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(54) **SUBSTITUTED AZETIDINE DIHYDROTHIENOPYRIDINES AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS**

SUBSTITUIERTE AZETIDINDIHYDROTHIENOPYRIMIDINE UND IHRE VERWENDUNG ALS PHOSPHODIESTERASE-INHIBITOREN

AZÉTIDINE DIHYDROTHIÉNOPYRIDINES SUBSTITUÉES ET LEUR UTILISATION EN TANT QU'INHIBITEURS DE PHOSPHODIESTÉRASE

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to novel substituted azetidine dihydrothienopyridines with phosphodiesterase inhibitory activity, and to their use in therapy, and to pharmaceutical compositions comprising the compounds and to methods of treating diseases with the compounds.

BACKGROUND OF THE INVENTION

[0002] Phosphodiesterases are enzymes that catalyse the hydrolysis of cyclic AMP and/or cyclic GMP in cells to 5-AMP and 5-GMP, respectively, and as such they are critical to cellular regulation of cAMP or cGMP levels. Of the 11 phosphodiesterases identified so far, phosphodiesterase (PDE) 4, PDE7 and PDE8 are selective for cAMP. PDE4 is the most important modulator of cAMP expressed in immune and inflammatory cells such as neutrophils, macrophages and T-lymphocytes. As cAMP is a key second messenger in the modulation of inflammatory responses, PDE4 has been found to regulate inflammatory responses of inflammatory cells by modulating proinflammatory cytokines such as TNF-α, IL-2, IFN-γ, GM-CSF and LTB4. Inhibition of PDE4 has therefore become an attractive target for the therapy of inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, atopic dermatitis, psoriasis, inflammatory bowel disease such as Crohn's disease etc. (M.D. Houslay et al., Drug Discovery Today 10 (22), 2005, pp. 1503-1519). As atopic dermatitis (AD) patients have increased PDE-activity, PDE4-inhibition would also appear to be a viable treatment of AD (Journal of Investigative Dermatology (1986), 87(3), 372-6).

[0003] The PDE4 gene family consists at least of four genes, A, B, C and D, which have a high degree of homology (V. Boswell Smith and D. Spina, Curr. Opinion Investig. Drugs 6(11), 2006, pp. 1136-1141). The four PDE4 isoforms are differentially expressed in different tissues and cell types. Thus, PDE4B is predominantly expressed in monocytes and neutrophils, but not in cortex and epithelial cells, while PDE4D is expressed in lung, cortex, cerebellum and T-cells (C. Kroegel and M. Foerster, Exp. Opinion Investig. Drugs 16(1), 2007, pp. 109-124).

[0004] Numerous PDE4 inhibitors have been studied for their therapeutic effect on inflammatory diseases, primarily asthma and COPD.

[0005] WO 2006/111549, US 20070259846, WO 2009/050236, WO 2009/050242, and WO 2009/053268, (all Boehringer Ingelheim International) each disclose dihydrothieno-pyrimidines which are substituted with piperazine for the treatment of respiratory or inflammatory diseases. The compounds are stated to inhibit the PDE4 enzyme.

[0006] WO 2007/118793, WO 2009/050248, and WO 2013/026797 (all Boehringer Ingelheim International) each disclose dihydrothieno-pyrimidines which are substituted with piperidine for the treatment of respiratory or inflammatory diseases. The compounds are stated to inhibit the PDE4 enzyme.

[0007] WO 2014/066659, Tetra Discovery Partners, discloses bicyclic heteroaryl compounds which are stated to be inhibitors of PDE4.

[0008] WO 2014/124860 discloses PDE4 inhibitors for the treatment of diabetes mellitus. WO 2011/124525 describes combinations comprising a PDE4 inhibitor and an EP4 antagonist for the treatment of respiratory illnesses. WO 2010/097334 discloses combinations comprising a PDE4 inhibitor and a non-steroidal anti-inflammatory drug.

[0009] There is a continuous need for developing novel PDE4 inhibitors which have a more favourable therapeutic window, i.e. fewer adverse effects, while retaining their therapeutic effect.

SUMMARY OF THE INVENTION

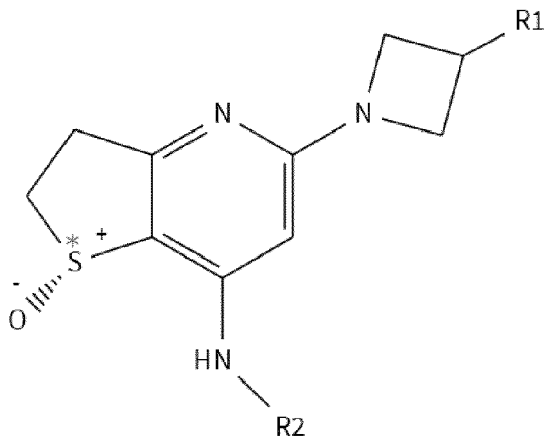
[0010] It is an object of the present invention to provide novel substituted azetidine dihydrothienopyridines. In one aspect the present invention relates to PDE4 inhibitors that could be useful as therapeutic agents for diseases mediated by PDE4, including dermal diseases or conditions, inflammatory allergic diseases, autoimmune diseases; acute or chronic cutaneous wound disorders, and the like.

[0011] The compounds of the present invention could have favourable oral bioavailability, solubility, absorption and metabolic stability. They could also have a favourable safety profile making them better tolerated than other PDE4 inhibitors.

[0012] The compounds of the present invention could have low clearance in human liver microsomes thus making them suitable for oral use.

[0013] The compounds of the present invention could have an improved window over nausea and emesis side effect, relative to other PDE4 inhibitors, thus allowing them to be dosed at higher multiples of their PDE4 potencies for greater therapeutic effect.

[0014] The present invention is defined by the claims. In one aspect the invention provides a compound of general formula (I)



(I)

wherein

R^1 is selected from the group consisting of phenyl, 6 membered heteroaryl, phenoxy and 6 membered heteroaryloxy; all of which are optionally substituted with one or more substituents independently selected from R^3; and

R^2 is selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl, bridged $(C_3\text{-}C_7)$cycloalkyl and (4-7 membered) heterocycloalkyl; all of which are optionally substituted with one or more substituents independently selected from R^4; and

R^3 is selected from the group consisting of halogen, -CN, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and

R^4 is selected from the group consisting of fluoro, -CN, -OH, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $-OR^x$, $-S(O)_2R^x$, $-S(O)_2NR^aR^b$, $-C(O)R^x$, $-C(O)(OR^x)$, and $-C(O)NR^aR^b$; and

R^x is selected from the group consisting of $(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and

S^* represents a chiral sulfur atom with (R) stereochemistry; and

pharmaceutically acceptable salts, enantiomers, mixtures of enantiomers, diastereomers, mixtures of diastereomers, hydrates and solvates thereof.

[0015] In another aspect, the invention provides pharmaceutical compositions comprising a compound of the invention as defined above together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s), optionally together with one or more other therapeutically active compound(s).

[0016] Also disclosed is the use of a compound of the invention, for the manufacture of pharmaceutical compositions for the prophylaxis, treatment, prevention or amelioration of a disease, disorder or condition responsive to PDE4 inhibitory activity.

[0017] Also described is a method for treatment, prevention or alleviation of diseases, disorders or conditions responsive to PDE4 inhibitory activity, and which method comprises the step of administering to a living animal body a therapeutically effective amount of the compound of the invention.

[0018] Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DESCRIPTION OF THE INVENTION

Definitions of the invention

[0019] As used throughout the present specification and appended claims, the following terms have the indicated meaning:

The term "alkyl" is intended to indicate a radical obtained when one hydrogen atom is removed from a branched or linear hydrocarbon. Said alkyl comprises 1-6, such as 1-4, such as 1-3, such as 2-3 or such as 1-2 carbon atoms. The term includes the subclasses normal alkyl (n-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl and isohexyl.

[0020] The terms "alkyloxy" and "alkoxy" are intended to indicate a radical of the formula -OR', wherein R' is alkyl as indicated herein, wherein the alkyl group is appended to the parent molecular moiety through an oxygen atom, e.g. methoxy (-OCH_3), ethoxy (-OCH_2CH_3), n-propoxy, isopropoxy, butoxy, tert-butoxy, and the like.

[0021] The term "hydroxyalkyl" is intended to indicate an alkyl group as defined above substituted with one or more hydroxy, e.g. hydroxymethyl, hydroxyethyl, or hydroxypropyl.

[0022] The term "halogen" is intended to indicate a substituent from the 7th main group of the periodic table, such as fluoro, chloro and bromo, preferably fluoro.

[0023] The term "haloalkyl" is intended to indicate an alkyl group as defined herein substituted with one or more halogen atoms as defined herein, e.g. fluoro or chloro, such as fluoromethyl, difluoromethyl or trifluoromethyl.

[0024] The terms "haloalkyloxy" and "haloalkoxy" are intended to indicate a haloalkyl group as defined herein which is appended to the parent molecular moiety through an oxygen atom, such as difluoromethoxy or trifluoromethoxy.

[0025] The term "cycloalkyl" is intended to indicate a saturated cycloalkane hydrocarbon radical, as described herein. Said cycloalkyl comprises 3-7 carbon atoms, such as 3-6 carbon atoms, such as 3-5 carbon atoms or such as 3-4 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

[0026] The term "bridged cycloalkyl" is intended to indicate a saturated carbocyclic ring having the indicated number of carbon atoms and containing one or two carbon bridges. Representative examples include, but are not limited to, norbornyl, nortricyclyl, and bicyclo[1.1.1]pentyl.

[0027] The term "heteroaryl" is intended to indicate radicals of monocyclic heteroaromatic rings comprising 5- or 6-membered ring which contains from 1-5 carbon atoms and from 1-4 heteroatoms selected from O, N, or S. The heteroaryl radical may be connected to the parent molecular moiety through a carbon atom or a nitrogen atom contained anywhere within the heteroaryl group. Representative examples of (5-6) membered heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, and triazolyl.

[0028] The term "6 membered heteroaryl" is intended to indicate radicals of monocyclic heteroaromatic rings, comprising a 6-membered ring, i.e. having a ring size of 6 atoms, which contain from 1-5 carbon atoms and from 1-5 heteroatoms, such as 1 heteroatom, such as 1-2 heteroatoms, such as 1-3 heteroatoms, such as 1-4 heteroatoms, where the heteroatom is N. Representative examples of 6 membered heteroaryl groups include, but are not limited to pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, and triazinyl.

[0029] The term "heteroaryloxy" as used herein refers to the radical heteroaryl-O-, where "heteroaryl" is as described above. Representative examples of 6 membered heteroaryloxy groups include, but are not limited to pyrazinyloxy, pyridazinyloxy, pyridyloxy, pyrimidinyloxy, and triazinyloxy.

[0030] The term "hydrocarbon radical" is intended to indicate a radical containing only hydrogen and carbon atoms, it may contain one or more double and/or triple carbon-carbon bonds, and it may comprise cyclic moieties in combination with branched or linear moieties. Said hydrocarbon comprises 1-6 carbon atoms, and preferably comprises 1-5, e.g. 1-4, e.g. 1-3, e.g. 1-2 carbon atoms. The term includes alkyl, cycloalkyl and aryl, as indicated herein.

[0031] In some instances, the number of carbon atoms in a hydrocarbon radical (e.g. alkyl, cycloalkyl and aryl) is indicated by the prefix "(C_a-C_b)", wherein a is the minimum number and b is the maximum number of carbons in the hydrocarbon radical. Thus, for example (C_1-C_4)alkyl is intended to indicate an alkyl radical comprising from 1 to 4 carbon atoms, and (C_3-C_6)cycloalkyl is intended to indicate a cycloalkyl radical comprising from 3 to 6 carbon ring atoms.

[0032] The term "oxo" is intended to indicate an oxygen atom which is connected to the parent molecular moiety via a double bond (=O).

[0033] The group "CN" is intended to represent cyano.

[0034] The group "OH" is intended to represent hydroxy.

[0035] The group "C(O)" is intended to represent a carbonyl group (C=O).

[0036] The group "$S(O)_2$" is intended to represent a sulfonyl group ($S(=O)_2$).

