Abstract: A compound of formula (I) wherein at least one of X and Y is N and the other of X or Y is either N or CR. Such compounds may be useful in the therapy of inflammatory disorders, allergic disorders, dermatological disorders, autoimmune disease, lymphatic disorders, and immunodeficiency disorders.
PYRIDOPYRIMIDINES AND THEIR THERAPEUTIC USE

Field of the Invention

The present invention relates to compounds based on the pyrido[2,3-d]pyrimidine scaffold, and their therapeutic use. More particularly, it relates to compounds, pharmaceutical compositions containing them, and their use for the modulation of the histamine H₄ receptor and for the treatment of disease states, disorders and conditions mediated by histamine H₄ receptor activity.

Background of the Invention

The histamine H₄ receptor (H₄R) is a recently identified receptor for histamine. It is part of the histamine receptor family that also consists of the histamine H₁ receptor (H₁R), histamine H₂ receptor (H₂R) and histamine H₃ receptor (H₃R). Modulation of H₄ receptors controls the release of inflammatory mediators and inhibits leukocyte recruitment, thus providing the ability to prevent and/or treat H₄-mediated diseases and conditions, including the deleterious effects of allergic responses such as inflammation. In some cases it may be beneficial to also simultaneously modulate the H₁R or H₃R in addition to the H₄R and with which certain compounds described herein interact.


WO2006/135993 discloses pyrido (3,2-d) pyrimidines for treating hepatitis C.

WO2009/003669 discloses pyrido (3,2-d) pyrimidines for use as immunosuppressive agents.

Summary of the Invention

In one aspect, the invention relates to compounds of formula (I)
A compound according to claim 1, for use in the therapy of a condition selected from inflammatory disorders, allergic disorders, dermatological disorders, autoimmune disease, lymphatic disorders, and immunodeficiency disorders.

A compound of formula (I):

\[
\begin{array}{c}
\text{wherein:}
\end{array}
\]
at least one of X and Y is N and the other of X or Y is either N or CR₂:
R₂ is H, Ci-C₄ alkyl, C₂-C₅ alkenyl or C₂-C₅ alkynyl;
R₆, R₇ and R₈ are independently selected from H, halogen, C₁₄ alkyl, C₂-5 alkenyl, C₂-5 alkynyl, C₁₄ alkoxy, C₁₄ alkylthio, (CH₂)₃₋₅C₃₋₅cycloalkyl, O-C₃₋₅ cycloalkyl, aryl, O-aryl, NH-aryl, S-aryl, O-Ci₋₄ alkyl-aryl, C₁₄ alkyl-aryl, CF₃, O-CF₃, S-CF₃, hydroxy, nitro, cyano, 0-Ci₋₄ alkyl-N(CH₃)₂, heteroaryl, O-heteroaryl, NH - heteroaryl, S-heteroaryl, C₁₋₄ alkyl-heteroaryl, Cl-C₄ alkyl-heteroaryl and NRmRn, wherein Rm and Rn are independently selected from H, C₁₋₄ alkyl, aryl and phenethyl;
R₃ and R₄ are independently selected from H, halogen, C₁₋₄ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, (CH₂)₀₋₅C₅₋₇cycloalkyl, O-C₅₋₇ cycloalkyl, aryl, O-aryl, NH-aryl, S-aryl, O-Ci₋₄ alkyl-aryl, C₁₋₄ alkyl-aryl, CF₃, O-CF₃, S-CF₃, hydroxy, nitro, cyano, O-Ci₋₄ alkyl-N(CH₃)₂, heteroaryl, O-heteroaryl, NH - heteroaryl, S-heteroaryl, Ci-C₄ alkyl-heteroaryl, Cl-C₄ alkyl-heteroaryl and NRmRn, wherein Rm and Rn are independently selected from H, C₁₋₄ alkyl, aryl and phenethyl, or R₃ and R₄, are taken together with the attached C atoms to form a 5-7 membered cycloalkyl ring;
wherein any alkyl, cycloalkyl, aryl or heteroaryl group mentioned above can independently be optionally substituted with one or more substituents selected from halogen C₁₋₄ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, (CH₂)₀₋₅C₅₋₇cycloalkyl, O-C₅₋₇ cycloalkyl, aryl, O-aryl, heteroaryl, NH-aryl, S-aryl, O-Ci₋₄ alkyl-aryl, C₁₋₄ alkyl-aryl, CF₃, O-CF₃, S-CF₃, hydroxy, nitro amino, cyano and O-Ci₋₄ alkyl-N(CH₃)₂;
  n is 1, 2 or 3; and
  m is 0, 1 or 2,
or a pharmaceutically acceptable salt or ester thereof.

Description of the Invention

The term "alkyl" as used herein includes straight-chain and branched hydrocarbon groups. Examples are methyl, ethyl, propyl and isopropyl. Preferably, it contains 1 to 6, more preferably 1 to 4 carbon atoms.

The term "alkenyl" as used herein includes straight-chain and branched hydrocarbon groups as above with at least one carbon-carbon double bond (sp²). Preferably, it contains 2 to 6, more preferably 2 to 4 carbon atoms.

The term "alkynyl" as used herein includes straight-chain and branched hydrocarbon groups as above with at least one carbon-carbon triple bond (sp).
Hydrocarbons having a mixture of double bonds and triple bonds are grouped as alkynyls herein. Preferably, it contains 2 to 6, more preferably 2 to 4 carbon atoms.

The term "alkoxy" as used herein includes straight-chain and branched alkyl groups with a terminal oxygen linking the alkyl group to the rest of the molecule. Alkyl is as defined above.

The term "aryl" as used herein includes any functional group or substituent comprising an aromatic ring and from 4 to 8 ring atoms. In particular the aryl may be selected from moieties comprising a phenyl, benzyl, naphthyl or biphenyl. The aryl may comprise one or more heteroatoms, in which case the aryl may be referred to as "heteroaryl". Preferred examples of heteroaryl groups include pyridine, furane, thiophene, pyrrole, imidazole, thiazole, oxazole, and triazole.

The term "cycloalkyl" as used herein includes saturated or partially saturated, monocyclic, fused polycyclic, or spiro polycyclic carbocycle having from 3 to 7 ring atoms per carbocycle. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and bicyclo[2.1.1]hex-2-ylidene.

The term "heterocyclic" refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated or partially saturated and has from 4 to 8 ring atoms per ring structure selected from carbon atoms and up to three heteroatoms selected from nitrogen, oxygen and sulfur. The ring structure may optionally contain up to two oxo groups in carbon or sulfur ring members.

All groups defined above may be optionally substituted by one or more substituents (preferably 1, 2 or 3, with the upper limit dependent on the valency of the member being substituted, and known to the skilled person) selected from halogen C_1-4 alkyl, C_2-5 alkenyl, C_2-5 alkynyl, C_1-4 alkoxy, C_1-4 alkylthio, (CH_2)_0-3C_3, 7 cycloalkyl, 0-C_3-6 cycloalkyl, aryl, O-aryl, heteroaryl, NH-aryl, S-aryl, 0-Cl C_1-4 alkyl-aryl, C_1-4 alkyl-aryl, CF_3, 0-CF_3, S-CF_3, hydroxy, nitro amino, cyano and O-C_1-4 alkyl-N(CH_3)_2.

It is understood that substitutions and combinations of substitutions recited herein refer to substitutions that are consistent with the valency of the member being substituted.

Preferably, at least one of R_3 and R_4 is H. Preferably, R_4 is H.
Preferably, \( R_4 \) is H and \( R_3 \) is selected from Ci-C_4 alkyl, cycloalkyl, cyano or halogen.

Preferably, \( R_1 \) is structure K or B or I. When the structure is B or K, preferably, each \( R_6 \) is independently selected from H or Ci-C_4 alkyl.

Preferably, \( X \) is N.

Preferably, \( Y \) is CR_2.

Preferably, \( R_2 \) is H.

Preferably, when \( Y \) is CR_2, \( R_2 \) is H.

