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- **STARK H: "Recent advances in histamine H3/H4 receptor ligands" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 13, no. 6, 2003, pages 851-865, XP002298271 ISSN: 1354-3776 cited in the application**
- **TERZIOGLU N ET AL: "Synthesis and structure-activity relationships of indole and benzimidazole piperazines as histamine H4 receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 21, 1 November 2004 (2004-11-01), pages 5251-5256, XP004580509 ISSN: 0960-894X cited in the application**

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Description

[0001] This invention relates to pyrimidine derivatives and to processes for the preparation of, compositions containing and the uses of, such derivatives.

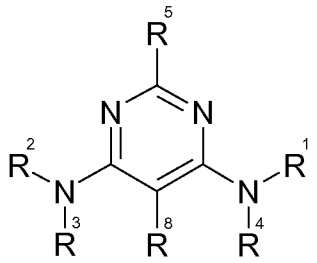
[0002] The pyrimidine derivatives of the present invention are histamine H_4 receptor ligands and have therefore a number of therapeutic applications, particularly in the treatment of asthma, allergic rhinitis, chronic obstructive pulmonary disorder (COPD) and histamine-mediated inflammatory diseases.

[0003] The histamine H_4 receptor is a 390 amino-acid, seven-transmembrane G protein coupled receptor with approximately 40 % homology to the histamine H_3 receptor. In contrast to the H_3 receptor, which is primarily located in the brain, the H_4 receptor is expressed at greater levels in eosinophils and mast cells, among other inflammatory cells. H_4 receptor ligands should thus be suitable for the treatment of various inflammatory disorders. Examples of diseases where treatment with H_4 ligands is particularly appropriate are inflammatory bowel disease, Crohn's disease, colitis ulcerosa, dermatitis, psoriasis, conjunctivitis, rheumatoid arthritis, respiratory diseases such as adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis, allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion and allergic congestion.

[0004] Recently some histamine H_4 receptor ligands have been developed. An overview of the current advance in H_4 ligand research and patenting is given in Expert Opin. Ther. Patents (2003) 13(6). Examples of Histamine H_4 receptor ligands can be found in WO 02/072548, WO 04/022537 and in Terzioglu et al., J. Bioorg. Med. Chem. Lett. 14 (2004), 5251-5256.

[0005] Although H_4 ligands are known there is still a need to further provide new H_4 ligands that are good drug candidates. In particular, preferred compounds should bind potently to the histamine H_4 receptor whilst showing little affinity for other receptors. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects.

[0006] The present invention thus relates to pyrimidine derivatives of formula (I):



or a pharmaceutically and/or veterinarily acceptable derivative thereof, wherein:

R^1 is C_{1-8}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl- optionally substituted with methyl, alkoxyalkyl containing 3 to 8 carbon atoms, het-C_{0-6}alkyl-, CF_3-C_{1-6}alkyl-, CF_3OC_{2-3}alkyl-, aryl-C_{0-6}alkyl- or C_{1-6}hydroxyalkyl;

R^3 and R^2 together with the nitrogen atom to which they are bound form a 4 to 8 membered non-aromatic heterocyclic group which optionally contains one or more further heteroatoms or groups independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group, a spiro bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl, provided that the ring system as a whole contains at least two nitrogen atoms or contains one nitrogen atom and is substituted by a group which contains at least one nitrogen atom;

R^4 is H;

R^5 is H or NH_2;