[0037] If substituents are described as being independently selected from a group, each substituent is selected independent of the other. Each substituent may therefore be identical or different from the other substituent(s).

[0038] The term "optionally substituted" means "unsubstituted or substituted", and therefore the general formulas described herein encompass compounds containing the specified optional substituent(s) as well as compounds that do not contain the optional substituent(s).

[0039] The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula (I), which comprise a basic moiety, with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroacetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic,

succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxy ethanesulfonic acid, toluenesulfonic, sulfamic, fumaric and ethylenediaminetetraacetic acid. Pharmaceutically acceptable salts of compounds of formula (I) comprising an acidic moiety may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, silver hydroxide, ammonia or the like, or suitable non-toxic amines, such as lower alkylamines, hydroxy-lower alkylamines, cycloalkylamines, or benzylamines, or L-arginine or L-lysine. Further examples of pharmaceutical acceptable salts are listed in Berge, S.M.; J. Pharm. Sci.; (1977), 66(1), 1-19.

[0040] The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula (I), and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a crystalline form. When water is the solvent, said species is referred to as a hydrate.

[0041] The term "protic solvent" is intended to indicate a solvent which has an acidic hydrogen, such as water, or such as alcohols, e.g. methanol, ethanol or isopropanol.

[0042] The term "aprotic solvent" is intended to indicate a solvent which does not have an acidic hydrogen, such as for example dichloromethane, acetonitrile, dimethylformamide, dimethyl sulfoxide or acetone.

[0043] The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the amelioration, alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The term may also include prevention of the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects.

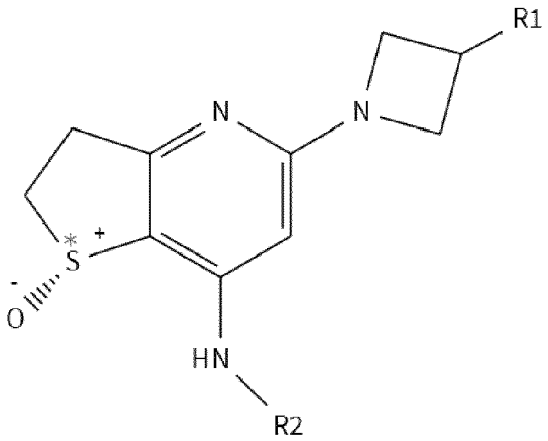
[0044] The terms "disease", "condition" and "disorder" as used herein are used interchangeably to specify a state of a patient which is not the normal physiological state of man.

[0045] The term "medicament" as used herein means a pharmaceutical composition suitable for administration of the pharmaceutically active compound to a patient.

[0046] The term "pharmaceutically acceptable" as used herein means suited for normal pharmaceutical applications, i.e. giving rise to no adverse events in patients etc.

Embodiments of the invention

[0047] In one aspect the invention provides a compound of general formula (I)



(I)

wherein

R^1 is selected from the group consisting of phenyl, 6 membered heteroaryl, phenoxy and 6 membered heteroaryloxy; all of which are optionally substituted with one or more substituents independently selected from R^3; and

R^2 is selected from the group consisting of (C_3-C_7)cycloalkyl, bridged (C_3-C_7)cycloalkyl and (4-7 membered) heterocycloalkyl; all of which are optionally substituted with one or more substituents independently selected from R^4; and

R^3 is selected from the group consisting of halogen, -CN, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl and (C_3-C_6)cycloalkyl; and

R^4 is selected from the group consisting of fluoro, -CN, -OH, $(C_1$-$C_4)$alkyl, halo$(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, $-OR^x$, $-S(O)_2R^x$, $-S(O)_2NR^aR^b$, $-C(O)R^x$, $-C(O)(OR^x)$, and $-C(O)NR^aR^b$; and

R^x is selected from the group consisting of $(C_1$-$C_4)$alkyl and $(C_3$-$C_6)$cycloalkyl; and

R^a and R^b are independently selected from the group consisting of hydrogen, $(C_1$-$C_4)$alkyl and $(C_3$-$C_6)$cycloalkyl; and

S* represents a chiral sulfur atom with (R) stereochemistry; and

pharmaceutically acceptable salts, enantiomers, mixtures of enantiomers, diastereomers, mixtures of diastereomers, hydrates and solvates thereof.

[0048] In another embodiment of the present invention, R^1 is phenyl or phenoxy, optionally substituted with one of R^3.

[0049] In another embodiment of the present invention, R^3 is fluoro.

[0050] In another embodiment of the present invention, R^2 is piperidinyl, pyrrolidinyl or tetrahydropyranyl, all of which are optionally substituted with one or more substituents independently selected from R^4.

[0051] In another embodiment of the present invention, R^2 is piperidinyl or pyrrolidinyl, both of which are independently substituted with one of $-C(O)R^x$ or $-C(O)(OR^x)$, and R^x is methyl.

[0052] In another embodiment of the present invention, R^2 is tetrahydropyranyl.

[0053] In another embodiment the invention provides a compound selected from the following:

(1R)-5-(3-(4-Fluorophenyl)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine 1-oxide;
Methyl (3R)-3-[[(1R)-5-[3-(4-fluorophenyl)azetidin-1-yl]-1-oxido-2,3-dihydrothieno-[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate;
Methyl (3R)-3-[[(1R)-5-(3-(4-phenylazetidin-1-yl)-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate;
(1R)-5-(3-(4-Fluorophenoxy)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide;
Methyl (3S)-3-[[(1R)-5-[3-(4-fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridine-7-yl]amino]pyrolidine-1-carboxylate;
1-[(3S)-3-[[(1R)-5-[3-(4-Fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]pyrrolidin-1-yl]ethenone;
(1R)-5-(3-Phenylazetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide;
or a pharmaceutically acceptable salt, enantiomer, mixture of enantiomers, diastereomer, mixture of diastereomers, hydrate and solvate thereof.

[0054] The compounds of the invention may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or re-crystallisation from an organic solvent or mixture of said solvent and a co-solvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline forms, such as polymorphs and pseudopolymorphs, and also mixtures thereof.

[0055] The compounds of the invention may or may not comprise asymmetrically substituted (chiral) carbon atoms which give rise to the existence of isomeric forms, e.g. enantiomers and possibly diastereomers. The present invention relates to all such isomers, either in optically pure form or as mixtures thereof (e.g. racemic mixtures or partially purified optical mixtures). Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of procedures known in the art. The various isomeric forms may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. high pressure liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by selective crystallization of their diastereomeric salts which may be formed with optically active amines or with optically active acids. Optically purified compounds may subsequently be liberated from said purified diastereomeric salts. Enantiomers may also be resolved by the formation of diastereomeric derivatives. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. If a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chiral pure starting materials. Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomer, as separated, pure or partially purified geometric isomers or mixtures thereof

are included within the scope of the invention.

[0056] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labelled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labelled reagent in place of the non-labelled reagent otherwise employed.

Medical use

[0057] As the Compounds of the invention could exhibit PDE4 inhibitory activity, the Compounds could be useful as therapeutic agents for inflammatory allergic diseases such as bronchial asthma, COPD, allergic rhinitis, and nephritis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease ulcerative colitis, vitiligo, lupus, systemic lupus erythematosus, and discoid lupus erythematosus; acute or chronic cutaneous wound disorders; diseases of the central nervous system such as depression, amnesia, and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock, and cerebrovascular diseases, and the like; insulin-resistant diabetes; wounds, and the like.

[0058] In one embodiment, the Compounds of the present invention are considered useful for the treatment, prevention or alleviation of dermal diseases or conditions.

[0059] In another embodiment, the Compounds of the present invention are considered useful for the treatment, prevention or alleviation of dermal diseases or conditions selected from the group consisting of proliferative and inflammatory skin disorders, dermatitis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis, hand dermatitis, psoriasis, psoriasis vulgaris, inverse psoriasis, psoriatic arthritis, spondyloarthritis, epidermal inflammation, alopecia, alopecia areata, rosacea, skin atrophy, steroid induced skin atrophy, photo skin ageing, SAPHO syndrome, (synovitis, acne, pustulosis, hyperostosis and osteitis), acne vulgaris, hidradenitis suppurativa, urticaria, pruritis, and eczema.

[0060] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of atopic dermatitis.

[0061] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of psoriasis, psoriasis vulgaris, inverse psoriasis or psoriatic arthritis.

[0062] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of psoriasis.

[0063] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of alopecia areata.

[0064] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of acne.

[0065] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of pruritis.

[0066] In another embodiment, the Compounds of the present invention are considered useful for the treatment or alleviation of eczema.

[0067] Compounds of the invention, optionally in combination with other active compounds, could be useful for the treatment of dermal diseases or conditions, in particular for the treatment of proliferative and inflammatory skin disorders, dermatitis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis, hand dermatitis, psoriasis, psoriasis vulgaris, inverse psoriasis, psoriatic arthritis, spondyloarthritis, epidermal inflammation, alopecia, alopecia areata, rosacea, skin atrophy, steroid induced skin atrophy, photo skin ageing, SAPHO syndrome, (synovitis, acne, pustulosis, hyperostosis and osteitis), acne vulgaris, hidradenitis suppurativa, urticaria, pruritis, and eczema.

[0068] Besides being useful for human treatment, the compounds of the present invention could also be useful for veterinary treatment of animals including mammals such as horses, cattle, sheep, pigs, dogs, and cats.

Pharmaceutical Compositions of the invention

[0069] For use in therapy, compounds of the present invention are typically in the form of a pharmaceutical composition. The invention therefore relates to a pharmaceutical composition comprising a compound of formula (I), optionally together with one or more other therapeutically active compound(s), together with a pharmaceutically acceptable excipient or vehicle. The excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0070] Conveniently, the active ingredient comprises from 0.0001-50 % by weight of the formulation.

[0071] In the form of a dosage unit, the compound could be administered one or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner. Conveniently, a dosage unit of a formulation contain between 0.001 mg and 1000 mg, preferably between 0.01 mg and 250 mg, such as 0.1-100 mg of a compound of formula (I).

[0072] A suitable dosage of the compound of the invention will depend, inter alia, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound could be administered either orally, parenterally or topically according to different dosing schedules, e.g. daily or with weekly intervals. In general a single dose will be in the range from 0.001 to 10 mg/kg body weight, e.g. in the range from 0.01 to 5 mg/kg body weight. The compound could be administered as a bolus (i.e. the entire daily dose is administered at once) or in divided doses two or more times a day.

[0073] In the context of topical treatment it could be more appropriate to refer to a "usage unit", which denotes unitary, i.e. a single dose which is capable of being administered to a patient, and which could be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers. A "usage unit" is capable of being administered topically to a patient in an application per square centimetre of the skin of from 0.1 mg to 50 mg and preferably from 0.2 mg to 5 mg of the final formulation in question.

[0074] It is also envisaged that in certain treatment regimes, administration with longer intervals, e.g. every other day, every week, or even with longer intervals could be beneficial.

[0075] If the treatment involves administration of another therapeutically active compound it is recommended to consult Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, for useful dosages of said compounds.

[0076] The administration of a compound of the present invention with one or more other active compounds could be either concomitantly or sequentially.

[0077] The formulations include e.g. those in a form suitable for oral (including sustained or timed release), rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous), transdermal, ophthalmic, topical, dermal, nasal or buccal administration.

[0078] The formulations may conveniently be presented in dosage unit form and may be prepared by but not restricted to any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, The Science and Practice of Pharmacy, 21 ed., 2005. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier, semisolid carrier or a finely divided solid carrier or combinations of these, and then, if necessary, shaping the product into the desired formulation.

[0079] For oral administration, including sustained or timed release, the compound of formula (I) could typically be present in an amount of from 0.001 to 20% by weight of the composition, such as 0.01% to about 10 %.

[0080] Formulations of the present invention suitable for oral and buccal administration could be in the form of discrete units as capsules, sachets, tablets, chewing gum or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder, granules or pellets; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of a gel, a nano- or microemulsion, an oil-in-water emulsion, a water-in-oil emulsion or other dispensing systems. The oils may be edible oils, such as but not restricted to e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural surfactants and viscosifying agents such as but not restricted to tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbomers, polyvinylpyrrolidone, polysorbates, and sorbitan fatty acid esters. The active ingredients could also be administered in the form of a bolus, electuary or paste.