The "pharmaceutically acceptable salt, ester or solvate thereof" refers to those salts, ester forms and solvates of the compounds of the present invention that would be apparent to the pharmaceutical chemist, i.e. those that are non-toxic and that would favourably affect the pharmacological properties of said compounds of the present invention. Those compounds having favourable pharmacological properties would be apparent to the pharmaceutical chemist, i.e. those that are non-toxic and that possess such pharmacological properties to provide sufficient palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, that are important in the selection are cost of raw materials, ease of crystallisation, yield, stability, hygroscopicity, and flowability of the resulting bulk drug.

Representative acids that may be used in the preparation of pharmaceutically acceptable salts include but are not limited to the following: acetic acid, 2,2-dichlorolactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulphonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulphonic acid, (+)-(1S)-camphor-10-sulphonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulphuric acid, ethane-1,2-disulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, a-oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactid acid, (t)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulphonic acid, naphthalene-2-sulphonic acid naphthalene-1,5-disulphonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid,
L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulphuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulphonic acid and undecylenic acid.

Representative bases that may be used in the preparation of pharmaceutically acceptable salts include the following: ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazone, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

Examples of suitable esters include C$_{1,7}$ alkyl, C$_{5,7}$ cycloalkyl, phenyl, substituted phenyl, and phenyl-d-6 alkyl esters. Preferred esters include methyl esters.

Any formula given herein is also intended to represent unlabelled forms as well as isotopically labelled forms of the compounds. Isotopically labelled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as $^2$H, $^3$H, $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, $^{36}$Cl, $^{127}$I, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with $^{14}$C), reaction kinetic studies (with, for example $^2$H or $^3$H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{18}$F or $^{11}$C labelled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labelled compounds of this invention can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.
The present invention includes prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible in vivo into the bio-active compound. Thus, in the uses of the compounds for methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound that may not be specifically disclosed, but that converts to the specified compound in vivo after administration to the patient. Analogously, the term "compound", when applied to compounds of this invention, shall encompass any specific compound according to the present invention or any compound (or prodrug) that converts to the specifically disclosed compound in vivo after administration, even if such prodrug is not explicitly disclosed herein.

Examples of prodrugs include compounds having an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino or hydroxyl group of a compound of formula (I). Examples of amino acid residues include the twenty naturally occurring amino acids, commonly designated by three letter symbols, as well as 4-hydroxyproline, hydroxylsine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.


An active agent of the present invention may be administered to treat inflammation. Inflammation may be associated with various diseases, disorders, or conditions, such as inflammatory disorders, allergic disorders, dermatological
disorders, autoimmune disease, lymphatic disorders, and immunodeficiency disorders and cancer, including the more specific conditions and diseases given below. Regarding the onset and evolution of inflammation, inflammatory diseases or inflammation-mediated diseases or conditions include, but are not limited to, acute inflammation, allergic inflammation, and chronic inflammation.

Illustrative types of inflammation treatable with a histamine H$_4$ receptor-modulating agent according to the invention include inflammation due to any one of a plurality of conditions such as allergy, asthma, dry eye, chronic obstructed pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (including colitis, Crohn's disease, and ulcerative colitis), psoriasis, pruritis, itchy skin, atopic dermatitis, urticaria (hives), ocular inflammation (e.g., post-surgical ocular inflammation), conjunctivitis (e.g. allergic conjunctivitis or vernal keratoconjunctivitis), dry eye, nasal polyps, allergic rhinitis, nasal itch, scleroderma, autoimmune thyroid diseases, immune-mediated (also known as type 1) diabetes mellitus and lupus, which are characterised by excessive or prolonged inflammation at some stage of the disease. Other autoimmune diseases that lead to inflammation include Myasthenia gravis, autoimmune neuropathies, such as Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, such as Wegener's granulomatosis, Behcet's disease, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland, polymyositis, dermatomyositis, spondyloarthopathies, such as ankylosing spondylitis, and Sjogren's syndrome.

Pruritis treatable with a histamine H$_4$ receptor-modulating agent according to the invention includes that which is a symptom of cutaneous diseases (such as atopic dermatitis, urticaria and hives) and other metabolic disorders (such as chronic renal failure, hepatic cholestasis, and diabetes mellitus). Pruritis treatable with a histamine H$_4$ receptor-modulating agent according to the invention includes that which is a side-effect of administered drugs (i.e. drug-induced pruritis). A well known example is opiate-induced pruritis resulting from the administration of opiates.
In a preferred embodiment, an active agent of the present invention is administered to treat allergy, asthma, autoimmune diseases, or pruritis.

Thus, the active agents may be used to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through histamine H₄ receptor activity. The term "treat" or "treating" as used herein is intended to refer to administration of an active agent or composition of the invention to a subject for the purpose of effecting a therapeutic or prophylactic benefit through modulation of histamine H₄ receptor activity. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity of, or preventing a disease, disorder, or condition, or one or more symptoms of such disease, disorder or condition mediated through modulation of histamine H₄ receptor activity. The term "subject" refers to a mammalian patient in need of such treatment, such as a human. "Modulators" include both inhibitors and activators, where "inhibitors" refer to compounds that decrease, prevent, inactivate, desensitize or down-regulate histamine H₄ receptor expression or activity, and "activators" are compounds that increase, activate, facilitate, sensitize, or up-regulate histamine H₄ receptor expression or activity.

In treatment methods according to the invention, an effective amount of at least one active agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. An "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition. When referring to modulating the target receptor, an "effective amount" means an amount sufficient to affect the activity of such receptor. Measuring the activity of the target receptor may be performed by routine analytical methods. Target receptor modulation is useful in a variety of settings, including assays. Effective amounts or doses of the active agents of the present invention may be ascertained by routine methods such as modelling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An exemplary dose is in the range of from
about 0.001 to about 200 mg of active agent per kg of subject's body weight per
day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, or
about 0.1 to 10 mg/kg daily in single or divided dosage units (e.g., BID, TID,
QID). For a 70-kg human, an illustrative range for a suitable dosage amount is
from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

Once improvement of the patient's disease, disorder, or condition has
occurred, the dose may be adjusted for preventative or maintenance treatment.
For example, the dosage or the frequency of administration, or both, may be
reduced as a function of the symptoms, to a level at which the desired
therapeutic or prophylactic effect is maintained. Of course, if symptoms have
been alleviated to an appropriate level, treatment may cease. Patients may,
however, require intermittent treatment on a long-term basis upon any
recurrence of symptoms.

In addition, the active agents of the invention may be used in combination
with additional active ingredients in the treatment of the above conditions. The
additional active ingredients may be co-administered separately with an active
agent of formula (I) or included with such an agent in a pharmaceutical
composition according to the invention. In an exemplary embodiment, additional
active ingredients are those that are known or discovered to be effective in the
treatment of conditions, disorders, or diseases mediated by histamine H₄
receptor activity, such as another histamine H₄ receptor modulator or a
compound active against another target associated with the particular condition,
disorder, or disease. The combination may serve to increase efficacy (e.g., by
including in the combination a compound potentiating the potency or
effectiveness of an agent according to the invention), decrease one or more side
effects, or decrease the required dose of the active agent according to the
invention.

The active agents of the invention are used, alone or in combination with
one or more additional active ingredients, to formulate pharmaceutical
compositions of the invention. A pharmaceutical composition of the invention
comprises an effective amount of at least one active agent in accordance with
the invention. Such compositions may further comprise a pharmaceutically
acceptable excipient.
A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

For oral administration, the active agents of the invention can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the active agents may be formulated to yield a dosage of, e.g., from about 0.05 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like.

Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated
with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilised or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

The active agents of this invention may also be administered by non-oral routes. For example, compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the agents of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 [mu]/kg/minute of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

For topical administration, the agents may be mixed with a pharmaceutical carrier at a concentration of about 0.1 % to about 10% of drug to
vehicle. Another mode of administering the agents of the invention may utilize a patch formulation to affect transdermal delivery.