R^6 and R^7 are each independently selected from H, C_{1-6}alkyl and $(CH_2)_jC_{3-7}$cycloalkyl; or R^6 and R^7, together with the nitrogen atom to which they are bound, form a 4, 5 or 6 membered heterocyclic group; R^8 is H;

aryl is phenyl, naphthyl, anthracyl or phenanthryl, each optionally substituted by one or more groups independently selected from C_{1-8}alkyl, C_{1-8}alkoxy, OH, halo, CF_3, CHF_2, OCF_3, $OCHF_2$, SCF_3, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkyl-S-C_{1-4}alkyl, aryl^1, het^1, Oaryl^1, Ohet^1, Saryl^1, Shet^1, CF_2CF_3, CH_2CF_3, CF_2CH_3, $C(O)NR^{13}R^{14}$, C_{3-8}cycloalkyl, C_{3-7}cycloalkyl-C_{1-4}alkyl, C_{3-7}cycloalkyl-C_{1-4}alkoxy;

a, b, c, d, j and m are each independently selected from 0, 1, 2 and 3;

n is 1, 2 or 3;
y is independently selected from 1, 2 and 3;
het is 4 to 8 membered non-aromatic heterocyclic group which contains at least one heteroatom or group independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl; and
het^1 is an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 4-, 5- or 6- membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom.

Preferably aryl is phenyl.
For embodiments in which the groups "aryl", "aryl^1", "het" and "het^1" may be a substituent on more than one part of the compound, it is to be understood that each separate substituent may be the same or different to the other substituent(s) defined by the same term. For example, if R^1 and R^2 both comprise a "het" group, then the two het groups may be the same or different.

[0007] It has been found that the compounds defined above are ligands of the Histamine H_4 receptor.

[0008] In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is C_{3-7}cycloalkyl-C_{0-6}alkyl- optionally substituted with methyl.
In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is C_{3-5}cycloalkyl-C_{0-1}alkyl- optionally substituted with methyl.
In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is cyclopropyl, cyclopropyl-methyl or methyl-cyclopropyl.
In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is C_1-C_8 alkyl.
In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is C_1-C_6 alkyl.
In a further embodiment, R^2, R^3, R^5 and R^8 are as defined above, R^4 is hydrogen and R^1 is ethyl, propyl, butyl, 1-methyl-propyl, 2-methyl-propyl, 2,2-dimethyl-propyl, 2-methyl-butyl, ter-butyl, 1-methyl-butyl, 3-methyl-butyl, 3,3-dimethyl-butyl, 1,2-dimethyl-propyl or isopropyl.

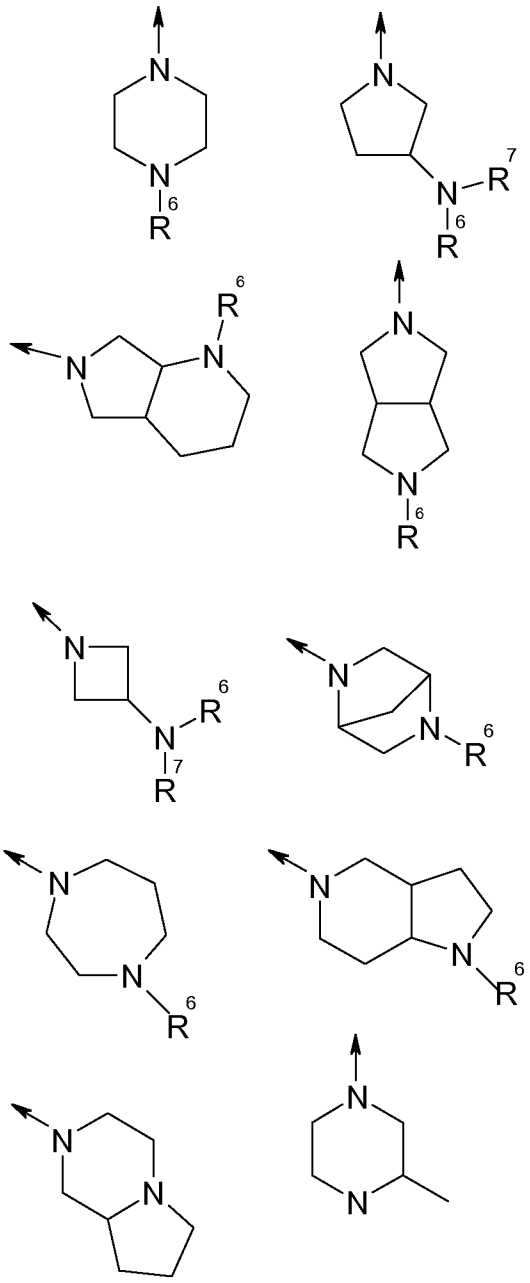
[0009] In a further embodiment, R^1, R^4, R^5 and R^8 are as defined above, and R^3 and R^2 together with the nitrogen atom to which they are bound form a 4 to 8 membered non-aromatic heterocyclic group which optionally contains one or more further heteroatoms or groups independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group, a spiro bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl, provided that the ring system as a whole contains at least two nitrogen atoms or contains one nitrogen atom and is substituted by a group which contains at least one nitrogen atom;