[0081] A tablet may be made by compressing, moulding or freeze drying the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or granules, optionally mixed by a binder and/or filler, such as e.g. lactose, glucose, mannitol starch, gelatine, acacia gum, tragacanth gum, sodium alginate, calcium phosphates, microcrystalline cellulose, carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, hydroxyethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent. Freeze dried tablets may be formed in a freeze-dryer from a solution of the drug substance. A suitable filler can be included.

[0082] Formulations for rectal administration may be in the form of suppositories in which the compound of the present invention is admixed with low melting point, water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

[0083] Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. Furthermore, the formulation may contain co-solvent, solubilising agent and/or complexation agents. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in e.g. Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

[0084] Alternatively, the compounds of formula (I) could be presented as a sterile, solid preparation, e.g. a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

[0085] Transdermal formulations may be in the form of a plaster, patch, microneedles, liposomal or nanoparticulate delivery systems or other cutaneous formulations applied to the skin.

[0086] Formulations suitable for ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in micro-crystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Technology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

[0087] Formulations suitable for topical, such as dermal, intradermal or ophthalmic administration include liquid or semi-solid preparations such as liniments, lotions, gels, applicants, sprays, foams, film forming systems, microneedles, micro- or nano-emulsions, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Compositions for ophthalmic treatment may additionally contain cyclodextrin.

[0088] For topical administration, the compound of formula (I) could typically be present in an amount of from 0.001 to 20% by weight of the composition, such as 0.01% to about 10 %, but could also be present in an amount of up to about 100% of the composition.

[0089] Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers. Such formulations are disclosed in greater detail in e.g. Modern Pharmaceutics, 2nd ed., G.S. Banker and C.T. Rhodes (Eds.), page 427-432, Marcel Dekker, New York; Modern Pharmaceutics, 3th ed., G.S. Banker and C.T. Rhodes (Eds.), page 618-619 and 718-721, Marcel Dekker, New York and Encyclopedia of Pharmaceutical Technology, vol. 10, J. Swarbrick and J.C. Boylan (Eds), page 191-221, Marcel Dekker, New York.

[0090] In addition to the aforementioned ingredients, the formulations of a compound of formula (I) may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourants, surface active agents, thickeners, penetration enhancing agents, solubility enhancing agents, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

[0091] When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic acids or bases, preferred salts are for instance easily watersoluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

[0092] The pharmaceutical composition may additionally comprise one or more other active components conventionally used in the treatment of dermal disease or conditions, e.g. selected from the group consisting of glucocorticoids, vitamin D and vitamin D analogues, antihistamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methylxanthines, β-adrenergic agents, COX-2 inhibitors, JAK inhibitors, other PDE inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol lowering agents, retinoids, zinc salts, salicylazosulfapyridine and calcineurin inhibitors.

METHODS OF PREPARATION

[0093] The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of synthesis. The compounds of the invention could for example be prepared using the reactions and techniques outlined below together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are carried out in solvents appropriate to the reagents and materials employed and suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognized by one skilled in the art. Not all compounds falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used.

[0094] The compounds of the present invention or any intermediate could be purified, if required, using standard methods well known to a synthetic organist chemist, e.g. methods described in "Purification of Laboratory Chemicals", 6th ed. 2009, W. Amarego and C. Chai, Butterworth-Heinemann.

[0095] Starting materials are either known or commercially available compounds, or may be prepared by routine

synthetic methods well known to a person skilled in the art. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker AVANCE 400 spectrometer at 400 MHz, and Bruker AVANCE 500 spectrometer at 500 MHz. Tetramethylsilane was used as an internal standard for proton spectra. The value of a multiplet, either defined doublet (d), triplet (t), quartet (q) or (m) at the approximate midpoint is given unless a range is quoted. (br) indicates a broad peak, whilst (s) indicates a singlet. Thin layer chromatography was performed using Merck 6OF254 silica-gel TLC plates. Visualisation of TLC plates was performed using UV light (254 nm). Mass spectra were obtained on a Shimadzu LCMS-2010EV spectrometer using electrospray ionization (ESI) and/or atmospheric-pressure chemical ionization (APCI).

[0096] The following abbreviations have been used throughout:

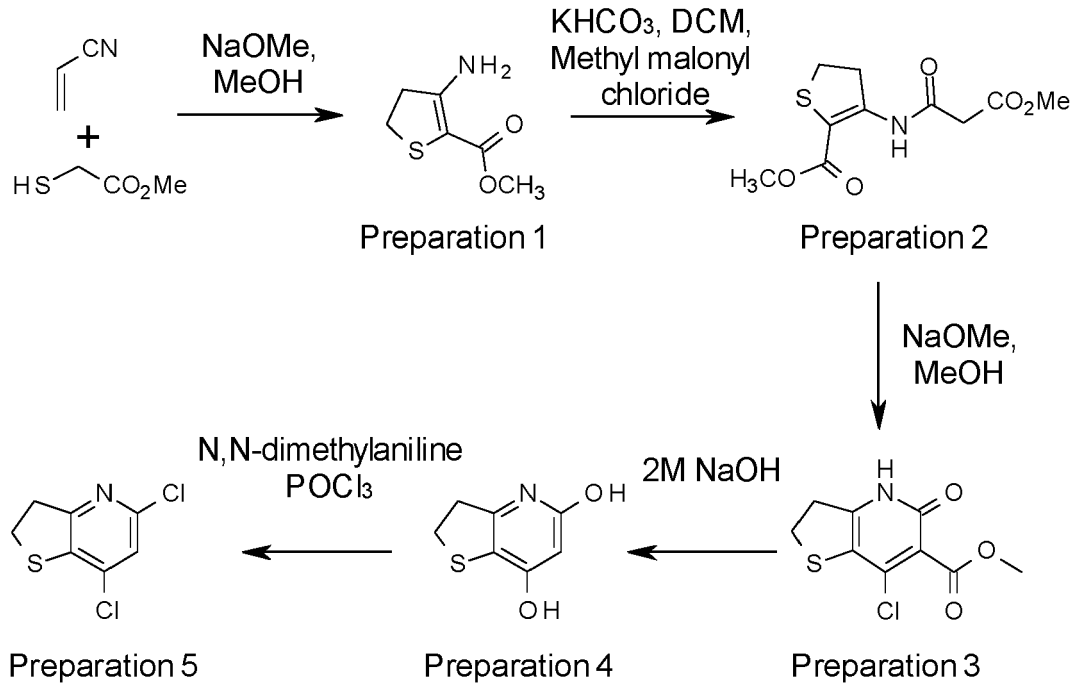
ABPR	automated back pressure regulator
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
dba	dibenzylideneacetone
DCM	dichloromethane
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
HPLC	high-performance liquid chromatograph
KO^{t}Bu	potassium tert-butoxide
LCMS	liquid chromatography-mass spectrometry
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
MTBE	methyl tert-butyl ether
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
ppm	parts per million
SFC	supercritical fluid chromatography
TLC	thin layer chromatography

General Methods

[0097] Compounds of the invention may be prepared according to the following non-limiting general methods and examples:

Scheme 1

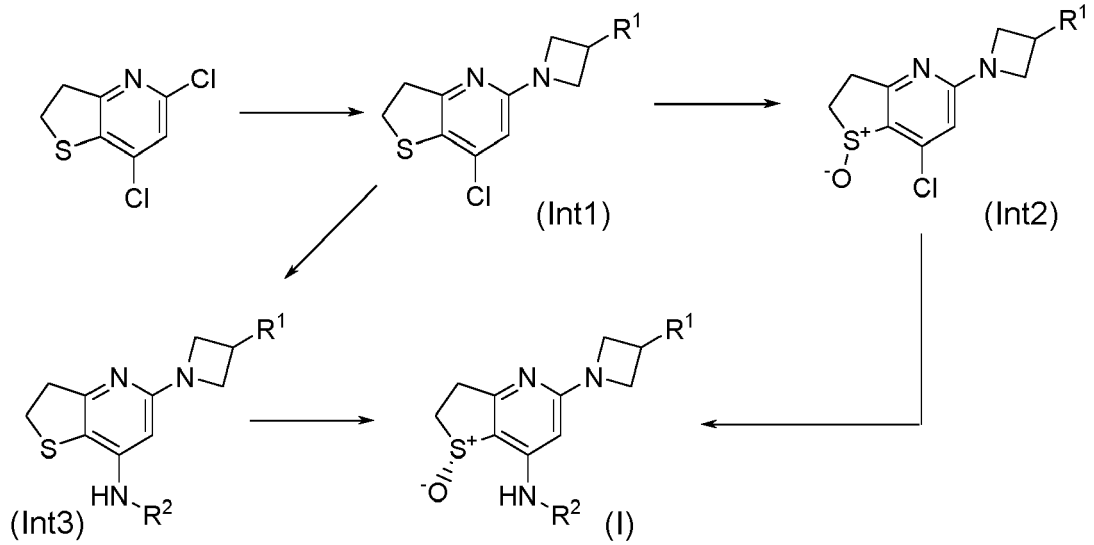
Synthesis of 5,7-dichloro-2,3-dihydrothieno[3,2-b]pyridine (Preparation 5)



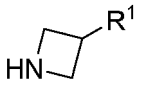
[0098] 5,7-Dichloro-2,3-dihydrothieno[3,2-b]pyridine can be prepared, as shown in Scheme 1, by the methods described in Preparations 1 to 5.

Scheme 2

Synthesis of a compound of general formula (I), wherein R^1 and R^2 are as previously defined:



[0099] Compounds of general formula (Int1) can be prepared, as shown in Scheme 2, by reaction of 5,7-dichloro-2,3-dihydrothieno[3,2-b]pyridine (Preparation 5) with amines of general formula (Int4), which are either commercially available or can readily be synthesised by methods known to those skilled in the art.



(Int4)

[0100] Typical reaction conditions involve reacting a solution of 5,7-dichloro-2,3-dihydrothieno[3,2-b]pyridine (Preparation 5) in a suitable solvent, or solvent mixture, such as 1,4-dioxane, with an amine of formula (Int4) in the presence of a palladium catalyst and an inorganic or organic base, such as potassium ^{t}butoxide, potassium carbonate or caesium carbonate. A suitable palladium catalyst is $Pd_2(dba)_3$ in the presence of BINAP and a suitable base is potassium ^{t}butoxide, as exemplified in Preparation 6.

[0101] Sulfoxides of general formula (Int2) can be prepared, as shown in Scheme 2, by reaction of compounds of general formula (Int1) with a suitable oxidising agent in an appropriate solvent, optionally in the presence of a chiral catalyst. For example, a solution of compounds of general formula (Int1) in EtOH/water can be oxidised by treatment with $NaIO_4$, at a temperature between 0°C and room temperature as outlined in Preparation 9. Sulfoxides of general formula (Int2) can be prepared as single enantiomers or, alternatively, as mixtures of enantiomers which are then separated by methods known to those skilled in the art. Alternatively it may be preferable to take compounds forward as mixtures of enantiomers and separate the enantiomers at a later stage, as described in Example 1.

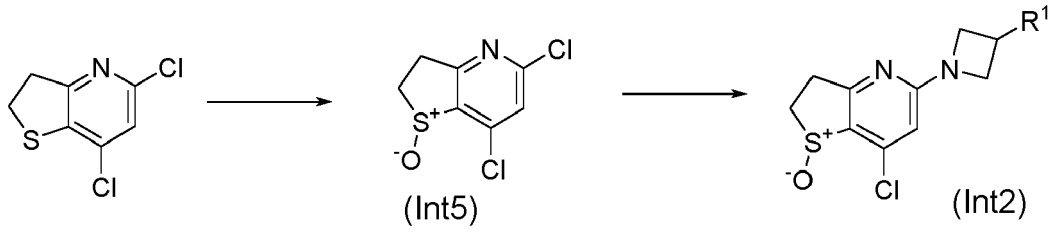
[0102] Compounds of general formula (I) can be prepared, as shown in Scheme 2, by reaction of compounds of general formula (Int2) with amines of general formula R^2NH_2, which are commercially available or can readily be synthesised by methods known to those skilled in the art. Typical reaction conditions involve reacting a solution of a compound of general formula (Int2) in a suitable solvent, or solvent mixture, such as 1,4-dioxane, with an amine of formula R^2NH_2 in the presence of a palladium catalyst and an inorganic or organic base, such as potassium ^{t}butoxide, potassium carbonate or caesium carbonate. A suitable palladium catalyst is palladium acetate in the presence of BINAP and a suitable base is caesium carbonate, as exemplified in Example 1. The compounds of general formula (I) may initially be synthesised as mixtures of enantiomers, which are then separated by methods known to those skilled in the art.