Active agents may alternatively be administered in methods of this invention by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

The compounds of the invention can be prepared according to processes within the skill of the art and/or according to processes of this invention, such as those described in the schemes and examples that follow and by matrix or combinatorial methods.

Illustrative preparations are presented in the following Schemes. Other compounds of the invention may be made in the same general way, using modifications that will be apparent to those of ordinary skill in the art.

The following Examples illustrate the invention.

**Examples**

**Scheme 1**

![Chemical structure diagram]

- **Reagents and conditions.**
  1. potassium vinyl trifluoroborate, Pd(PPh$_3$)$_4$, PhCH$_3$, trifluoroethanol, MW, 130 °C. ii. H$_2$/Pd/10% C, EtOH, r.t. iii. a. Choroform amidine, dimethyl sulphone, sulfolane, 165 °C. b. TsCl, K$_2$CO$_3$, CH$_3$CN, Δ. iv. methylpiperazine, DIPEA, 1,4-dioxane, rt.

**Ethyl 3-amino-5-vinylpicolinate**

A mixture of 3-amino-5-bromo-pyridine-2-carboxilic ester (100 mg, 415 µmol), Pd(PPh$_3$)$_4$ (25 mg, 21 µmol), potassium vinyl trifluoroborate (77 mg, 498 µmol), PhCH$_3$ (2.6 mL), and EtOH (1.4 mL). The mixture was degassed with nitrogen for 10 min and the vial was closed. The mixture was heated at 130 °C
for 30 minutes by microwave irradiation, cooled down to r.t., filtered, washed with EtOH (25 mL) and the solvent removed by evaporation. The crude was purified by silica gel column chromatography eluted with ethyl acetate:pentane, 1:1, v/v. Yield: 90%, 72 mg; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.55 (d, \(J = 2.5\) Hz, 1H), 6.94 (d, \(J = 2.5\) Hz, 1H), 6.56 (dd, \(J = 17.5\) and 12.5 Hz, 1H), 5.38 (d, \(J = 10\) Hz), 4.37 (q, \(J = 7.5\) Hz, 2H), 1.38 (t, \(J = 7.5\) Hz, 3H); MS (ESI) m/z 193.

**Ethyl 3-amino-ethylpicolinate**

A suspension of ethyl 3-amino-5-vinylpicolinate (930 mg, 4.84 mmol), Pd 10% C (15 mg) and trifluoroethanol (15 mL) was stirred at r.t. for 3 hours. Then, the mixture was filtered, the solvent removed by evaporation and the crude purified by silica gel column chromatography eluted with ethyl acetate:hexane, 1:4, v/v. Yield: 86%, 808 mg; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.87 (d, \(J = 2.5\) Hz, 1H), 6.77 (s, 1H), 5.60 (se, 2H), 4.37 (q, \(J = 7.5\) H, 2H), 2.53 (q, \(J = 7.5\) H, 2H), 1.38 (t, \(J = 7.5\) Hz, 3H), 1.16 (t, \(J = 7.5\) Hz, 3H); MS (ESI) m/z 195.

**2-amino-7-ethylpyrido[3,2-d]pyridine-4-yl 4-methylbenzenesulfolane**

A mixture of ethyl 3-amino-ethylpicolinate (200 mg, 1.03 mmol), chloroform amide hydrochloride (1.17 g, 10.31 mmol), dimethylsulfoxone (200 mg, 2.06 mmol), and sulfolane (100 \(\mu\)L) was stirred at 120 °C for 1 hour. Then 5 mL of water was added, the mixture neutralized to pH 7 with NaOH 1M aq. solution, filtered, washed with acetone and dried. Then a suspension of the obtained crude, K₂C₂O₃ (211 mg, 1.55 mmol), tosyl chloride (236 mg, 1.24 mmol) and CH₃CN (10 mL) was heated at 110 °C and stirred for 2 hours. The reaction mixture was cooled down to r.t and filtered. The solvent was removed by evaporation and the crude purified by silica gel chromatography eluted with ethyl acetate. Yield: 15%, 53 mg; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.53 (d, \(J = 4.0\) Hz, 1H), 8.08 (d, \(J = 8.0\) Hz, 2H), 7.58 (d, \(J = 4.0\) Hz, 1H), 7.37 (d, \(J = 8.0\) Hz, 2H), 5.55 (se, 2H), 2.79 (q, \(J = 7.5\) H, 2H), 2.46 (s, 3H), 1.31 (t, \(J = 7.5\) Hz, 3H); MS (ESI) m/z 345.

**7-ethyl-4-(4-methylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-2 -amine**

A solution of 2-amino-7-ethylpyrido[3,2-d]pyridine-4-yl 4-methylbenzenesulfolane (50 mg, 145 \(\mu\)mol), 1-methylpiperazine (33 \(\mu\)L, 291 \(\mu\)mol), DIEPA (52 \(\mu\)L, 304 \(\mu\)mol), and 1,4-dioxane (1 mL) was stirred at r.t. for 1
hour after which the solvent was removed. The crude product was dissolved in ethyl acetate (15 mL), washed with water 10 mL and brine (2x10 mL), the organic layer dried over MgSO$_4$, filtered and the solvent removed by evaporation. The crude was purified over silica gel eluting with CHCl$_3$/MeOH/TEA : 90/5/5, v/v/v. Yield: 21%, 20 mg; $^1$H NMR (CDCl$_3$) $\delta$ 8.26 (s, 1H), 7.49 (s, 1H), 4.84 (se, 2H), 4.42 (se, 4H), 2.73 (q, $J = 7.5$ Hz, 2H), 2.54 (m, 4H), 2.33 (s, 3H), 1.29 (t, $J = 7.5$ Hz, 3H); MS (ESI) m/z 273.

Scheme 2$^a$

Reagents and conditions. i. Urea, 160 °C, 0.2 M NaOH. ii. POCI$_3$, DIPEA, PhCH$_3$, 130 °C. iii. a. azetidin-3-ylmethyl-carbamic acid tert-butyl ester, DIPEA, 1,4-Dioxane, rt; b. NH$_3$/EtOH, MW, 150 °C. iv. a. potassium vinyltetrafluoroborate, Pd(PPh$_3$)$_4$, PhCH$_3$, EtOH, Mw, 130 °C; b. H$_2$/Pd/10% C, EtOH, r.t.. v. Zn(CN)$_2$, Pd(PPh$_3$)$_4$, DMF, Mw, 150°C. vi HCl (4M) in 1,4-Dioxane, rt.
7-bromopyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione

A mixture of 3-amino-5-bromo-pyridine-2-carboxilic ester (4.0 g, 18.5 mmol) and urea (11.11 g, 185 mmol) was stirred at 160 °C for 6 hours. Then 50 mL of water was added, the mixture cooled down to room temperature and filtered. The obtained crude was dissolved in a 0.2 M solution of NaOH (50 mL) stirred again at 100 °C for 20 min and cooled down to room temperature. The solution was filtered, washed with H₂O/MeOH, 1/1, v/v and dried. Yield: 90%, 4.0 g; ¹H NMR (DMSO-d₆) δ 8.48 (d, J = 4.0 Hz, 1H), 7.74 (d, J = 4.0 Hz, 1H); MS (ESI) m/z 242.