[0010] In a still further embodiment, R^1, R^4, R^5 and R^8 are as defined above, and R^2 and R^3, together with the nitrogen atom to which they are bound, form a 4 to 8 membered non-aromatic heterocyclic group which optionally contains one or more further heteroatoms or groups independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl, provided that the ring system as a whole contains at least two nitrogen atoms or contains one nitrogen atom and is substituted by a group which contains at least one nitrogen atom.

[0011] In a further embodiment, R^1, R^4, R^5 and R^8 are as defined above, and R^2 and R^3, together with the nitrogen atom to which they are bound, form a 4 to 8 membered non-aromatic heterocyclic group which optionally contains one or more further nitrogen atoms, wherein the heterocyclic group is optionally a bridged bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one nitrogen atom, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl, provided that the ring system as a whole contains at least two nitrogen atoms or contains one nitrogen atom and is substituted by a group which contains at least one nitrogen atom.

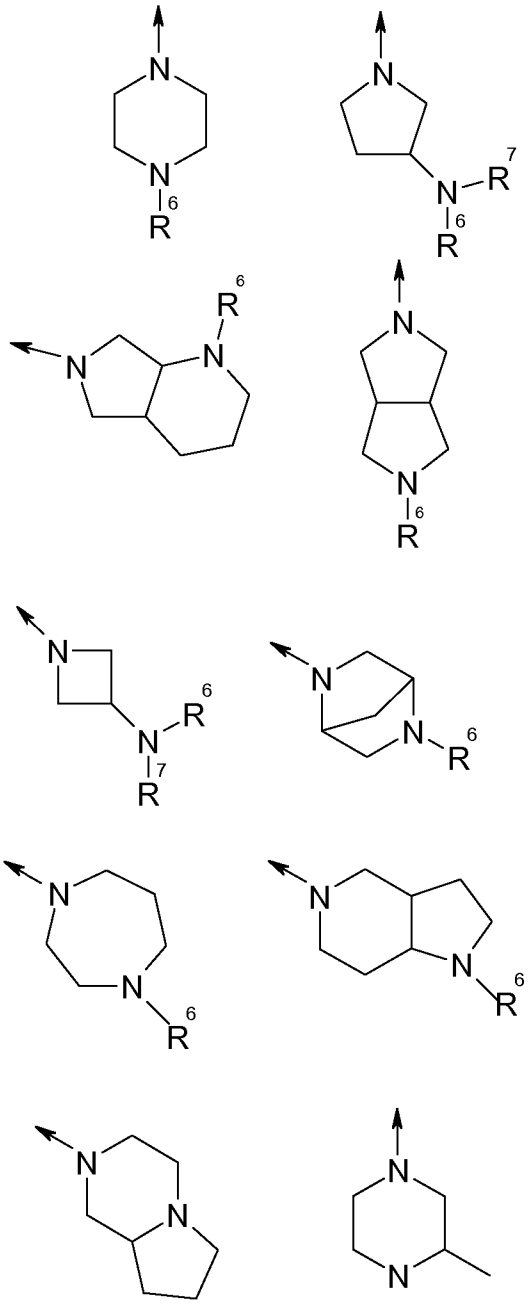
[0012] In a yet still further embodiment, R^1, R^4, R^5 and R^8 are as defined above, and R^2 and R^3, together with the

nitrogen atom to which they are bound, form a 4 to 8 membered non-aromatic heterocyclic group selected from the following ring systems:



wherein the ring system as a whole may be substituted by one or more C_{1-6}alkyl or $(CH_2)_aC_{3-6}$cycloalkyl groups.