[0103] Alternatively, compounds of general formula (Int3) can be prepared, as shown in Scheme 2, by reaction of compounds of general formula (Int1) with amines of general formula R^2NH_2, which are commercially available or can readily be synthesised by methods known to those skilled in the art. Typical reaction conditions involve reacting a solution of a compound of general formula (Int1) in a suitable solvent, or solvent mixture, such as 1,4-dioxane, with an amine of formula R^2NH_2 in the presence of a palladium catalyst and an inorganic or organic base, such as potassium ^{t}butoxide, potassium carbonate or caesium carbonate. A suitable palladium catalyst is $Pd_2(dba)_3$ in the presence of BINAP and a suitable base is potassium ^{t}butoxide, as exemplified in Preparation 12.

[0104] Compounds of general formula (I) can then be prepared, as shown in Scheme 2, by reaction of compounds of general formula (Int3) with a suitable oxidising agent in an appropriate solvent, optionally in the presence of a chiral catalyst. For example, a solution of compounds of general formula (Int3) in EtOH/water can be oxidised by treatment with $NaIO_4$, at a temperature between 0°C and room temperature as outlined in Example 7.

Scheme 3

Alternative synthesis of a compound of general formula (Int2), wherein R^1 and R^2 are as previously defined:



(Int5) (Int2)

[0105] The sulfoxide of formula (Int5) can be prepared, as shown in Scheme 3, by reaction of 5,7-dichloro-2,3-dihydrothieno[3,2-b]pyridine (Preparation 5) with a suitable oxidising agent in an appropriate solvent, optionally in the presence of a chiral catalyst. For example, a solution of 5,7-dichloro-2,3-dihydrothieno[3,2-b]pyridine (Preparation 5) in EtOH/water can be oxidised by treatment with $NaIO_4$, at a temperature between 0°C and room temperature.

[0106] Compounds of general formula (Int2) can be prepared, as shown in Scheme 3, by reaction of the sulfoxide (Int5) with amines of general formula (Int4), which are either commercially available or can readily be synthesised by

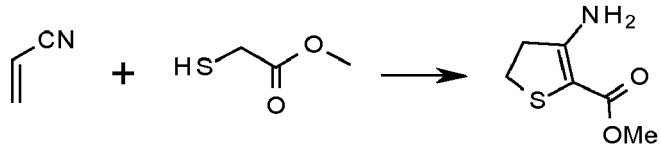
methods known to those skilled in the art. Typical reaction conditions involve reacting the sulfoxide (Int5) and the appropriate amine of formula (Int3) in a suitable protic, or polar aprotic, solvent at a temperature between room temperature and the boiling point of the solvent, in the presence of an added organic or inorganic base.

[0107] Alternatively, a compound of general formula (Int2) can be prepared from the sulfoxide (Int5) by reaction with an amine of general formula (Int4) in a suitable solvent, or solvent mixture, such as 1,4-dioxane, in the presence of a palladium catalyst and a suitable inorganic or organic base, such as potassium ^{t}butoxide, potassium carbonate or caesium carbonate.

PREPARATIONS AND EXAMPLES

Preparation 1

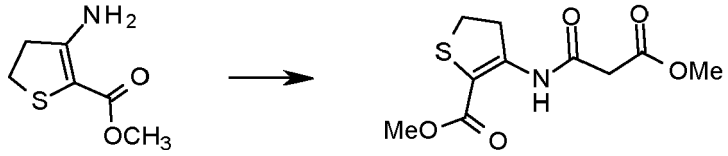
[0108] Methyl 3-amino-4,5-dihydrothiophene-2-carboxylate



[0109] Acrylonitrile (76.2 mL, 1.13 mol) was added to a stirred solution of NaOMe (61.0 g, 1.13 mol) and methyl 2-sulfanylacetate (86 mL, 0.943 mol) in MeOH (600 mL) at 0°C. The reaction mixture was stirred for 2 days at room temperature. The reaction mass was cooled to 0°C and quenched with aq. citric acid solution (1000 mL). The reaction mass was then extracted with EtOAc and the organic layer was washed with water. The resultant organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. MTBE was added to the crude product and the resultant solid was filtered to afford the title compound as a solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.12 - 7.04 (m, 2H), 3.57 (s, 3H), 2.98 - 2.88 (m, 2H), 2.85 - 2.76 (m, 2H); LCMS (ESI): *m/z* 160 $[M+H]^+$; 99%; RT = 1.40 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 2

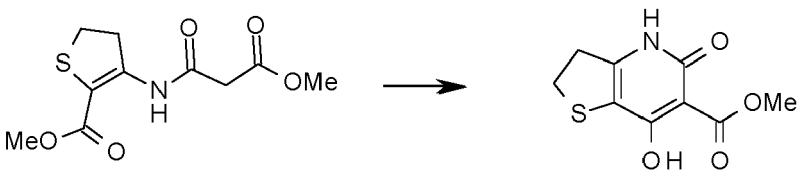
[0110] Methyl 3-(3-methoxy-3-oxopropanamido)-4,5-dihydrothiophene-2-carboxylate



[0111] $KHCO_3$ (118.6 g, 1.18 mol) was added to a stirred solution of the compound of Preparation 1 (42.0 g, 264.2 mmol) in DCM (500 mL) at 0°C. After stirring for 5 minutes a solution of methyl malonyl chloride (42.6 mL, 396.2 mmol) in DCM (150 mL) was added slowly to it at 0°C. The reaction mixture was stirred for 2 hours at room temperature. After completion of the reaction the solids were filtered off and the filtrate was concentrated under vacuum to afford the crude product. MTBE (65 mL) was added to the crude mass and the resultant suspension was filtered to afford the title compound as a solid. The compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 11.08 - 10.98 (m, 1H), 3.81 (d, J=6.6 Hz, 6H), 3.63 (t, J=8.6 Hz, 2H), 3.44 (s, 2H), 3.18 (t, J=8.7 Hz, 2H); LCMS (ESI): *m/z* 260 $[M+H]^+$; 97%; RT = 1.85 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 3

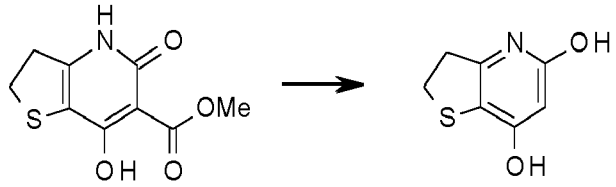
[0112] Methyl 7-chloro-5-oxo-2,3,4,5-tetrahydrothieno[3,2-b]pyridine-6-carboxylate



[0113] A solution of the compound of Preparation 2 (42.0 g, 174 mmol) and 30% NaOMe in MeOH (193 mL, 1.04 mol) was stirred at 70°C for 1 hour. After consumption of all starting material (by TLC) the reaction mass was cooled to 0°C and an aq. solution of citric acid was added to it to give a pH of approximately 4. The resulting precipitate was filtered and washed with cold water to afford the pure title compound as a solid. ^{1}H NMR (DMSO-d6, 400 MHz): δ (ppm) 13.20 - 13.14 (m, 1H), 12.08 - 11.98 (m, 1H), 3.80 (s, 3H), 3.36 - 3.32 (m, 2H), 3.19 - 3.08 (m, 2H); LCMS (ESI): *m*/*z* 228 $[M+H]^+$; 99%; RT = 1.29 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 4

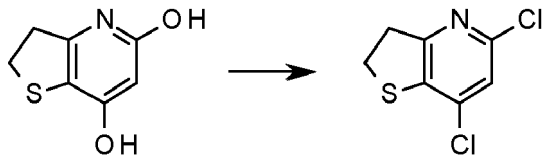
[0114] 2,3-Dihydrothieno[3,2-b]pyridine-5,7-diol



[0115] A mixture of the compound of Preparation 3 (2.20 g, 9.69 mmol) and 2M NaOH (46 mL, 92 mmol) was heated at reflux for 3 hours. The reaction mixture was cooled to 0°C and an aq. solution of citric acid was added to it to achieve a pH of approximately 7. The resulting precipitate was filtered, washed with cold water and dried under reduced pressure to afford the title compound. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.33 - 11.00 (m, 1H), 11.52 - 10.81 (m, 1H), 5.48 - 5.38 (m, 1H), 3.25 - 3.20 (m, 2H), 3.09 - 2.95 (m, 2H); LCMS (ESI): *m*/*z* 170 $[M+H]^+$; 98%; RT = 1.42 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 5

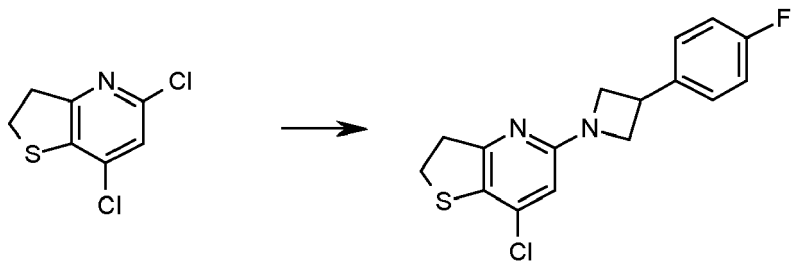
[0116] 5,7-Dichloro-2,3-dihydrothieno[3,2-b]pyridine



[0117] N,N-dimethyl aniline (10.1 mL, 79.8 mmol) was added slowly at 0°C to a stirred solution of the compound of Preparation 4 (3.0 g, 17.8 mmol) in $POCl_3$ (6.76 mL, 72.8 mmol) and the reaction mixture was stirred at 155°C in sealed tube for 16 hours. The reaction mixture was then cooled to room temperature and poured into ice cold water. The mixture was extracted with EtOAc (2 x 100 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (100-200 mesh) column chromatography (5-15% EtOAc in pet ether as eluent) to afford the title compound as a solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.12 (s, 1H), 3.67 - 3.17 (m, 4H); LCMS (ESI): *m*/*z* 206 $[M+H]^+$; 88%; RT = 2.10 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 6

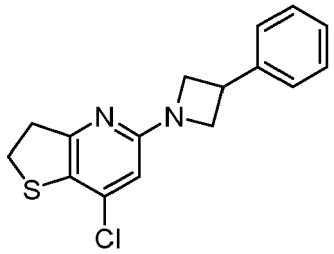
[0118] 7-Chloro-5-(3-(4-fluorophenyl)azetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine



[0119] KO^{t}Bu (3.90 g, 35.0 mmol) was added to a stirred solution of the compound of Preparation 5 (2.4 g, 11.7 mmol) and 3-(4-fluorophenyl)azetidine (2.19 g, 11.7 mmol) in 1,4-dioxane (23 mL). After stirring for 5 min, $Pd_2(dba)_3$ (1.06 g, 1.16 mmol) and BINAP (720 mg, 1.16 mmol) were added. The reaction mixture was heated for 2 hours at 70°C then cooled to room temperature and filtered through a celite pad, washing with EtOAc. The filtrate was concentrated under reduced pressure to give the crude product which was subjected to flash chromatography using 20% EtOAc in hexane as eluent to afford the pure title compound as a solid. ^{1}H NMR (DMSO-d6, 400 MHz): δ(ppm) 7.52 - 7.38 (m, 2H), 7.25 - 7.14 (m, 2H), 6.38 (s, 1H), 4.31 (t, *J*=8.0 Hz, 2H), 3.99 - 3.90 (m, 1H), 3.89 - 3.82 (m, 2H), 3.38 - 3.34 (m, 2H), 3.29 - 3.22 (m, 2H); LCMS (ESI): *m*/*Z* 320[M+H]$^+$; 99%; RT = 2.01 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 7