7-bromo-2,4-dichloropyrido[3,2-d]pyrimidine

A suspension of 7-bromopyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (1.3 g, 5.39 mmol), POCl₃ (2 mL), DIPEA (2.1 mL, 11.32 mmol), and toluene (10 mL) was refluxed during 4 hours. The volatiles were evaporated and ice-water and dichloromethane were added to the crude. After stirring for 10 min the mixture was extracted with dichloromethane (3x50 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed by evaporation. The crude was purified by silica gel column chromatography eluting with ethyl acetate:hexane, 1:1, v/v. Yield: 62%, 932 mg. ¹H NMR (CDCl₃) δ 9.04 (d, J = 4 Hz, 1H), 8.42 (d, J = 4 Hz, 1H).

tert-butyl(1-(2-amino-7-bromopyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate

7-bromo-2,4-dichloropyrido[3,2-d]pyrimidine (510 mg, 2.12 mmol) was dissolved in dried 1,4-dioxane (10 mL), azetidin-3-ylmethyl-carbamic acid tert-butyl ester (524 mg, 4.24 mmol) and DIPEA (790 µL, 4.45 mmol) were added and the mixture was stirred at room temperature for 3 hours. Then, the solvent was removed, the crude dissolved in ethyl acetate, and the solution washed with water (20 mLx2), brine (20 mLx2) and ammonium chloride (20 mLx2). The organic layer was dried, filtered and the solvent removed by evaporation. The obtained crude was purified by silica gel column chromatography eluting with ethyl acetate. The compound was dissolved in a saturated solution of ethanol-ammonia (10 mL) and the solution heated by microwave irradiation at 150 °C for 30 minutes. Then, the solvent removed and the crude purified by a silica gel
column chromatography eluted with gradient of ethyl acetate and MeOH 100:0 to 95:5, v/v. Yield: 49%, 425 mg; $^1$H NMR (CDCl$_3$) δ 8.66 (d, $J = 4$ Hz, 1H), 8.12 (d, $J = 4$ Hz, 1H), 5.07 (m, 2H), 4.88 (m, 1H), 4.58 (m, 1H), 4.42 (m, 1H), 2.98 (s, 3H), 1.47 (s, 9H); MS (ESI) m/z 411.

**ferf-butyl (1-(2-amino-7-ethylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate**

A solution of tert-butyl (1-(2-amino-7-bromopyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (280 mg, 680 µmol), potassium vinyl trifluoroborate (110 mg, 820 µmol), palladium tetrakis (39 mg, 34 µmol), K$_2$CO$_3$ (189 mg, 1.37 mmol) and ethanol/toluene:1/2 (v/v) was degassed with nitrogen for 10 min. Then, the mixture was heated by microwave irradiation at 130 °C for 30 min. The solvent was removed, the crude dissolved in ethyl acetate and extracted, the organic layers dried over MgSO$_4$, filtered and the solvent removed by evaporation. The crude was purified by column chromatography eluting with ethyl acetate:hexanes, 1:1, v/v. The obtained compound was dissolved in ethanol and Pd/10% C (24 mg) was added. The resulting suspension was stirred under a hydrogen atmosphere at room temperature overnight. The suspension was filtered over celite and the solvent removed by evaporation. Yield: 67%, 581 mg; $^1$H NMR (CDCl$_3$) δ 8.20 (s, 1H), 7.41 (s, 1H), 5.29 (se, 2H), 5.00 (se, 2H), 4.78 (se, 1H), 4.26 (se, 1H), 4.25 (se, 1H), 2.68 (s, 3H), 2.67 (q, $J = 7.5$ Hz, 2H), 1.44 (s, 9H), 1.24 (t, $J = 7.5$ Hz, 3H); MS (ESI) m/z 359.

**7-ethyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine tert-butyl**

(1-(2-amino-7-ethylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3yl)(methyl)carbamate (80 mg, 196 µmol) was dissolved in 1,4-dioxane (2 mL), HCl 4 M (2 mL) was added and the mixture stirred at room temperature for 2 hours. Then, the solvent was removed by evaporation. The crude was dissolved in H$_2$O (10 mL), the solution basified to pH 12 and extracted with CHCl$_3$ (3x50 mL), the organic layers dried over MgSO$_4$, filtered and the solvent removed by evaporation. The crude was purified by silica gel column chromatography eluting with CHCl$_3$:MeOH:TEA, 90:5:5, v/v/v. Yield: 49%, 25 mg; $^1$H NMR (CDCl$_3$) δ 8.26 (d, $J = 4.0$ Hz, 1H), 7.48 (d, $J = 4.0$ Hz, 1H), 5.29 (se, 2H), 5.00 (se, 1H), 4.50 (se, 2H), 4.01 (se,
To a solution of tert-butyl (1-(2-amino-7-bromopyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (100 mg, 240 µmol) and Pd(PPh₃)₄ in DMF (5 mL) was added Zn(CN)₂ (57 mg, 488 µmol) and the mixture was heated by microwave irradiation to 150 °C for 30 min. Then, ethyl acetate (10 mL) was added and the solution was washed with water (10 mL), brine (10 mL) and ammonium chloride (10 mL). The organic phase was dried over MgSO₄, filtered and the solvent was removed by evaporation. The crude was dissolved in MeOH/H₂O, 1/1, v/v and the solution was heated by microwave irradiation to 150 °C for two hours. The solvent was removed by evaporation and the crude purified by silica gel chromatography eluted with CHCl₃:MeOH:TEA, 95:5:5, v/v/v. Yield: 25%, 15 mg; ¹H NMR (CDCl₃) δ 8.46 (d, J = 4.0 Hz, 1H), 7.88 (d, J = 4.0 Hz, 1H), 4.99 (se, 2H), 4.45 (se, 2H), 3.97 (se, 1H), 3.74 (m, 2H), 2.47 (s, 3H); MS (ESI) m/z 256.
**Scheme 3**

1. 2-cyano-3-nitro-5-bromo pyridine, CaCl₂, H₂O, EtOH, rt.
2. Chloroform amidine hydrochloride, dimethyl sulfone, sulfolane, 165 °C.
3. Ac₂O, Δ.
4. a. POCl₃, DIEA, PhCH₃, Δ. b. N,N-methyl-BOC-pyrolidine, DIPEA, 1,4-dioxane, rt.
5. v. a. propeneboronic acid, Pd(PPh₃)₄, PhCH₃, EtOH, MW, 130 °C; b. H₂/Pd/10% C, EtOH. vi. HCl (4M) in dioxane, 1,4-dioxane, rt.

**Reagents and conditions.**

- i. 2-cyano-3-nitro-5-bromo pyridine, CaCl₂, H₂O, EtOH, rt.
- ii. chloroform amidine hydrochloride, dimethyl sulfone, sulfolane, 165 °C.
- iii. Ac₂O, Δ.
- iv. a. POCl₃, DIEA, PhCH₃, Δ. b. N,N-methyl-BOC-pyrolidine, DIPEA, 1,4-dioxane, rt.
- v. a. propeneboronic acid, Pd(PPh₃)₄, PhCH₃, EtOH, MW, 130 °C; b. H₂/Pd/10% C, EtOH. vi. HCl (4M) in dioxane, 1,4-dioxane, rt.

3-amino-5-bromopicolinamide was synthesized according to a procedure from literature (Herdwijn, P. A.; Maurits, M. WO2006/1 35993).

2-amino-7-bromopyrido[3,2-d]pyrimidin-4-ol was synthesized according to a procedure from literature (Herdwijn, P. A.; Maurits, M. WO2006/1 35993).

N-(7-bromo-4-hydroxy pyrido[3,2-d]pyrimidin-2-yl)acetamide was synthesized according to a procedure from literature (Herdwijn, P. A.; Maurits, M. WO2006/1 35993).
(R)-tert-butyl (1-(2-acetamido-7-bromopyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate

A mixture of N-(7-bromo-4-hydroxypyrido[3,2-d]pyrimidin-2-yl)acetamide (1.0 g, 3.56 mmol), POCl₃ (6 mL), DIPEA (0.61 mL, 3.56 mmol) and PhCH₃ (10 mL) was refluxed for 3 hours. Then, the excess of POCl₃ was evaporated, ice-water was added to the crude, 40 mL of dichloromethane was added and the mixture was extracted with dichloromethane. The organic layers were dried over MgSO₄, filtered and the solvent was removed by evaporation. The obtained crude intermediate was directly dissolved in 1,4-dioxane (20 mL), and tert-Butyl N-methyl-N-[(3R)-pyrrolidin-3-yl]carbamate (800 mg, 4.01 mmol), and DIPEA (1.2 mL, 7.01 mmol). The mixture was stirred at room temperature for 3 hours. Then, the solvent was removed, the crude dissolved in ethyl acetate (25 mL), washed with water (20 mL), brine (20 mL×3), the organic phase dried over MgSO₄. The solvent was removed by evaporation and the obtained crude was purified by silica gel chromatography eluting with chloroform:diethyl ether, 1/1 v/v. Yield: 9%, 150 mg; ¹H NMR (CDCl₃) δ 8.53 (d, J = 4.0 Hz, 1H), 8.15 (s, 1H), 8.07 (d, J = 4.0 Hz, 1H), 4.99 (s, 1H), 4.85 (s, 1H), 4.61 (s, 1H), 4.01 (s, 1H), 3.64 (s, 1H), 2.59 (s, 3H), 2.33 (s, 2H), 1.42 (s, 9H). MS (ESI) m/z 465.