[0013] In a yet still further embodiment, R^1, R^4, R^5 and R^8 are as defined above, and R^2 and R^3, together with the nitrogen atom to which they are bound, form a 4 to 8 membered non-aromatic heterocyclic group selected from the following ring systems:



wherein R^6 and R^7 are independently selected from H or CH_3.

[0014] In a further embodiment, R^1, R^2, R^3, R^4 and R^8 are as defined above, and R^5 is H or NH_2.

[0015] In the here above formula "halo" denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo, in particular fluoro or chloro.

[0016] The term "alkyl" includes both straight-chain and branched chain groups. This also applies if they carry substituents such as a hydroxy substitutent or occur as substituents of other radicals, for example alkoxy groups. For example, the term C_{1-4}alkyl includes methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, sec-butyl and *tert*-butyl moieties. Examples of the corresponding alkoxy moieties are methoxy, ethoxy, n-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy. Furthermore, examples of suitable C_{1-4}alkyl moieties substituted by an hydroxyl group are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, etc.

[0017] The term C_3-C_7 cycloalkyl includes bridged bicyclic cycloalkyl such as bicyclo[1.1.1]pentyl. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and bicyclo[1.1.1]pentyl.

[0018] Preferred "4 to 8 membered heterocyclic group which optionally contains one or more further heteroatoms or groups independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is a spiro bicyclic group" are 2,8-diaza-spiro[4.5]dec-2-yl and 2,7-diaza-spiro[4.4]non-2-yl.

[0019] The skilled person will of course appreciate that it is not possible to substitute some of the defined heterocyclic ring groups of Formula I in all positions with some of the optional substituents defined above. It is to be understood that such substitutions do not form part of the invention.

[0020] Example compounds that fall within the above definition of the invention include:

N-(3,3-Dimethylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
6-[3-(Dimethylamino)pyrrolidin-1-yl]-*N*-(3,3-dimethylbutyl)pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-6-[(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidin-4-amine,
6-[3-(Dimethylamino)azetidin-1-yl]-*N*-(3,3-dimethylbutyl)pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-6-[5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-*N'*-[pyrrolidin-3-yl]pyrimidine-4,6-diamine,
N-(3,3-Dimethylbutyl)-*N'*-[1-methylpyrrolidin-3-yl]pyrimidine-4,6-diamine,
N^4-(Cyclopropylmethyl)-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-Isobutyl-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N-Ethyl-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N-Isobutyl-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N-(Cyclopropylmethyl)-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-6-[3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
6-[3-(Dimethylamino)pyrrolidin-1-yl]-*N*-(3,3-dimethylbutyl)pyrimidin-4-amine,
N-(Cyclopropylmethyl)-6-[3-(dimethylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
6-[3-(Dimethylamino)pyrrolidin-1-yl]-*N*-isobutylpyrimidin-4-amine,
6-[3-(Dimethylamino)pyrrolidin-1-yl]-*N*-ethylpyrimidin-4-amine,
6-[3-(Dimethylamino)pyrrolidin-1-yl]-*N*-(2,2-dimethylpropyl)pyrimidin-4-amine,
N^4-(3,3-Dimethylbutyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Isopropyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Methyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Isobutyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(3-Methylbutyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclopropyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopentylmethyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
6-[5-Methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-Methyl-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
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N^4-(3-Methylbutyl)-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
N^4-Cyclopropyl-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
Cyclopropylmethyl-[6-(3-methylamino-azetidin-1-yl)-pyrimidin-4-yl]-amine,
(3-Fluoro-benzyl)-[6-(3-methylamino-azetidin-1-yl)-pyrimidin-4-yl]-amine,
N-Isopropyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-(4-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-Ethyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
2-({6-[3-(Methylamino)azetidin-1-yl]pyrimidin-4-yl}amino)ethanol,
N-Benzyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-(2-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-Methyl-1-[6-(4-methylpiperidin-1-yl)pyrimidin-4-yl]azetidin-3-amine,
N-(2-Methoxyethyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
6-[3-(Methylamino)azetidin-1-yl]-*N*-(3-methylbutyl)pyrimidin-4-amine,