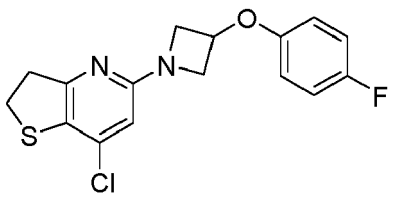
[0120] 7-Chloro-5-(3-phenylazetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine



[0121] The title compound was prepared using the same method as Preparation 6, starting from the compound of Preparation 5 and 3-phenylazetidine. The product was obtained as a solid. ^{1}H NMR (DMSO-d6, 400 MHz): δ(ppm) 7.38 - 7.28 (m, 4H), 7.28 - 7.18 (m, 1H), 6.38 (s, 1H), 4.32 (t, J=7.9 Hz, 2H), 3.97 - 3.90 (m, 1H), 3.90 - 3.86 (m, 2H), 3.38 - 3.33 (m, 2H), 3.29 - 3.22 (m, 2H); LCMS (ESI): *m*/*z* 303 [M+H]$^+$; 92%; RT = 2.73 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 8

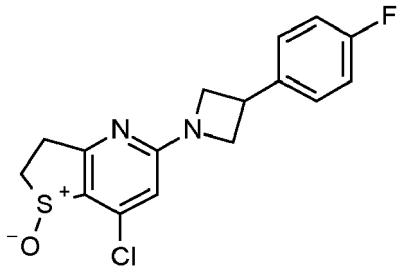
[0122] 7-Chloro-5-(3-(4-fluorophenoxy)azetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine



[0123] The title compound was prepared using the same method as Preparation 6, starting from the compound of Preparation 5 and 3-(4-fluorophenoxy)azetidine. The product was obtained as a solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.05 - 6.94 (m, 2H), 6.79 - 6.60 (m, 2H), 6.14 (s, 1H), 5.12 - 4.97 (m, 1H), 4.42 - 4.25 (m, 2H), 4.09 - 3.91 (m, 2H),3.36-3.32(m, 2H),3.26-3.23(m, 2H);LCMS (ESI): *m*/*z* 337 [M+H]$^+$; 93%; RT = 2.43 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 9

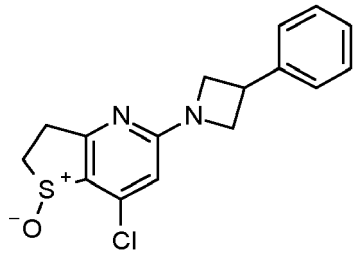
[0124] 7-Chloro-5-(3-(4-fluorophenyl)azetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide



[0125] $NaIO_4$ (2.1 g, 9.96 mmol) was added to a stirred solution of the compound of Preparation 6 (2.9 g, 9.06 mmol) in EtOH/H_2O (6.0 mL, 1:1 ratio) and the reaction was stirred at room temperature for 16h. After completion of the reaction (monitored by TLC) the reaction mass was diluted with EtOAc and the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound as a solid which was used without further purification. LCMS (ESI): *m*/*z* 337 $[M+H]^+$; 76%; RT = 2.01 min; (AQUITY UPLC BEH C18 column, 0.1% FA in water with MeCN).

Preparation 10

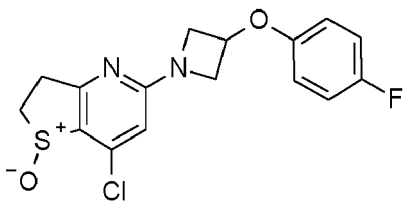
[0126] 7-Chloro-5-(3-phenylazetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide



[0127] According to the method of Preparation 9, the compound of Preparation 7 was reacted to give the title compound as a solid. LCMS (ESI): *m*/*z* 319 $[M+1]^+$; 93%; RT = 1.90 min; (AQUITY UPLC BEH C18 column, 0.1% FA in water with MeCN).

Preparation 11

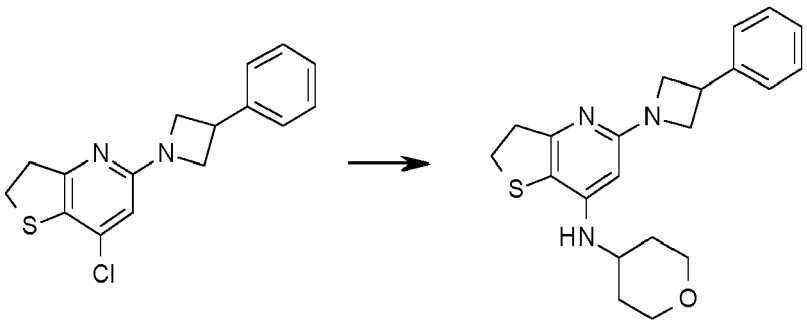
[0128] 7-Chloro-5-(3-(4-fluorobenzyl)azetidin-1-yl)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide



[0129] According to the method of Preparation 9, the compound of Preparation 8 was reacted to give the title compound as a solid. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.09 - 6.86 (m, 2H), 6.79 - 6.58 (m, 2H), 6.20 (s, 1H), 5.15 -5.01 (m, 1H), 4.55 - 4.36 (m, 2H), 4.22 - 4.11 (m, 2H), 3.96 - 3.76 (m, 1H), 3.36 - 3.07 (m, 3H)LCMS (ESI): *m*/*z*353 $[M+H]^+$; 98%; RT = 1.75 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN).

Preparation 12

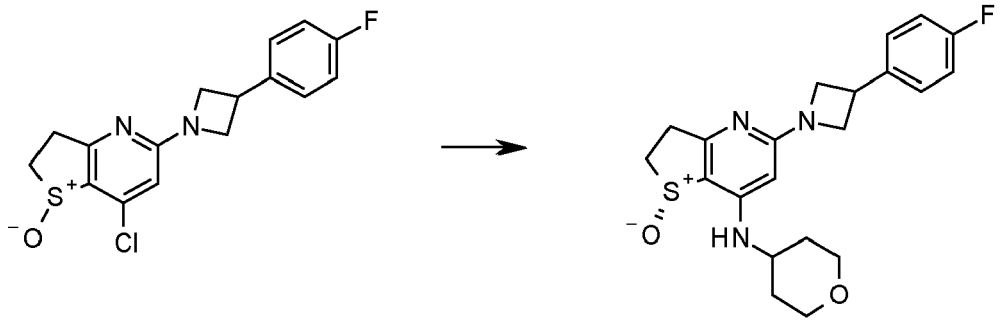
[0130] 5-(3-Phenylazetidin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrothieno[3,2-b]pyridin-7-amine



[0131] The title compound was prepared, as a solid, according to the method of Example 1 using the compound of Preparation 7 and tetrahydropyran-4-amine. LCMS (ESI): *m/z* 368 $[M+H]^+$; 83%; RT = 1.93 min; (AQUITY UPLC BEH C18 column, 0.1% FA in water with MeCN).

Example 1

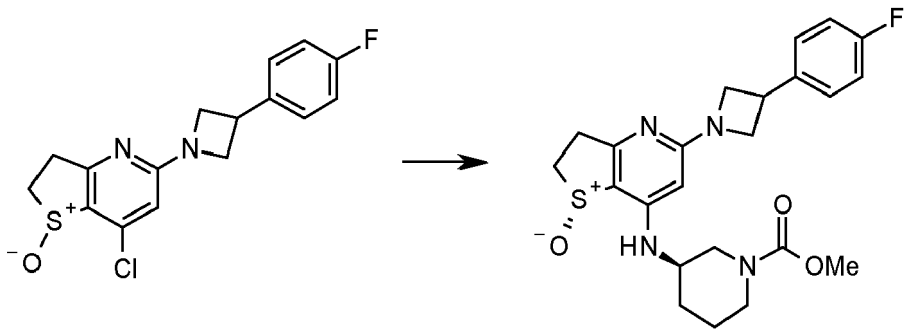
[0132] (1R)-5-(3-(4-Fluorophenyl)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine 1-oxide



[0133] Cs_2CO_3 (8.1 g, 25.0 mmol) and BINAP (518 mg, 0.83 mmol) were added to a stirred solution of the compound of Preparation 9 (2.8 g, 8.33 mmol) and tetrahydropyran-4-amine (1.2 g, 12.5 mmol) in 1,4-dioxane (30 mL), followed by palladium acetate (186 mg, 0.83 mmol). The reaction mixture was heated for 16 hours at 100°C. The reaction mixture was cooled to room temperature and filtered through a celite pad, washing with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product. Purification by flash chromatography using 3% MeOH/DCM as eluent gave the racemic product (1.6 g, 50%). Further purification was then carried out by chiral SFC using a (R,R) WHELK-01 column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.44 - 7.36 (m, 2H), 7.18 (t, J=8.9 Hz, 2H), 6.40 (d, J=8.2 Hz, 1H), 5.44 (s, 1H), 4.40-4.32 (m, 2H), 3.98 - 3.81 (m, 5H), 3.73 - 3.63 (m, 1H), 3.52 - 3.35 (m, 3H), 3.27 - 3.21 (m, 1H), 3.05-2.95 (m, 1H), 2.93 - 2.86 (m, 1H), 1.92 - 1.85 (m, 2H), 1.64 - 1.51 (m, 2H); LCMS (ESI): *m/z* 402 $[M+H]^+$; 99%; RT = 1.64 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC~99% SFC METHOD: Injection volume: 14 µl, Co-Solvent: Methanol, Column: (R,R)WHELK-01(4.6*250) mm,5u, Temperature:30°C, Flow:4, Pressure: 100, RT:5.39 min.

Example 2

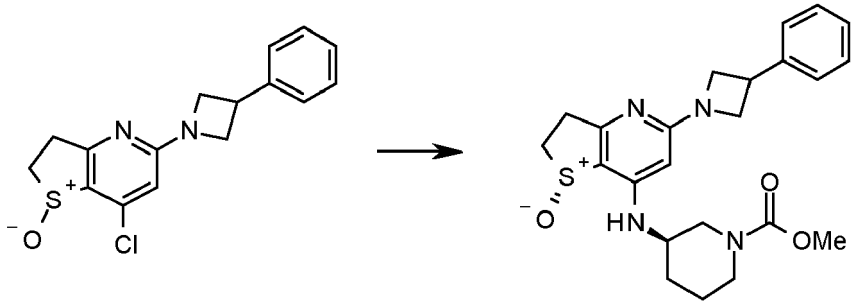
[0134] Methyl (3R)-3-[[(1R)-5-[3-(4-fluorophenyl)azetidin-1-yl]-1-oxido-2,3-dihydrothieno-[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate



[0135] The title compound was prepared in the same manner as the compound of Example 1 using the compound of Preparation 9 and methyl (3R)-3-aminopiperidine-1-carboxylate. Final purification was by chiral SFC using a Chiralpak AD-H column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.46 - 7.35 (m, 2H), 7.23 - 7.13 (m, 2H), 6.45 - 6.35 (m, 1H), 5.55 -5.43 (m, 1H), 4.41 - 4.32 (m, 2H), 4.12 - 3.80 (m, 5H), 3.58 (s, 3H), 3.50 - 3.41 (m, 2H), 3.30 - 3.25 (m, 1H), 3.08 - 2.95 (m, 1H), 3.01 - 2.85 (m, 1H), 2.83 - 2.63 (m, 2H), 2.05 - 1.88 (m, 1H), 1.71 - 1.56 (m, 2H), 1.54 - 1.43 (m, 1H); LCMS (ESI): *m/z* 459 $[M+H]^+$; 99%; RT = 1.40 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~99% SFC METHOD: Column: Chiralpak AD-H (4.6*250) mm,5u, Co-solvent: 0.5% DEA in Methanol, Total flow: 4 g/mn , % Co-solvent: 40%, Temperature:30°C, ABPR: 100 bar, RT: 2.16 min.