(R)-tert-butyl (1-(2-acetamido-7-isopropylpyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate

A mixture of (R)-tert-butyl (1-(2-acetamido-7-bromopyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (130 mg, 280 μmol), Pd(PPh₃)₄ (1.62 mg, 14 μmol), potassium carbonate (77 mg, 560 μmol), propeneboronic acid (57 mg, 336 μmol), ethanol (1 mL) and PhCH₃ (2 mL) was degassed with nitrogen for 10 min and the vial was closed. The mixture was heated at 130 ºC for 1 hour by microwave irradiation, cooled down to room temperature and washed with EtOAc (25 mL). The solvent was removed by evaporation and the crude was purified by silica gel column chromatography eluting with a gradient of ethyl acetate and methanol from 100:0 to 97.5:2.5, v/v. The purified compound was dissolved in ethanol 10 mL and Pd/ on 10% C was added. The suspension was stirred at room temperature under a hydrogen atmosphere for 3 hours. Then, the suspension was filtered over celite and the solvent removed by evaporation.
Yield: 47%, 53 mg; ¹H NMR (CDCl₃) δ 8.30 (s, 1H), 7.89 (s, 1H), 5.18 (s, 2H), 4.82 (se, 1H), 4.10 (se, 2H), 3.75 (m, 1H), 2.98 (m, 1H), 2.82 (s, 3H), 2.10 (m, 2H), 1.46 (s, 9H), 1.29 (d, J = 8.0 Hz, 6H). MS (ESI) m/z 387.

(R)-N-(7-isopropyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-yl)acetamide

A mixture of (R)-tert-butyl (1-(2-acetamido-7-isopropylpyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (44 mg, 114 µmol) HCl (4M) (400 µL) and 1,4-dioxane (1 mL) was stirred at r.t. for 4 hours. Then, the solvent was removed, 10 mL of water was added and the solution basified to pH 12 with 1 N NaOH aq. The aqueous phase was extracted with chloroform (2x20 mL), the organic layers were dried over MgSO₄ and the solvent was removed by evaporation. The crude was purified by silica gel chromatography eluted with CHCl₃:MeOH:TEA, 90:5:5, v/v/v. Yield: 49%, 15 mg; ¹H NMR (CDCl₃) δ 8.31 (s, 1H), 7.50 (s, 1H), 5.31 (s, 2H), 4.43 (se, 2H), 3.88 (se, 1H), 3.60 (m, 1H), 3.39 (m, 1H), 2.99 (m, 1H), 2.48 (s, 3H), 2.20 (m, 1H), 1.75 (se, 1H), 1.29 (d, J = 8.0 Hz, 6H). MS (ESI) m/z 287.
**Scheme 4**

a Reagents and conditions. i. Urea, 160 °C, 0.2 M NaOH. ii. PCl₅, POCl₃, Mw, 160 °C. iii. a. azetidin-3-ylmethyl-carbamic acid tert-butyl ester, DIPEA, 1,4-Dioxane, rt. iv. Pd(OAc)₂, Xantphos, K₂CO₃, AcNH₂, Mw, 130 °C. v. a. 2-(Cyclopenten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, Pd(PPh₃)₄, PhCH₃, EtOH, Mw, 130 °C; b. H₂/Pd/10% C, EtOH, r.t.. vi. HCl (4M) in 1,4-Dioxane, rt.

pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione was synthesized according to a procedure from literature (Abdellatif Tikad, Sylvain Routier, Mohamed Aksira, Jean-Michel Leger, Christian Jarry, and Gerald Guillaumet. Org. letters.; 2007, 4673-4676).

2,4,7-trichloropyrido[3,2-d]pyrimidine was synthesized according to a procedure from literature (Abdellatif Tikad, Sylvain Routier, Mohamed Aksira, Jean-Michel Leger, Christian Jarry, and Gerald Guillaumet. Org. letters.; 2007, 4673-4676).
tert-butyl (1-(2,7-dichloropyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate

The compound 2,4,7-trichloropyrido[3,2-d]pyrimidine (650 mg, 2.77 mmol) was dissolved in dried 1,4-dioxane (10 mL), azetidin-3-ylmethyl-carbamic acid tert-butyl ester (680 mg, 5.44 mmol) and DIPEA (1.03 mL, 5.83 mmol) were added and the mixture stirred at room temperature for 3 hours. Then, the solvent was removed, the crude dissolved in ethyl acetate, and the solution washed with water (20 mLx2), brine (20 mLx2) and ammonium chloride (20 mLx2). The organic layer dried, filtered and the solvent removed by evaporation. The obtained crude purified by a silica gel column chromatography eluted with ethyl acetate. Yield: 94%, 1.0 g; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.55 (d, \(J = 4\) Hz, 1H), 7.91 (d, \(J = 4\)H, 1H), 5.10 (m, 2H), 4.88 (m, 1H), 4.56 (m, 1H), 4.41 (m, 1H), 2.97 (s, 3H), 1.46 (s, 9H); MS (ESI) m/z 384.

tert-butyl (1-(2-acetamido-7-chloropyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate

A suspension of tert-butyl (1-(2,7-dichloropyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (200 mg, 520 \(\mu\)mol), acetamide (61 mg, 1.04 mmol), K\(_2\)CO\(_3\) (144 mg, 1.04 mmol), Pd(OAc)\(_2\) (6.5 mg, 26 \(\mu\)mol), Xantphos (30 mg, 52 \(\mu\)mol) and 1,4-dioxane (6 mL) was heated by microwave irradiation at 130°C for 30 min. then the solvent was removed, the crude dissolved in DCM (25 mL). Then 20 mL of water was added and the aqueous phase was extracted with DCM. The organic phases were dried over MgSO\(_4\), filtered and the solvent was removed by evaporation. Yield: 57%, 121 mg; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.44 (d, \(J = 4\) Hz, 1H), 7.85 (d, \(J = 4\)H, 1H), 7.76 (s, 1H), 5.06 (m, 2H), 4.86 (m, 1H), 4.49 (m, 1H), 4.34 (m, 1H), 2.99 (s, 3H), 2.59 (s, 3H), 1.46 (s, 9H); MS (ESI) m/z 407.

tert-butyl (1-(2-amino-7-cyclopentylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate

In a microwave vial, a mixture of tert-butyl (1-(2-acetamido-7-chloropyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (120 mg, 300 \(\mu\)mol), palladium tetrakis (36 mg, 30 \(\mu\)mol), 2-(Cyclopenten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 360 \(\mu\)mol), K\(_2\)CO\(_3\) (80 mg, 900 \(\mu\)mol) and PhCH\(_2\)/H\(_2\)O (2.6/1.4 mL) was degassed with nitrogen for 10 min. The mixture was heated at
130°C for 2 hours by microwave irradiation, cooled down to rt, filtered, washed with EtOH (25 mL) and the solvent was removed by evaporation. The crude was purified by silica gel column chromatography eluting with EtOAc 100% to EtOAc/MeOH, 95/5. The suspension of the obtained compound, Pd/10% C (32 mg) and EtOH (5 mL) was stirred at rt for 20 hours under a Hydrogen atmosphere. Then, the mixture was filtered over celite and washed with EtOH. The solvent was removed by evaporation and the crude purified by silica gel column chromatography eluting with EtOAc 100% to 95% and 5% MeOH. Yield: 42%, 50 mg; 1H NMR (CDCl₃) δ 8.28 (d, J = 4.0 Hz, 1H), 7.46 (d, J = 4.0 Hz, 1H), 5.00 (s, 3H), 4.79 (se, 1H), 4.47 (se, 1H), 4.30 (se, 1H), 3.70 (m, 1H), 3.07 (m, 1H), 2.97 (s, 3H), 2.16 (m, 3H), 1.72 (m, 2H), 1.74 (m, 4H), 1.47 (s, 9H); MS (ESI) m/z 399.