N-Methyl-1-(6-piperidin-1-ylpyrimidin-4-yl)azetidin-3-amine,
N-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-Methyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,
N^4-Isopropyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-(3-Methylamino-azetidin-1-yl)-N^4-(3,3,3-trifluoro-propyl)-pyrimidine-2,4-diamine,
N^4-Cyclopropylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-(3,3-Dimethyl-butyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-(3-Methoxy-benzyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Cyclobutylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Cyclopentylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Methyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-Cyclopropyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(3-methylbutyl)pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-[4-(trifluoromethoxy)benzyl]pyrimidine-2,4-diamine,
4-[({2-Amino-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-yl}amino)methyl]benzonitrile,
N^4-(2-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-Benzyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-[3-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine,
N^4-(4-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbenzyl)pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(3-methylbenzyl)pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-[2-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-[4-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine,
N^4-(3-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(4-methylbenzyl)pyrimidine-2,4-diamine,
N^4-(2-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-(4-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-(3-Fluorobenzyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N^4-(3-Fluorobenzyl)-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine,
N^4-(3,3-Dimethylbutyl)-6-[3-methylpiperazin-1-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-methylpiperazin-1-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-[3-methylpiperazin-1-yl]pyrimidine-2,4-diamine,
N-(2,2-Dimethylpropyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-(3-Methylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N^4-(3,3-Dimethylbutyl)-N^6-[pyrrolidin-3-yl]pyrimidine-2,4,6-triamine,
N^4-(3,3-Dimethylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-Isopropyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-Isobutyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-(3-Methylbutyl)-N'-[pyrrolidin-3-yl]pyrimidine-4,6-diamine,
N^4-(3-Methylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N-(2-Methoxyethyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-(3,3-Dimethylbutyl)-6-piperazin-1-ylpyrimidin-4-amine,
6-(4-Methylpiperazin-1-yl)-*N*-[tetrahydrofuran-2-ylmethyl]pyrimidin-4-amine,
4-(4-Methylpiperazin-1-yl)-6-pyrrolidin-1-ylpyrimidine,
6-(4-Methylpiperazin-1-yl)-N-(3,3,3-trifluoropropyl)pyrimidin-4-amine,
N-Isobutyl-5-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine,
N-Ethyl-6-[5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidin-4-amine,
6-(3-Aminoazetidin-1-yl)-*N*-(3,3-dimethylbutyl)pyrimidin-4-amine,
N^4-Isopropyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N^4-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,

N^4-Isobutyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N-(Cyclopropylmethyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine,
N^4-(3,3-Dimethylbutyl)-6-[3,4-dimethylpiperazin-1-yl]pyrimidine-2,4-diamine,
N-Isobutyl-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine,
6-[6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine,
N-(2,2-Dimethylpropyl)-6-[octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbutyl)pyrimidine-2,4-diamine,
N^4-[(1*S*)-1,2-Dimethylpropyl]-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-Butyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-(1,4-Diazepan-1-yl)-N^4-isobutylpyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(2-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-Isobutyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-Isopropyl-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine,
N^4-Bicyclo[1.1.1]pent-1-yl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-(4-Aminopiperidin-1-yl)-N^4-ethylpyrimidine-2,4-diamine,
6-[3-Methyl-3-(methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-N^6-[2-(methylamino)ethyl]pyrimidine-2,4,6-triamine,
N^4-[2-(Dimethylamino)ethyl]-N^6-(2,2-dimethylpropyl)pyrimidine-2,4,6-triamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N-[(1R)-1-methylpropyl]pyrimidin-4-amine,
N-Butyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N^4-(tert-Butyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(1-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-(*tert*-Butyl)-6-[(4aS*,7aS*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-[(1S)-1-methylpropyl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-[(1R)-1-methylpropyl]pyrimidine-2,4-diamine, and,
N-(*sec*-Butyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine,

or a pharmaceutically and/or veterinarily acceptable derivative thereof.