Example 3

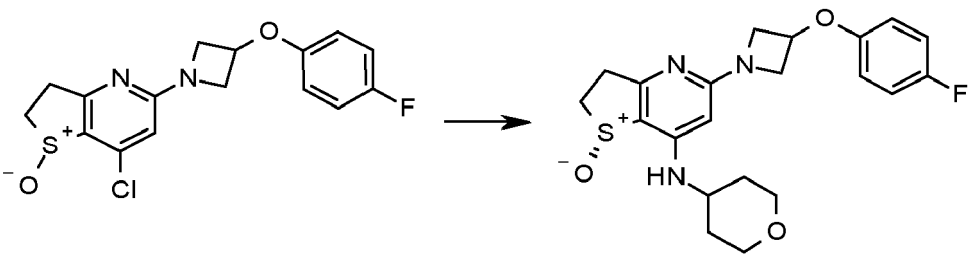
[0136] Methyl (3R)-3-[[(1R)-5-(3-(4-phenylazetidin-1-yl)-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate



[0137] The title compound was prepared in the same manner as the compound of Example 1 using the compound of Preparation 10 and methyl (3R)-3-aminopiperidine-1-carboxylate. Final purification was by chiral SFC using a Chiralpak AD-H column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.40 - 7.33 (m, 4H), 7.30 -7.22 (m, 1H), 6.45-6.37 (m, 1H), 5.55 - 5.43 (m, 1H), 4.43 - 4.33 (m, 2H), 4.09 - 3.80 (m, 5H), 3.58 (s, 3H), 3.51 - 3.42 (m, 2H), 3.31 - 3.24 (m, 1H), 3.06 - 2.95 (m, 1H), 3.05 - 2.95 (m, 1H), 2.85 - 2.62 (m, 2H), 2.01 - 1.90 (m, 1H), 1.72 - 1.58 (m, 2H), 1.53 - 1.44 (m, 1H); LCMS (ESI): *m/z* 441 $[M+H]^+$; 99%; RT = 1.39 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~98% SFC METHOD: Column: CHIRALCEL OD-H (4.6*250) mm 5u, Co-solvent: 0.5% DEA in Methanol, Total flow: 4 g/mn , % Co-solvent: 40%, Temperature:30°C, ABPR: 100 bar, RT: 4.47 min.

Example 4

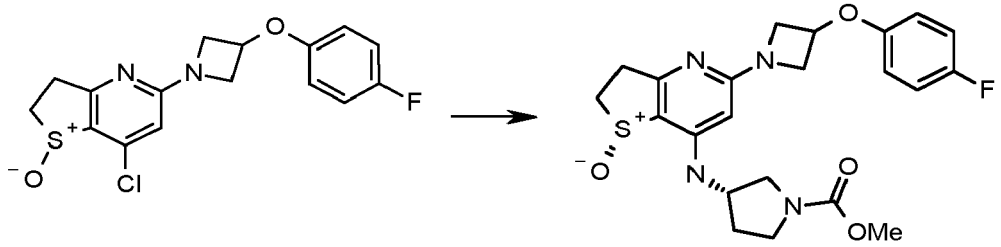
[0138] (1R)-5-(3-(4-Fluorophenoxy)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide



[0139] The title compound was prepared in the same manner as the compound of Example 1 using the compound of Preparation 11 and tetrahydropyran-4-amine. Final purification was by chiral SFC using a Chiralpak IC column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.19 - 7.05 (m, 2H), 6.94 - 6.84 (m, 2H), 6.39 (d, *J*=8.2 Hz, 1H), 5.46 (s, 1H), 5.16 - 5.06 (m, 1H), 4.49 - 4.38 (m, 2H), 3.96 - 3.80 (m, 4H), 3.73 - 3.62 (m, 1H), 3.49 - 3.37 (m, 3H), 3.28 - 3.23 (m, 1H), 3.05 - 2.94 (m, 1H), 2.92 - 2.86 (m, 1H), 1.85 - 1.74 (m, 2H), 1.63 - 1.51 (m, 2H); LCMS (ESI): *m/z* 418 $[M+H]^+$; 99%; RT = 1.64 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~99% SFC METHOD: Column: Chiralpak AS-H (4.6*250) mm 5u, Co-solvent: 0.5% DEA in Methanol, Total flow: 4 g/mn , % Co-solvent: 40%, Temperature:30°C, Outlet Pressure: 100 bar, RT: 2.18 min.

Example 5

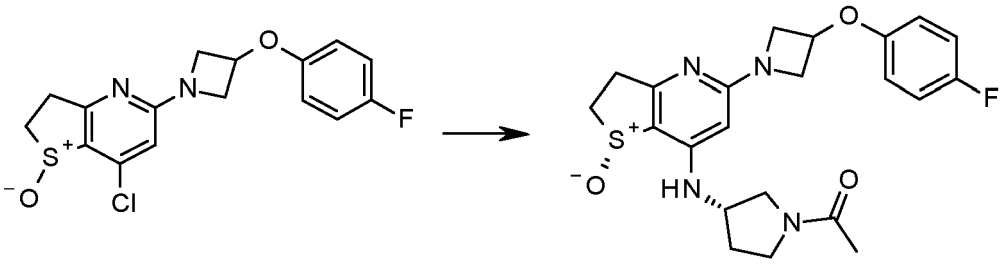
[0140] Methyl (3S)-3-[[(1R)-5-[3-(4-fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridine-7-yl]amino]pyrrolidine-1-carboxylate



[0141] The title compound was prepared in the same manner as the compound of Example 1 using the compound of Preparation 11 and methyl (3S)-3-aminopyrrolidine-1-carboxylate. Final purification was by chiral SFC using a Chiralpak AD-H column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.17 - 7.10 (m, 2H), 6.95 - 6.87 (m, 2H), 6.90 - 6.80 (m, 1H), 5.44 (s, 1H), 5.17 - 5.05 (m, 1H), 4.48 - 4.38 (m, 2H), 4.25 - 4.15 (m, 1H), 3.89 (td, J=3.2, 9.3 Hz, 2H), 3.65 - 3.58 (m, 2H), 3.62-3.54 (m, 2H), 3.53 - 3.40 (m, 2H), 3.37 - 3.34 (m, 1H), 3.27 - 3.20 (m, 2H), 3.05 - 2.95 (m, 1H), 2.93 - 2.86 (m, 1H), 2.30 -2.08 (m, 1H), 2.01 - 1.89 (m, 1H); LCMS (ESI): *m/z* 461 $[M+H]^+$; 96%; RT = 1.70 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~99% SFC METHOD: Column: Chiralpak AS-H (4.6*250) mm 5u, Co-solvent: 0.5% DEA in Methanol, Total flow : 3 g/mn , % Co-solvent: 40%, Back pressure: 1002, RT: 4.02 min.

Example 6

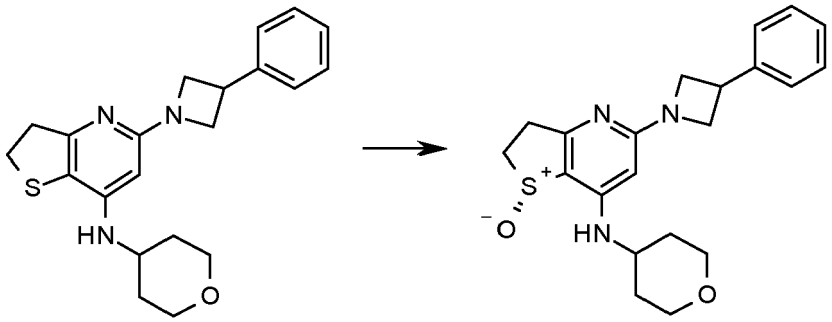
[0142] 1-[(3S)-3-[[(1R)-5-[3-(4-Fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]pyrrolidin-1-yl]ethanone



[0143] The title compound was prepared in the same manner as the compound of Example 1 using the compound of Preparation 11 and 1-[(3S)-3-aminopyrrolidin-1-yl]ethanone. Final purification was by chiral SFC using a Chiralpak AD-H column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.14 - 7.04 (m, 2H), 6.93 - 6.86 (m, 2H), 6.40 - 6.32 (m, 1H), 5.50 - 5.42 (m, 1H), 5.15 - 5.06 (m, 1H), 4.50 - 4.39 (m, 2H), 4.33 - 4.19 (m, 1H), 3.98 - 3.89 (m, 2H), 3.86 - 3.63 (m, 1H), 3.61 - 3.41 (m, 3H), 3.40 - 3.21 (m, 3H), 2.90 - 2.86 (m, 1H), 2.26 - 2.10 (m, 1H), 2.08 - 1.84 (m, 4H) ; LCMS (ESI): *m/z* 445 $[M+H]^+$; 99%; RT = 1.60 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~99% SFC METHOD: Column: Chiralpak AS-H (4.6*250) mm 5u, Co-solvent: 0.5% DEA in Methanol, Total flow: 4 g/mn , % Co-solvent: 40%, Temperature:30°C, Outlet Pressure: 100 bar, RT: 3.72 min.

Example 7

[0144] (1R)-5-(3-Phenylazetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide



[0145] According to the method of Preparation 9 the compound of Preparation 12 was reacted with $NaIO_4$ to give racemic title compound. Final purification was by chiral SFC using a Chiralcel OJ-H column and methanol as co-solvent. The solvent was removed in vacuo to afford the title compound as a solid. ^{1}H NMR (DMSO-d6, 500 MHz): δ (ppm) 7.38 - 7.32 (m, 4H), 7.29 -7.25 (m, 1H), 6.48 - 6.38 (m, 1H), 5.45 (s, 1H), 4.41 - 4.33 (m, 2H), 3.96 - 3.91 (m, 3H), 3.90 - 3.83 (m, 2H), 3.72 - 3.63 (m, 1H), 3.50 - 3.35 (m, 3H), 3.28 - 3.22 (m, 1H), 3.03 - 2.94 (m, 1H), 2.93 - 2.86 (m, 1H), 1.90 - 1.78 (m, 2H), 1.63 - 1.51 (m, 2H) ; LCMS (ESI): *m/z* 384 $[M+H]^+$; 97%; RT = 1.60 min; (AQUITY UPLC BEH C18 column, 0.1% FORMIC ACID in water with MeCN) and Chiral HPLC ~97% SFC METHOD: Column: CHIRALCEL OJ-H (4.6*250) mm 5u, Co-solvent: 0.5% DEA in Methanol, Total flow: 4 g/mn ,% Co-solvent: 40%, Temperature:30°C, ABPR: 100 bar, RT: 2.07 min.

PDE4 assay

[0146] The human PDE4D catalytic domain (UniProt no. Q08499 [S380-L740]) was incubated with a mixture of non-labelled cAMP (cyclic adenosine monophosphate) and fluorescein amidite (FAM) conjugated cAMP and titrated test or reference compound. Following brief incubation the enzymatic reaction was stopped by addition of binding buffer containing nanoparticles with immobilized trivalent metal ions capable of binding 1) AMP phospho groups and 2) terbium (Tb) donor fluorophores. Subsequent excitation of the Tb donor triggers time-resolved FRET to adjacent FAM acceptor molecules resulting in light emission. In the presence of a PDE4 inhibitor, AMP generation was reduced resulting in a lower fluorescence signal. The cAMP phosphodiester is not bound by the detection system.

[0147] The results were calculated as the molar concentrations resulting in 50% inhibition of the substrate cleavage compared to controls samples, and are expressed as IC_{50} (nM).

[0148] PDE4 IC_{50} ranges:

*	indicates that IC_{50} values are > 50 nM and < 150 nM
**	indicates that IC_{50} values are > 10 and < 50 nM
***	indicates that IC_{50} values are < 10 nM

TNF-α release

[0149] Human peripheral blood mononuclear cells (PBMC) were isolated from buffy coats. The blood is mixed with saline at a ratio of 1:1, and the PBMC were isolated using Lymphoprep tubesTM (Nycomed, Norway). The PBMC were

suspended in RPMI1640 with 0.5% human serum albumin, pen/strep and 2 mM L-glutamine at a concentration of 5 x 105 c/ml. The cells were pre-incubated for 30 minutes with the test compounds in 96 well tissue culture plates and stimulated for 18 hours with lipopolysaccharide 1 mg/ml (Sigma). TNF-α concentration in the supernatants was measured using homogeneous time-resolved fluorescence resonance (TR-FRET). The assay is quantified by measuring fluorescence at 665 nm (proportional to TNF-α concentration) and 620 nm (control).