7-cyclopentyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine
tert-butyl (1-(2-amino-7-cyclopentylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (50 mg, 125 µmol) was dissolved in 1,4-dioxane (2 mL), HCl 4M (2 mL) was added and the reaction was stirred at rt. overnight. Then, the solvent was removed by evaporation. The crude was dissolved in H₂O (10 mL), the solution basified to pH 12 and extracted with CHCl₃ (10 mL×3). The organic layers were dried over MgSO₄, filtered and the solvent was removed by evaporation. The crude was purified by silica gel column chromatography eluting with CHCl₃:MeOH:TEA, 90:5:5, v/v/v. Yield: 27%, 10 mg; 1H NMR (CDCl₃) δ 8.29 (d, J = 4.0 Hz, 1H), 7.45 (d, J = 4.0 Hz, 1H), 4.95 (se, 1H), 4.83 (se, 2H), 4.48 (se, 2H), 3.95 (se, 1H), 3.71 (m, 1H), 3.07 (m, 1H), 2.46 (s, 3H), 2.10 (m, 2H), 1.83 (m, 2H), 1.74 (m, 4H); MS (ESI) m/z 299.
Scheme 5 a

Reagents and conditions.  

i. Urea, 160 °C, 0.2 M NaOH.  

ii. PCI, POCI₃, Mw, 160 °C.  

iii. a. azetidin-3-ylmethyl-carbamic acid tert-butyl ester, DIPEA, 1,4-Dioxane, rt.  

iv. Pd(OAc)₂, Xantphos, K₂CO₃, AcNH₂, Mw, 130 °C.  

v. a. vinyl tetrafluoroborate, Pd(PPh₃)₄, PhCH₃, EtOH, Mw, 130 °C; b. H₂/Pd/10% C, EtOH, r.t.  

vi. HCl (4M) in 1,4-Dioxane, rt.

(R)-tert-butyl (1-(2,7-dichloropyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate  

2,4,7-trichloropyrido[3,2-d]pyrimidine (650 mg, 2.77 mmol) was dissolved in dried 1,4-dioxane (10 mL). Azetidin-3-ylmethyl-carbamic acid tert-butyl ester (1.11 g, 5.54 mmol) and DIPEA (1.03 mL, 5.82 mmol) were added and the mixture was stirred at room temperature for 3 hours. Then, the solvent was removed, the crude dissolved in ethyl acetate, and the solution washed with water (20 mL x2), brine (20 mL x2) and saturated ammonium chloride solution (20 mL x2). The organic layer was dried, filtered and the solvent removed by evaporation. The obtained crude was purified by a silica gel column chromatography eluting with ethyl acetate. Yield: 91%, 1.0 g; ¹H NMR (CDCl₃) δ
8.59 (d, J = 4.0 Hz, 1H), 7.95 (d, J = 4.0 Hz, 1H), 4.86 (s, 2H), 4.72 (se, 1H),
4.60 (se, 1H), 4.02 (se, 2H), 3.73 (se, 1H), ...

5 (R)-tert-butyl (1-(2-acetamido-7-chloropyrido[3,2-d]pyrimidin-4-
yl)pyrrolidin-3-yl)(methyl)carbamate

A suspension of (R)-tert-butyl (1-(2,7-dichloropyrido[3,2-d]pyrimidin-4-
yl)pyrrolidin-3-yl)(methyl)carbamate (1.0 g, 2.5 mmol), acetamide (176 mg, 3.01 mmol), K2CO3 (690 mg, 5.0 mmol), Pd(OAc)2 (31 mg, 125 µmol) and Xantphos (144 mg, 250 µmol) was heated by microwave irradiation at 130 °C for 30 min.

Then the solvent was removed, the crude dissolved in dichloromethane (25 mL) and 20 mL of water was added. The aqueous phase was extracted with DCM and the organic phases dried over MgSO4, filtered and the solvent removed by evaporation. Yield: 40%, 406 mg; 1H NMR (CDCl3) δ 8.46 (d, J = 4.0 Hz, 1H), 8.15 (se, 1H), 7.88 (d, J = 4.0 Hz, 1H), 4.86 (s, 1H), 4.70 (se, 1H), 4.14(se, 1H), 3.97 (se, 1H), 3.75 (se, 1H), 2.85 (s, 3H), 2.59 (s, 3H), 2.16 (s, 3H), 2.06 (m, 2H), 1.49 (s, 9H). MS (ESI) m/z 421.

(R)-tert-butyl (1-(2-amino-7-ethy1pyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-
yl)(methyl)carbamate

In a microwave tube, a mixture of (R)-tert-butyl (1-(2-acetamido-7-
chloropyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (300 mg, 710 µmol), Pd(PPh3)3 (85 mg, 71 µmol), potassium vinyl trifluoro borate (114 mg, 850 µmol), K2C03 (140 mg, 1.42 mmol) and PhCH3/EtOH (2.6/1.4 mL) was degassed with nitrogen for 10 min. The mixture was heated at 130 °C for 2 hours by microwave irradiation, cooled down to r.t., filtered and washed with EtOH (25 mL). The solvent was removed by evaporation and the crude was purified by silica gel column chromatography eluting with EtOAc 100% to EtOAc/MeOH, 95/5. A suspension of the obtained compound, Pd/10% C and EtOH (5 mL) was stirred at r.t. for 20 hours under a hydrogen atmosphere. Then, it was filtered over celite and washed with EtOH. The solvent was removed by evaporation and the crude was purified by silica gel chromatography eluting with EtOAc 100% to 95% and 5% MeOH. Yield: 35%, 92 mg; 1H NMR (CDCl3) δ 8.19 (d, J = 4.0 Hz, 1H), 7.39 (d, J = 4.0 Hz, 1H), 4.87 (s, 2H), 4.77 (se, 1H), 4.25 (se, 3H), 3.65 (m,
(R)-7-ethyl-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine

A mixture of (R)-tert-butyl (1-(2-amino-7-ethylpyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (90 mg, 250 µmol), HCl (4M) (0.8 mL) and 1,4-dioxane (1 mL) was stirred at r.t. for 4 hours. Then, the solvent was removed, 10 mL of water was added and the solution was basified to pH = 12. Then it was extracted with chloroform (20 mLx2) and the organic layers were dried over Na2SO4. The organic phase was filtered and the solvent was removed by evaporation. The crude was purified by silica gel chromatography eluting with EtOAc/MeOH/triethylamine, 95/2.5/2.5. Yield: 38%, (24 mg). 1H NMR (CDCl3) δ 8.22 (d, J = 4.0 Hz, 1H), 7.41 (d, J = 4.0 Hz, 1H), 4.95 (s, 2H), 4.75 (se, 3H), 3.96 (m, 1H), 3.31 (se, 1H), 2.69 (q, J = 7.5 Hz, 2H), 2.46 (s, 3H), 2.01 (se, 1H), 1.82 (se, 1H), 1.25 (t, J = 7.5 Hz, 2H), MS (ESI) m/z 273.
Scheme 6  

\[
\begin{align*}
\text{i.} & \quad \text{Urea, } 160^\circ \text{C}, 0.2 \text{ M NaOH.} \\
\text{ii.} & \quad \text{PCI}_5, \text{POCl}_3, \text{MW, } 160^\circ \text{C.} \\
\text{iii.} & \quad \text{a. azetidin-3-ylmethyl-carbamic acid tert-butyl ester, DIPEA, 1,4-Dioxane, r.t.} \\
\text{iv.} & \quad \text{Pd(OAc)}_2, \text{Xantphos, K}_2\text{C}_0_3, \text{AcNH}_2, \text{MW, } 130^\circ \text{C. v. potassium cyclopropyl trifluoroborate, Pd(OAc)}_2, \text{n-BuPAd}_2, \text{Cs}_2\text{C}_0_3, \text{PhCH}_3, \text{H}_2\text{O, MW, } 130^\circ \text{C; vi. HCl (4M) in 1,4-Dioxane, rt.}
\end{align*}
\]