[0021] An embodiment of the invention provides the following compounds:

N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate,
N^4-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diaminN-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N^4-(2,2-Dimethylpropyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclopropyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-(3-Methylamino-azetidin-1-yl)-N^4-(3,3,3-trifluoro-propyl)-pyrimidine-2,4-diamine,
N^4-Cyclopropylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-(3,3-Dimethyl-butyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Cyclopentylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbutyl)pyrimidine-2,4-diamine,
N^4-Butyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(2-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-Isobutyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine,

N^4-(Cyclopropylmethyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-Bicyclo[1.1.1]pent-1-yl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-[3-Methyl-3-(methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-(*tert*-Butyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(1-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-(*tert*-Butyl)-6-[(4aS*,7aS*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-piperazin-1-ylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine hydrochloride,
N^4-(2,2-Dimethylpropyl)-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine,
6-Piperazin-1-yl-N^4-propylpyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-Isopropyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
4-[3-(Methylamino)azetidin-1-yl]-6-(4-methylpiperidin-1-yl)pyrimidin-2-amine,
N^4-(Cyclopentylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N4-Cyclobutyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-propylpyrimidine-2,4-diamine, and,
N^4-Ethyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine,

or a pharmaceutically and/or veterinarily acceptable derivative thereof.

[0022] A further embodiment of the invention provides the following compounds:

N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine, and,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine hydrochloride,

or a pharmaceutically and/or veterinarily acceptable derivative thereof.

[0023] By pharmaceutically and/or veterinarily acceptable derivative it is meant any pharmaceutically or veterinarily acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compounds of formula (I) or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. Preferably, pharmaceutically and/or veterinarily acceptable derivative means any pharmaceutically or veterinarily acceptable salt or solvate of the compounds of formula (I)

[0024] Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof.

[0025] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[0026] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

[0027] Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

[0028] For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0029] Pharmaceutically acceptable salts of the compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;
(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or
(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or

by means of a suitable ion exchange column.

[0030] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[0031] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0032] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

[0033] The compounds of the invention include compounds of formula (I) as hereinbefore defined, including all polymorphs and crystal habits thereof, and optical, geometric and tautomeric isomers as hereinafter defined and isotopically-labeled compounds of formula (I).

[0034] Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[0035] Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate, /-tartrate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

[0036] Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

[0037] Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

[0038] Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin.

[0039] Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

[0040] The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

[0041] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[0042] Certain isotopically labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

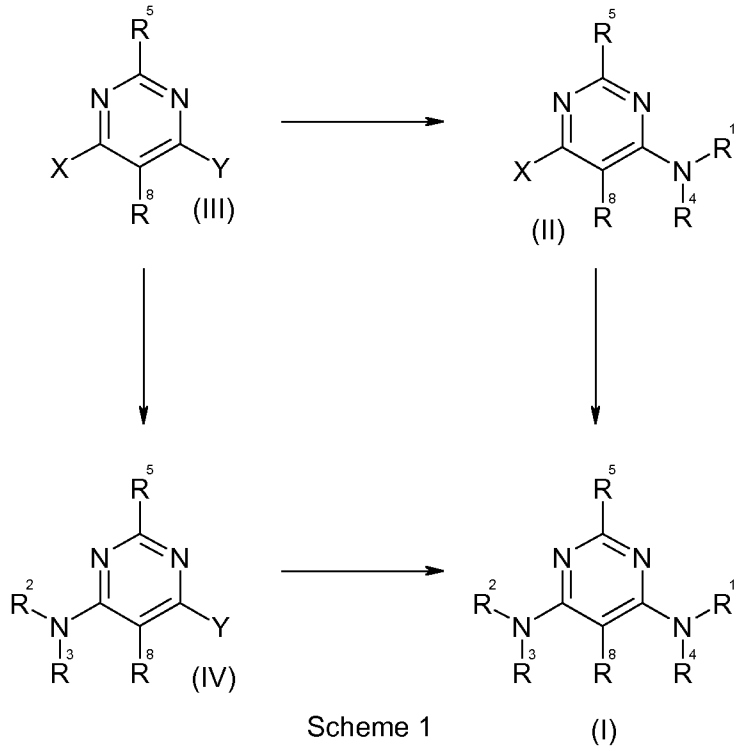
[0043] Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[0044] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0045] Isotopically labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically labelled reagent in place of the non-labelled reagent previously employed.