[0150] Results were expressed as IC_{50} values calculated from inhibition curves using as positive controls the secretion in LPS stimulated wells and as negative controls the secretion in unstimulated cells.

[0151] TNF-α IC_{50} ranges:

*	indicates that IC_{50} values are > 50 nM and < 150 nM
**	indicates that IC_{50} values are > 10 and < 50 nM
***	indicates that IC_{50} values are < 10 nM

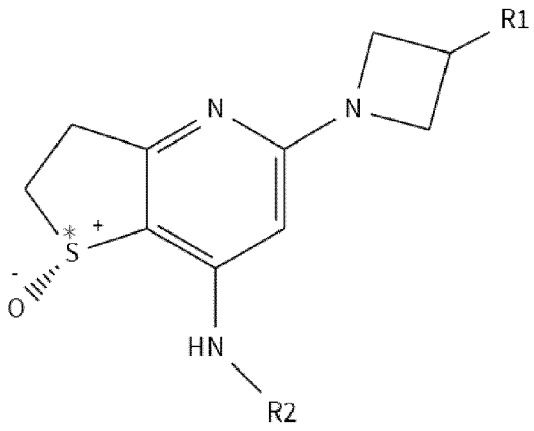
[0152] The results are shown in Table 1 below.

Table 1

Example	PDE4 IC_{50} range	TNF-α IC_{50} range
1	**	***
2	***	***
3	***	***
4	**	**
5	*	*
6	***	**
7	**	**

Claims

1. A compound of general formula (I)



(I)

wherein:

R^1 is selected from the group consisting of phenyl, 6 membered heteroaryl, phenoxy and 6 membered heteroaryloxy; all of which are optionally substituted with one or more substituents independently selected from R^3; and

R^2 is selected from the group consisting of (C_3-C_7)cycloalkyl, bridged (C_3-C_7)cycloalkyl and (4-7 membered) heterocycloalkyl; all of which are optionally substituted with one or more substituents independently selected from R^4; and

R^3 is selected from the group consisting of halogen, -CN, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and
R^4 is selected from the group consisting of fluoro, -CN, -OH, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $-OR^x$, $-S(O)_2R^x$, $-S(O)_2NR^aR^b$, $-C(O)R^x$, $-C(O)(OR^x)$, and $-C(O)NR^aR^b$; and
R^x is selected from the group consisting of $(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and
R^a and R^b are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl and $(C_3\text{-}C_6)$cycloalkyl; and
S^* represents a chiral sulfur atom with (R) stereochemistry;
or pharmaceutically acceptable salts, enantiomers, mixtures of enantiomers, diastereomers, mixtures of diastereomers, hydrates and solvates thereof.

2. A compound according to claim 1, wherein R^1 is phenyl or phenoxy, optionally substituted with one of R^3.

3. A compound according to claim 1 or 2, wherein R^3 is fluoro.

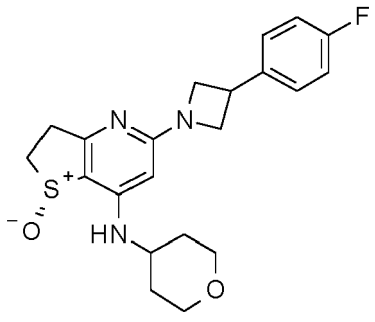
4. A compound according to any one of the claims 1-3, wherein R^2 is piperidinyl, pyrrolidinyl or tetrahydropyranyl, all of which are optionally substituted with one or more substituents independently selected from R^4.

5. A compound according to claim 4, wherein R^2 is tetrahydropyranyl.

6. A compound according to any one of the preceding claims selected from the group consisting of

(1R)-5-(3-(4-Fluorophenyl)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine 1-oxide;
Methyl (3R)-3-[[(1R)-5-[3-(4-fluorophenyl)azetidin-1-yl]-1-oxido-2,3-dihydrothieno-[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate;
Methyl (3R)-3-[[(1R)-5-(3-(4-phenylazetidin-1-yl)-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]piperidine-1-carboxylate;
(1R)-5-(3-(4-Fluorophenoxy)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide;
Methyl (3S)-3-[[(1R)-5-[3-(4-fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridine-7-yl]amino]pyrolidine-1-carboxylate;
1-[(3S)-3-[[(1R)-5-[3-(4-Fluorophenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]pyrrolidin-1-yl]ethenone;
(1R)-5-(3-Phenylazetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridine-1-oxide;
or a pharmaceutically acceptable salt, enantiomer, mixture of enantiomers, diastereomer, mixture of diastereomers, hydrate and solvate thereof.

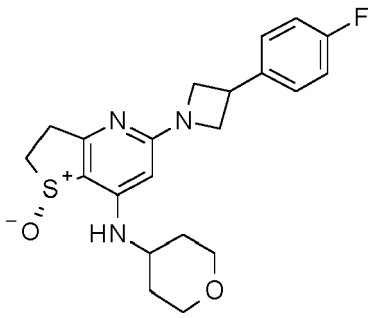
7. A compound according to any one of the preceding claims, wherein the compound has the structure



,

or a pharmaceutically acceptable salt, enantiomer, mixture of enantiomers, hydrate or solvate thereof.

8. A compound according to any one of the preceding claims, wherein the compound has the structure



,

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

9. A pharmaceutical composition comprising a compound according to any one of claims 1-8 together with a pharmaceutically acceptable vehicle or excipient or pharmaceutically acceptable carrier(s).

10. The compound according to any of the claims 1-8, for use as a medicament.

11. The compound according to any one of claims 1-8 for use in the treatment or amelioration of a dermal disease, disorder or condition, an inflammatory allergic disease, an autoimmune disease, an acute or chronic cutaneous wound disorder, a disease of the central cervous system, organopathy associated with ischemic reflux caused by cardiac failure, shock and cerebrovascular diseases, or insulin-resistant diabetes.

12. The compound for use according to claim 11, wherein the use is in the treatment or amelioration of a dermal disease, disorder or condition.

13. The compound for use according to claim 12, wherein the dermal disease, disorder or condition is selected from the group consisting of proliferative and inflammatory skin disorders, dermatitis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis, hand dermatitis, psoriasis, psoriasis vulgaris, inverse psoriasis, psoriatic arthritis, spondyloarthritis, epidermal inflammation, alopecia, alopecia areata, rosacea, skin atrophy, steroid induced skin atrophy, photo skin ageing, SAPHO syndrome, (synovitis, acne, pustulosis, hyperostosis and osteitis), acne vulgaris, hidradenitis suppurativa, urticaria, pruritis, and eczema.

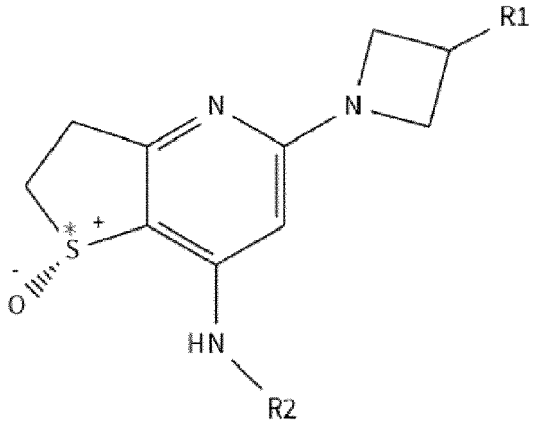
14. The compound for use according to claim 13, wherein the dermal disease, disorder or condition is an inflammatory skin disorder.

15. The compound for use according to claim 13, wherein the dermal disease, disorder or condition is dermatitis, atopic dermatitis, seborrheic dermatitis, contact dermatitis, including irritative contact dermatitis and allergic contact dermatitis or hand dermatitis.

16. The compound for use according to any one of claims 10-15, wherein the compound is used in combination with another active compound.

Patentansprüche

1. Verbindung der allgemeinen Formel (I)



(I)

wobei:

R^1 ausgewählt ist aus der Gruppe bestehend aus Phenyl, 6-gliedrigem Heteroaryl, Phenoxy und 6-gliedrigem Heteroaryloxy; von denen alle optional mit einem oder mehreren Substituenten unabhängig ausgewählt aus R^3 substituiert sind; und
R^2 ausgewählt ist aus der Gruppe bestehend aus (C_3-C_7)Cycloalkyl, verbrücktem (C_3-C_7)Cycloalkyl und (4-7-gliedrigem) Heterocycloalkyl; von denen alle optional mit einem oder mehreren Substituenten unabhängig ausgewählt aus R^4 substituiert sind; und
R^3 ausgewählt ist aus der Gruppe bestehend aus Halogen, -CN, (C_1-C_4)Alkyl, Halo(C_1-C_4)alkyl, Hydroxy(C_1-C_4)alkyl und (C_3-C_6)Cycloalkyl; und
R^4 ausgewählt ist aus der Gruppe bestehend aus Fluor, -CN, -OH, (C_1-C_4)Alkyl, Halo(C_1-C4)alkyl, Hydroxy(C_1-C_4)alkyl, -OR^x, -$S(O)_2R^x$, -$S(O)_2NR^aR^b$, -$C(O)R^x$, -$C(O)(OR^x)$ und - $C(O)NR^aR^b$; und
R^x ausgewählt ist aus der Gruppe bestehend aus (C_1-C_4)Alkyl und (C_3-C_6)Cycloalkyl; und
R^a und R^b unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, (C_1-C_4)Alkyl und (C_3-C_6)Cycloalkyl; und
S^* ein chirales Schwefelatom mit (R)-Stereochemie darstellt;
oder pharmazeutisch annehmbare Salze, Enantiomere, Mischungen von Enantiomeren, Diastereomere, Mischungen von Diastereomeren, Hydrate und Solvate davon.

2. Verbindung nach Anspruch 1, wobei R^1 Phenyl oder Phenoxy ist, optional substituiert mit einem von R^3.

3. Verbindung nach Anspruch 1 oder 2, wobei R^3 Fluor ist.

4. Verbindung nach einem der Ansprüche 1-3, wobei R^2 Piperidinyl, Pyrrolidinyl oder Tetrahydropyranyl ist, von denen alle optional mit einem oder mehreren Substituenten unabhängig ausgewählt aus R^4 substituiert sind.

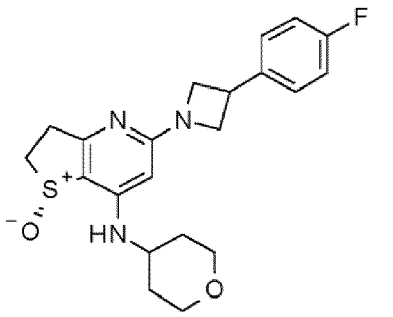
5. Verbindung nach Anspruch 4, wobei R^2 Tetrahydropyranyl ist.

6. Verbindung nach einem der vorhergehenden Ansprüche ausgewählt aus der Gruppe bestehend aus

(1R)-5-(3-(4-Fluorphenyl)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridin-1-oxid;
Methyl-(3R)-3-[[(1R)-5-[3-(4-fluorphenyl)azetidin-1-yl]-1-oxido-2,3-dihydrothieno-[3,2-b]pyridin-7-yl]amino]piperidin-1-carboxylat;
Methyl-(3R)-3-[[(1R)-5-(3-(4-phenylazetidin-1-yl)-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]piperidin-1-carboxylat;
(1R)-5-(3-(4-Fluorphenoxy)azetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridin-1-oxid;
Methyl-(3S)-3-[[(1R)-5-[3-(4-fluorphenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]pyrolidin-1-carboxylat;
1-[(3 S)-3-[[(1R)-5-[3-(4-Fluorphenoxy)azetidin-1-yl]-1-oxido-2,3-dihydrothieno[3,2-b]pyridin-7-yl]amino]pyrrolidin-1-yl]ethenon;

(1R)-5-(3-Phenylazetidin-1-yl)-7-((tetrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothieno[3,2-b]pyridin-1-oxid; oder einem pharmazeutisch annehmbaren Salz, Enantiomer, Mischung von Enantiomeren, Diastereomer, Mischung von Diastereomeren, Hydrat und Solvat davon.