\text{Reagents and conditions: i.} Urea, 160 °C, 0.2 M NaOH. \text{ii.} PCl\textsubscript{5}, POCI\textsubscript{3}, MW, 160 °C. \text{iii.} a. azetidin-3-ylmethyl-carbamic acid tert-butyl ester, DIPEA, 1,4-Dioxane, r.t. iv. Pd(OAc)\textsubscript{2}, Xantphos, K\textsubscript{2}C\textsubscript{0}\textsubscript{3}, AcNH\textsubscript{2}, MW, 130 °C. v. potassium cyclopropyl trifluoroborate, Pd(OAc)\textsubscript{2}, n-BuPAd\textsubscript{2}, Cs\textsubscript{2}C\textsubscript{0}\textsubscript{3}, PhCH\textsubscript{3}, H\textsubscript{2}O, MW, 130 °C; vi. HCl (4M) in 1,4-Dioxane, rt.

**tert-butyl (1-(2-amino-7-cyclopropylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate**

A mixture of tert-butyl (1-(2,7-dichloropyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (300 mg, 740 µmol), Pd(OAc)\textsubscript{2} (8 mg, 40 µmol), n-BuPAd\textsubscript{2} (20 mg, 56 µmol), potassium cyclopropyl trifluoroborate (131 mg, 890 µmol), Cs\textsubscript{2}C\textsubscript{0}\textsubscript{3} (710 mg, 2.22 mmol) and PhCH\textsubscript{3}/H\textsubscript{2}O, 10/1 mL, v/v was heated at 130 °C in the microwave heating for 30 min. LCMS showed conversion to the desired acetamide. The reaction was then filtered, the solvent removed and the crude dissolved in PhCH\textsubscript{3}/EtOH:2/1 (6 mL) with Na\textsubscript{2}C\textsubscript{0}\textsubscript{3} (3 equivalent). The
resulting mixture was heated at 130°C in the microwave heating for 2 hours. Then the solvent was removed by evaporation and the crude product purified by a silica gel chromatography eluting with a gradient of 100% EA to 95/5, EA/MeOH. Yield: 62%, 170 mg; 1H NMR (CDCl₃) δ 8.19 (d, J = 4 Hz, 1H), 7.17(d, J = 4 Hz, 1H), 5.10 (se, 2H), 5.00 (se, 2H), 4.46 (se, 1H), 4.28 (se, 1H), 3.76 (se, 1H), 2.96 (s, 3H), 1.92 (m, 1H), 1.46 (s, 9H), 1.06 (m, 2H), 0.80 (m, 2H); MS (ESI) m/z 371.

7-cyclopropyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine
tert-butyl (1-(2-amino-7-cyclopropylpyrido[3,2-d]pyrimidin-4-yl)azetidin-3-yl)(methyl)carbamate (120 mg, 320 µmol) was dissolved in HCl 4M (5 mL) and the reaction was stirred at r.t. for 4 hours. Then, the solvent was removed by evaporation, the crude dissolved in a 30% solution of ammonia and extracted with CHCl₃ (10 mL x 3), the organic layers were dried over MgSO₄, filtered and the solvent was removed by evaporation. Yield: 93%, 80 mg. 1H NMR (CDCl₃) δ 8.19 (d, J = 4 Hz, 1H), 7.15 (d, J = 4 Hz, 1H), 4.88 (se, 3H), 4.71 (se, 2H), 3.98 (se, 1H), 3.70 (m, 1H), 2.45 (s, 3H), 1.92 (m, 1H), 1.04 (m, 2H), 0.80 (m, 2H); MS (ESI) m/z 271.

(R)-ferf-butyl (1-(2-amino-7-cyclopentylpyrido[3,2-d]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate
A mixture of (R)-ferf-butyl (1-(2-acetamido-7-chloropyrido[3,2-c]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (0.2 g, 0.476 mmol), 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.11 g, 0.572 mmol), tetrakis (0.055 g, 0.048 mmol) potassium carbonate (0.197 g, 1.429 mmol), and Toluene/ethanol (2.6/1.4 ml) was heated by microwave irradiation at 130 °C for 60 min. Then the resulting suspension was filtered over celite, the solvent was removed by evaporation, and the crude dissolve in ethanol. Then palladium on carbon (0.0127 g, 0.120 mmol) was added and the mixture was stirred at room temperature under a hydrogen atmosphere overnight. The solvent was removed by evaporation and the crude was purified by silica gel chromatography eluting with EtOAc 95% and 5% MeOH. Yield 26% (50 mg); MS m/z 413 (M+H+).
(/?)-7-cyclopentyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine

(R)-tert-butyl (1-(2-amino-7-cyclopentylpyrido[3,2-c]pyrimidin-4-yl)pyrrolidin-3-yl)(methyl)carbamate dissolved in 1,4-dioxane (2 ml), HCl (4M) in 1,4-dioxane (1 ml) was added and the mixture was stirred at room temperature for 16 hours. The solvent was removed by evaporation and the crude dissolved in water. The pH of the solution was adjusted to pH = 12 (NaOH solution) and the aqueous phases were extracted with chloroform (25 mlx2). The organic layers were dried over Na₂SO₄, filtered and the solvent was removed by evaporation. The crude purified in silica gel chromatography eluted with ethyl acetate/methanol/triethylamine: 90/5/5. Yield 66% (25 mg). MS m/z 313 (M+H⁺). ¹H NMR (CDCl₃) δ 8.24 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 4.77 (s, 2H), 4.30 (m, 2H), 3.75 (m, 2H), 3.28 (s, 1H), 3.09 (m, 1H), 2.43 (s, 3H), 1.89 (m, 2H), 1.42 (m, 8H).

Several of the compounds were tested for their ability to bind the hERG channel, when compared to some quinazoline analogues, such as those disclosed in WO2010/146173. The results show a desirable decreased tendency to bind the hERG channel (results shown below). hERG is associated with an increased risk of suffering from sudden death as a result of QT prolongation and cardiac arrest.

Binding of compounds to the hERG channel can be studied as described in the exemplified [³H]astemizole binding assay given below.

[³H]astemizole binding assay
The [³H]astemizole binding assay is performed in a buffer containing 130 mM NaCl, 60 mM KCl, 10 mM HEPES, 1 mM EGTA, 0.8 mM MgSO₄ (pH 7.4 at 22°C), 0.5% BSA, approximately 0.5 nM [³H]astemizole, and membrane of HEK 293T cells transiently expressing hERG channel (mRNA accession number NM_000238.2), in the absence or presence of test compounds, in a total volume of 100 µl. After being incubated for 1 hour at room temperature, the membranes are harvested on a 96-well GF-C plate (PerkinElmer, USA) that is pretreated.
with 0.5% PEI solution, followed by three washes using ice-cold buffer containing 50 mM Tris and NaCl (pH 7.4 at 4°C). The residual radioactivity is quantified in a MicroBeta scintillation counter (PerkinElmer, USA), and the data are analyzed with Prism Graphpad 5.0.

Examples of compounds containing the pyrido[2,3-d]pyrimidine moiety binding to the hERG channel.

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<tr>
<th>Structure</th>
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<th>Structure</th>
<th>hERG $K_i$ (nM)</th>
<th>Structure</th>
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Binding of compounds to the histamine $H_4$R receptor can be studied as described in the exemplified $[^3]H$Histamine binding assay given below.