[0046] Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

[0047] Compounds of formula (I) may be prepared according to scheme 1 that follows.



Scheme 1

wherein R^1, R^2, R^3, R^4, R^5 and R^8 are as defined above, and X and Y are leaving groups.

[0048] According to scheme 1, compounds of formula (I) may be prepared by the reaction of a compound of formula (II) with a suitable amine. Conveniently reaction is effected by using an excess of the amine or stoichiometric quantity of the amine in the presence of a base such as a tertiary amine base (e.g. triethylamine or N-ethyl-N-isopropylpropan-2-amine); optionally in the presence of a suitable solvent (e.g. dimethyl sulphoxide or 1-methylpyrrolidin-2-one); optionally in the presence of a catalyst (such as caesium fluoride); and at elevated temperature, such as 120°C to 150°C.

[0049] Compounds of formula (II) may be prepared by reaction of a compound of formula (III) with a suitable amine. Conveniently reaction is effected by using an excess of the amine or stoichiometric quantity of the amine in the presence of a base such as a tertiary amine base (e.g. triethylamine or N-ethyl-N-isopropylpropan-2-amine); in the presence of a suitable solvent (e.g. ethanol, 2-propanol or 1-methylpyrrolidin-2-one); and at ambient or elevated temperature, such as ambient temperature to 85°C.

[0050] According to scheme 1, the groups X and Y represent a halogen atom (e.g. chlorine) or an alternative leaving group such as a sulphonate ester (e.g. 4-methylphenyl sulphonate) or a sulphonyl group (e.g. methane sulphonyl or phenyl sulphonyl) or a sulphinyl group (e.g. methane sulphinyl).

[0051] It will be appreciated by those skilled in the art that the transformations described may be carried out in a manner that does not require the isolation or purification of the intermediate compound of formula (II) but that requires sequential addition of suitable amines, with or without additional base (e.g. triethylamine or N-ethyl-N-isopropylpropan-2-amine) or solvent, to a compound or formula (III) in the presence of a suitable solvent (e.g. 1-methylpyrrolidin-2-one or dimethyl sulphoxide) with or without heating the reaction mixture between the addition of the two amines, and with or without the addition of a catalyst (such as caesium fluoride).

[0052] It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in the schemes in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

[0053] It will be appreciated by those skilled in the art that, as illustrated in the schemes above, it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. In particular, it may be necessary or desirable to protect amino groups. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, third edition, (John Wiley and Sons, 1999), in particular chapter 7, pages 494-653 ("Protection for the Amino Group"), incorporated herein by reference, which also describes methods for the removal of such groups.

[0054] Compounds of formula (III) are known in the literature or easily prepared by methods well known to those skilled

in the art.

[0055] The compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[0056] They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

[0057] Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

[0058] The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

[0059] Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

[0060] Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

[0061] The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

[0062] For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

[0063] Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

[0064] Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

[0065] Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

[0066] Other possible ingredients include anti-oxidants, colorants, flavouring agents, preservatives and taste-masking agents.