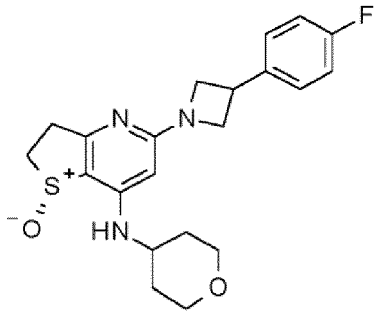
7. Verbindung nach einem der vorhergehenden Ansprüche, wobei die Verbindung die folgende Struktur aufweist:



,

oder ein pharmazeutisch annehmbares Salz, Enantiomer, Mischung von Enantiomeren,

8. Verbindung nach einem der vorhergehenden Ansprüche, wobei die Verbindung die folgende Struktur aufweist:



oder ein pharmazeutisch annehmbares Salz, Hydrat oder Solvat davon.

9. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1-8 zusammen mit einem pharmazeutisch annehmbaren Vehikel oder Hilfsstoff oder (einem) pharmazeutisch annehmbaren Träger(n).

10. Verbindung nach einem der Ansprüche 1-8 zur Verwendung als Medikament.

11. Verbindung nach einem der Ansprüche 1-8 zur Verwendung bei der Behandlung oder Besserung einer/eines dermalen Erkrankung, Störung oder Zustands, einer entzündlichen allergischen Erkrankung, einer Autoimmunerkrankung, einer akuten oder chronischen Hautwundstörung, einer Erkrankung des zentralen Nervensystems, Organopathie in Verbindung mit ischämischem Reflux verursacht durch Herzinsuffizienz, Schock und zerebrovaskuläre Erkrankungen, oder insulinresistenter Diabetes.

12. Verbindung zur Verwendung nach Anspruch 11, wobei die Verwendung in der Behandlung oder Besserung einer/eines dermalen Erkrankung, Störung oder Zustands ist.

13. Verbindung zur Verwendung nach Anspruch 12, wobei die/der dermale Erkrankung, Störung oder Zustand ausgewählt ist aus der Gruppe bestehend aus proliferativen und entzündlichen Hautstörungen, Dermatitis, atopischer Dermatitis, seborrhoischer Dermatitis, Kontaktdermatitis, beinhaltend irritative Kontaktdermatitis und allergische Kontaktdermatitis, Handdermatitis, Psoriasis, Psoriasis vulgaris, inverser Psoriasis, Psoriasis-Arthritis, Spondyloarthritis, epidermaler Entzündung, Alopezie, Alopecia areata, Rosacea, Hautatrophie, steroidinduzierter Hautatrophie, Photohautalterung, SAPHO-Syndrom (Synovitis, Akne, Pustulose, Hyperostose und Osteitis), Akne vulgaris, Hidradenitis suppurativa, Urtikaria, Juckreiz und Ekzem.

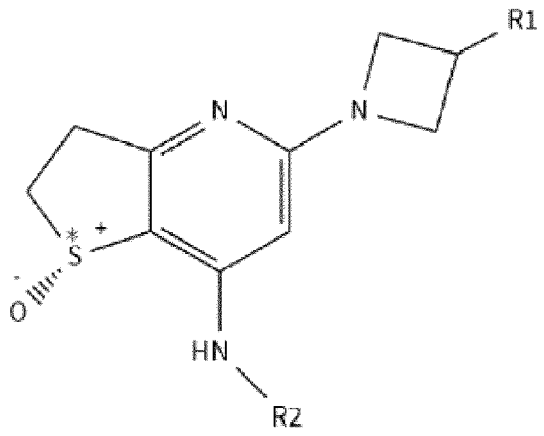
14. Verbindung zur Verwendung nach Anspruch 13, wobei die/der dermale Erkrankung, Störung oder Zustand eine entzündliche Hautstörung ist.

15. Verbindung zur Verwendung nach Anspruch 13, wobei die/der dermale Erkrankung, Störung oder Zustand Dermatitis, atopische Dermatitis, seborrhoische Dermatitis, Kontaktdermatitis, beinhaltend irritative Kontaktdermatitis und allergische Kontaktdermatitis, oder Handdermatitis ist.

16. Verbindung zur Verwendung nach einem der Ansprüche 10-15, wobei die Verbindung in Kombination mit einer weiteren aktiven Verbindung verwendet wird.

Revendications

1. Composé de formule générale (I)



(I)

où :

R^1 est sélectionné dans le groupe constitué de phényle, hétéroaryle à 6 chaînons, phénoxy et hétéroaryloxy à 6 chaînons ; qui sont tous optionnellement substitués par un ou plusieurs substituants indépendamment sélectionnés dans R^3; et
R^2 est sélectionné dans le groupe constitué de $(C_3\text{-}C_7)$cycloalkyle, $(C_3\text{-}C_7)$cycloalkyle et hétérocycloalkyle (4-7 chaînons) pontés ; qui sont tous optionnellement substitués par un ou plusieurs substituants indépendamment sélectionnés dans R^4 ; et
R^3 est sélectionné dans le groupe constitué de : halogène, -CN, $(C_1\text{-}C_4)$alkyle, halo$(C_1\text{-}C_4)$alkyle, hydroxy$(C_1\text{-}C_4)$alkyle et $(C_3\text{-}C_6)$cycloalkyle ; et
R^4 est sélectionné dans le groupe constitué de : fluoro, -CN, -OH, $(C_1\text{-}C_4)$alkyle, halo$(C_1\text{-}C4)$alkyle, hydroxy$(C_1\text{-}C_4)$alkyle, $-OR^x$, $-S(O)_2R^x$, $-S(O)_2NR^aR^b$, $-C(O)R^x$, $-C(O)(OR^x)$, et $-C(O)NR^aR^b$; et
R^x est sélectionné dans le groupe constitué de $(C_1\text{-}C_4)$alkyle et $(C_3\text{-}C_6)$cycloalkyle ; et
R^a et R^b sont indépendamment sélectionnés dans le groupe constitué de : hydrogène, $(C_1\text{-}C_4)$alkyle et $(C_3\text{-}C_6)$cycloalkyle ; et
S^* représente un atome de soufre chiral avec (R) stéréochimie ;
ou des sels, énantiomères, mélanges d'énantiomères, diastéréomères, mélanges de diastéréomères, hydrates et solvates de qualité pharmaceutique de ces éléments.

2. Composé selon la revendication 1, dans lequel R^1 est phényle ou phénoxy, optionnellement substitué par l'un de R^3.

3. Composé selon la revendication 1 ou 2, où R^3 est fluoro.

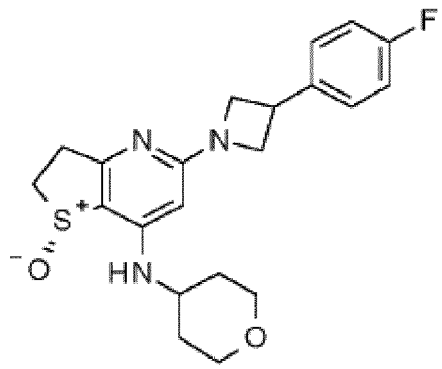
4. Composé selon l'une quelconque des revendications 1-3, où R^2 est pipéridinyle, pyrrolidinyle ou tétrahydropyranyle, qui sont tous optionnellement substitués par un ou plusieurs substituants indépendamment sélectionnés dans R^4.

5. Composé selon la revendication 4, où R^2 est tétrahydropyranyle.

6. Composé selon l'une quelconque des revendications précédentes, sélectionné dans le groupe constitué de

(1R)-5-(3-(4-Fluorophényl)azétidin-1-yl)-7-((tétrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothiéno[3,2-b]pyridine 1-oxyde ;
Méthyl(3R)-3-[[(1R)-5-[3-(4-fluorophényl)azétidin-1-yl]-1-oxydo-2,3-dihydrothiéno-[3,2-b]pyridin-7-yl]amino]pipéridine-1-carboxylate ;
Méthyl(3R)-3-[[(1R)-5-(3-(4-phénylazétidin-1-yl)-1-oxydo-2,3-dihydrothiéno[3,2-b]pyridin-7-yl]amino]pipéridine-1-carboxylate ;
(1R)-5-(3-(4-Fluorophénoxy)azétidin-1-yl)-7-((tétrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothiéno[3,2-b]pyridine-1-oxyde ;
Méthyl(3S)-3-[[(1R)-5-[3-(4-fluorophénoxy)azétidin-1-yl]-1-oxydo-2,3-dihydrothiéno[3,2-b]pyridine-7-yl]amino]pyrolidine-1-carboxylate ;
1-[(3S)-3-[[(1R)-5-[3-(4-Fluorophénoxy)azétidin-1-yl]-1-oxydo-2,3-dihydrothiéno[3,2-b]pyridin-7-yl]amino]pyrrolidin-1-yl]éthénone ;
(1R)-5-(3-Phénylazétidin-1-yl)-7-((tétrahydro-2H-pyran-4-yl)amino)-2,3-dihydrothiéno[3,2-b]pyridine-1-oxyde ;
ou sel, énantiomère, mélange d'énantiomètres, diastéréomère, mélange de diastéréomères, hydrate et solvate de qualité pharmaceutique de ces éléments.

7. Composé selon l'une quelconque des revendications précédentes, le composé ayant la structure



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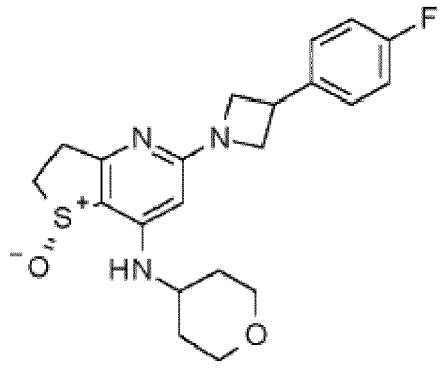
ou sel, énantiomère, mélange d'énantiomères, hydrate ou solvate de qualité pharmaceutique dudit composé.

8. Composé selon l'une quelconque des revendications précédentes, le composé ayant la structure



1

ou sel, hydrate ou solvate de qualité pharmaceutique dudit composé.

9. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1-8 conjointement avec un véhicule ou excipient de qualité pharmaceutique ou un ou des supports de qualité pharmaceutique.

10. Composé selon l'une quelconque des revendications 1-8, pour utilisation comme médicament.

11. Composé selon l'une quelconque des revendications 1-8 pour utilisation dans le traitement ou l'amélioration d'une maladie, d'une affection ou d'un trouble cutané, d'une maladie allergique inflammatoire, d'une maladie auto-immune, d'un trouble à lésion cutanée aiguë ou chronique, d'une maladie du système nerveux central, d'une organopathie associée à un reflux ischémique causé par une insuffisance cardiaque, un choc et des maladies cérébrovasculaires, ou d'un diabète insulino-résistant.

12. Composé pour utilisation selon la revendication 11, où l'utilisation est dans le traitement ou l'amélioration d'une maladie, d'une affection ou d'un trouble cutané.

13. Composé pour utilisation selon la revendication 12, où la maladie, l'affection ou le trouble cutané est sélectionné dans le groupe constitué de : troubles cutanés prolifférants et inflammatoires, dermatite, dermatite atopique, dermatite séborrhéique, dermatite de contact, y compris dermatite de contact irritative et dermatite de contact allergique, dermatite des mains, psoriasis, psoriasis simple, psoriasis inversé, polyarthrite psoriasique, spondyloarthrite, inflammation épidermique, alopécie, alopécie en aires, rosacée, atrophie cutanée, atrophie cutanée due aux stéroïdes, photovieillissement cutané, syndrome SAPHO, (synovite, acné, pustulose, hyperostose et ostéite), acné simple, hidrosadénite suppurée, urticaire, prurit, et eczéma.

14. Composé pour utilisation selon la revendication 13, où la maladie, l'affection ou le trouble cutané est un trouble cutané inflammatoire.

15. Composé pour utilisation selon la revendication 13, où la maladie, l'affection ou le trouble cutané est : dermatite, dermatite atopique, dermatite séborrhéique, dermatite de contact, y compris dermatite de contact irritative et dermatite de contact allergique ou dermatite des mains.

16. Composé pour utilisation selon l'une quelconque des revendications 10-15, où le composé est utilisé en combinaison avec un autre composé actif.

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