**Typical radioligand displacement studies at the human $H_4$ receptor**

**Cell culture and transfection.** HEK 293T cells were maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 50 IU/ml penicillin, and 50 µg/ml streptomycin in 5% CO2 humidified atmosphere at 37 °C. Approximately 4 million cells were seeded in a 10-cm dish and cultured overnight before transfection. For transfection of each dish of cells, the transfection mixture was prepared in 1 ml serum-free DMEM and contained 5 µg of human $H_4$R receptor plasmid and 15 µl of 1 mg/ml 25 kDa linear polyethyleneimine (Polyscience, Inc., USA). The mixture was incubated for 10-15 minutes at room temperature before it was added into the monolayer cell
culture loaded with 5 ml fresh cell culture medium. Two days after transfection the cells were washed with PBS containing 1 mM EDTA, collected as pellet by centrifuging, and stored at -20°C until use.

Representative [³H]Histamine binding assay. For the radioligand binding study, pellets of transfected cells were homogenized in H₄R binding buffer (100 mM Tris-HCl, pH 7.4). The saturation binding assay was performed using different concentrations of [³H]histamine (Perkin-Elmer Life Science, Inc., USA), while non-specific binding was determined by incubation in the presence of 3-10 µM of JNJ 7777120 in a total assay volume of 200 µl. For the displacement binding assay, the membranes were typically incubated with 10⁻⁴ to 10⁻¹¹ M of ligands (stock concentration was 10 mM 1 DMSO) in the presence of [³H]histamine in a total volume of 200 µl. The reaction mixtures were incubated for 1 hour at room temperature (22°C), and harvested on 96-well glass fiber plates that were pretreated with 0.3% 750 kDa PEL. The binding assay data were analyzed using Prism 4.0 (Graphpad Software Inc., USA).
Examples of most preferred compounds containing the pyrido[2,3-d]pyrimidene moiety and their binding to the H₄R.

<table>
<thead>
<tr>
<th>Structure</th>
<th>H₄R Kᵢ (nM)</th>
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CLAIMS

1. A compound of formula (I):

\[
\begin{array}{c}
R_1 \\
\end{array}
\]

wherein:

\[
R_1 \text{ is }
\]

at least one of X and Y is N and the other of X or Y is either N or CR₂;

R₂ is H, c₁-c₄ alkyl, C₂-C₅ alkenyl or C₂-C₅ alkynyl;

R₆, R₇ and R₈ are independently selected from H, halogen, c₁₄ alkyl, C₂-5

alkenyl, C₂-5 alkynyl, c₁₄ alkoxy, c₁₄ alkylthio, (CH₂)₀-3c₃-7cycloalkyl, O-C₃-6
cycloalkyl, aryl, O-aryl, NH-aryl, S-aryl, o-c₁₄ alkyl-aryl, c₁₄ alkyl-aryl, CF₃, O-
CF₃, S-CF₃, hydroxy, nitro, cyano, o-c₁₄ alkyl-N(CH₃)₂, heteroaryl, O-heteroaryl,
NH-heteroaryl, S-heteroaryl, C₁-C₄ alkyl-heteroaryl, c₁-C₄ alkyl-heteroaryl and
NRmRn, wherein Rm and Rn are independently selected from H, c₁₄ alkyl, aryl
and phenethyl;

R₃ and R₄ are independently selected from H, halogen, c₁₄ alkyl, C₂-5

alkenyl, C₂-5 alkynyl, c₁₄ alkoxy, c₁₄ alkylthio, (CH₂)₀-3c₃-7cycloalkyl, O-C₃-6
cycloalkyl, aryl, O-aryl, NH-aryl, S-aryl, o-c₁₄ alkyl-aryl, c₁₄ alkyl-aryl, CF₃, O-
CF₃, S-CF₃, hydroxy, nitro, cyano, o-c₁₄ alkyl-N(CH₃)₂, heteroaryl, O-heteroaryl,
NH-heteroaryl, S-heteroaryl, c₁-C₄ alkyl-heteroaryl, c₁-C₄ alkyl-heteroaryl and
NRmRn, wherein Rm and Rn are independently selected from H, c₁₄ alkyl, aryl
and phenethyl, or R₃ and R₄, are taken together with the attached C atoms to
form a 5-7 membered cycloalkyl ring;

wherein any alkyl, cycloalkyl, aryl or heteroaryl group mentioned above
can independently be optionally substituted with one or more substituents
selected from halogen c₁₄ alkyl, C₂-5 alkenyl, C₂-5 alkynyl, c₁₄ alkoxy, c₁₄
alkylthio, (CH₂)₀-3c₃-7cycloalkyl, O-C₃-6 cycloalkyl, aryl, O-aryl, heteroaryl, NH-
aryl, S-aryl, o-c₁₄ alkyl-aryl, c₁₄ alkyl-aryl, CF₃, O-CF₃, S-CF₃, hydroxy, nitro
amino, cyano and o-c₁₄ alkyl-N(CH₃)₂;

each n is independently 1, 2 or 3; and

each m is independently 0, 1 or 2.

or a pharmaceutically acceptable salt or ester thereof.

A compound according to claim 1, wherein at least one of R₃ and R₄ is H,
preferably wherein R₄ is H.
3. A compound according to claim 1 or claim 2, wherein $R_1$ is selected from structure K, B or I.

4. A compound according to any preceding claim, wherein $X$ is N.

5. A compound according to any preceding claim, wherein $Y$ is CR$_2$.

6. A compound according to any preceding claim, wherein $R_2$ is H.

7. A compound according to any preceding claim, which is:
   - 7-ethyl-4-(4-methylpiperazin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - 2-amino-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidine-7-carbonitrile;
   - 7-isopropyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - (R)-7-isopropyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - 7-ethyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - (R)-7-ethyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - 7-cyclopropyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - (R)-7-cyclopropyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - 7-cyclopentyl-4-(3-(methylamino)azetidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine;
   - (R)-7-cyclopentyl-4-(3-(methylamino)pyrrolidin-1-yl)pyrido[3,2-d]pyrimidin-2-amine,
   or a pharmaceutically acceptable salt or ester thereof.

8. A pharmaceutical composition comprising a compound according to any preceding claim.

9. A compound according to any preceding claim, for use in therapy.

10. A compound according to claim 9, wherein the therapy is of a condition selected from inflammatory disorders, allergic disorders, dermatological disorders, autoimmune disease, lymphatic disorders, and immunodeficiency disorders.

11. A compound according to claim 10, wherein the condition is selected from allergy, asthma, dry eye, chronic obstructive pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (including colitis, Crohn’s disease, and ulcerative colitis), psoriasis, pruritis, itchy skin, atopic dermatitis, urticaria (hives), ocular inflammation (e.g., post-surgical ocular inflammation), (allergic) conjunctivitis, dry eye, nasal polyps, allergic rhinitis, nasal itch, scleroderma, autoimmune thyroid diseases, immune-mediated (also known as type 1) diabetes mellitus and lupus.
12. A compound according to claim 10, wherein the therapy is of a condition selected from myasthenia gravis, autoimmune neuropathies, such as Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, such as Wegener's granulomatosis, Behcet's disease, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland, polymyositis, dermatomyositis, spondyloarthropathies, such as ankylosing spondylitis, and Sjogren's syndrome.

13. A compound according to claim 9, wherein the therapy is of allergic asthma, atopic dermatitis, pruritus or rheumatoid arthritis.
**INTERNATIONAL SEARCH REPORT**

**PCT/EP2012/071321**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D471/04 A61K31/519 A61P37/08

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)**

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. X 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 application or patent but published on or after the international filing date
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- **A** document member of the same patent family

**Date of the actual completion of the international search**

7 January 2013

**Date of mailing of the international search report**

13/02/2013

Name and mailing address of the ISA:
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NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-2016

Authorized officer

Gutke, Hans-Jurgen
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