroxyl, hydroxymethyl, or hydroxyethyl.

19. A compound as claimed in any of claims 16 to 18 wherein R_1 is pyrrolidin-1-yl or piperidin-1-yl.

20. A compound as claimed in claim 16 wherein R_1 is C_1-C_6 alkylamino or C_3-C_8 cycloalkylamino.

21. A compound as claimed in claim 20 wherein R_1 is methylamino, ethylamino, isopropylamino, or cyclopropylamino.

22. A compound as claimed in any of claims 16 to 21 wherein R_2 is methyl- or ethyl- substituted by an optionally substituted 5- or 6-membered heteroaryl ring.

23. A compound as claimed in any of claims 16 to 21 wherein R_2 is methyl- or ethyl- substituted by a 5- or 6-membered heteroaryl ring optionally substituted by fluoro, chloro, bromo, cyano, methyl, trifluoromethyl, ethyl, hydroxyl, hydroxymethyl, or hydroxyethyl.

24. A compound as claimed in any of claims 16 to 21 wherein R_2 is C_1-C_6 alkyl substituted by pyridyl.

25. A compound as claimed in any of claims 16 to 21 wherein R_2 is pyrid-3-ylmethyl or 1-(pyrid-3-yl)ethyl.

26. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier.

27. The use of a compound as claimed in any of claims 1 to 25 in the manufacture of a medicament for the treatment of disorders mediated by the adenosine A_{2B} receptor.

28. A method of treating a disorder mediated by the adenosine A_{2B} receptor comprising the administration to a subject suffering such a disorder an effective amount of a compound as claimed in any of claims 1 to 25.

29. The use as claimed in claim 27, or a method as claimed in claim 28 wherein the disorder mediated by the adenosine A_{2B} receptor is nociception, asthma, COPD, inflammatory disorders, diabetes, diabetic retinopathy, or cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003180

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/33 A61P11/00

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 practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/02409 A (VERNALIS RES LTD [GB]; GILLESPIE ROGER JOHN [GB]; GILES PAUL RICHARD [) 11 January 2001 (2001-01-11) abstract; claims; examples	1,16, 26-28

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2008	07/11/2008

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/003180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0102409 A	11-01-2001	AT 302205 T	15-09-2005
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		DE 60022042 D1	22-09-2005
		DE 60022042 T2	29-06-2006
		EP 1192164 A1	03-04-2002
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		US 6787541 B1	07-09-2004