[0067] Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

[0068] Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

[0069] The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

[0070] Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

[0071] The compound of formula (I) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (I) may be in the form of multiparticulate beads.

[0072] The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

[0073] Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

[0074] Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

[0075] Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0076] Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

[0077] The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[0078] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

[0079] The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

[0080] The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

[0081] Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

[0082] The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

[0083] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.)* injection.

[0084] Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0085] The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

[0086] The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[0087] Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method,

such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

[0088] Capsules (made, for example, from gelatin or hydroxypropyl-methylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

[0089] A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

[0090] Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

[0091] Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0092] In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount or the drug product is packaged as discrete single dose units for use in the inhaler device. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 μg to 4000 μg of the compound of formula (I). The overall daily dose will typically be in the range 1 μg to 20 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

[0093] The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

[0094] Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0095] The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

[0096] Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

[0097] The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

[0098] Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

[0099] Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

[0100] Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

[0101] The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

[0102] For administration to human patients, the total daily dose of the compounds of the invention is typically in the

range 0.001 mg to 2000 mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1 mg to 2000 mg, while an intravenous dose may only require from 0.01 mg to 100 mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

[0103] These dosages are based on an average human subject having a weight of about 60 kg to 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

[0104] For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

[0105] According to another embodiment of the present invention, the compounds of the invention can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result. The second and more additional therapeutic agents may also be a compound of the formula (I) or a pharmaceutically and/or veterinarily acceptable derivative thereof, or one or more histamine H_4 receptor ligands known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

[0106] As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the compounds of the invention and one or more other therapeutic agents, is intended to mean, and does refer to and include the following:

- simultaneous administration of such combination of compound(s) of formula (I) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,
- substantially simultaneous administration of such combination of compound(s) of formula (I) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,
- sequential administration of such combination compound(s) of formula (I) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- sequential administration of such combination of compound(s) of formula (I) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlapingly administered at the same and/or different times by said patient,

where each part may be administered by either the same or different route.

[0107] Suitable examples of other therapeutic agents which may be used in combination with the compound(s) of the invention or compositions thereof, include, but are by no means limited to :

- Histamine H_1 receptor antagonists, in particular loratidine, desloratidine, fexofenadine and cetirizine
- Histamine H_3 receptor antagonists
- Histamine H_2 receptor antagonists
- Leukotriene antagonists, including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4; for example Montelukast
- Phosphodiesterase inhibitors, including PDE3 inhibitors, PDE4 inhibitors, PDE5 inhibitors, PDE7 inhibitors and inhibitors of two or more phosphodiesterases, such as dual PDE3/PDE4 inhibitors
- neurotransmitter re-uptake inhibitors, in particular fluoxetine, setraline, paroxetine, ziprasidone
- 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists
- α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use
- Muscarinic M3 receptor antagonists or anticholinergic agents
- β_2-adrenoceptor agonists
- Dual acting β_2/M3 agents
- Xanthines, such as theophylline and aminophylline
- Non-steroidal anti-inflammatories, such as sodium cromoglycate and nedocromil sodium
- Ketotifen
- COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors
- Oral or inhaled Glucocorticosteroids
- Monoclonal antibodies active against endogenous inflammatory entities
- Anti-tumor necrosis factor (anti-TNF-α) agents
- Adhesion molecule inhibitors including VLA-4 antagonists

- Kinin-B_1 - and B_2 -receptor antagonists
- Immunosuppressive agents
- Inhibitors of matrix metalloproteases (MMPs)
- Tachykinin NK_1, NK_2 and NK_3 receptor antagonists
- Elastase inhibitors
- Adenosine A2a receptor agonists
- Inhibitors of urokinase
- Compounds that act on dopamine receptors, e.g. D2 agonists
- Modulators of the NFκb pathway, e.g. IKK inhibitors
- Agents that can be classed as mucolytics or anti-tussive
- Antibiotics
- Modulators of cytokine signaling pathways, such as p38 MAP kinase inhibitors, syk tyrosine kinase inhibitors or JAK kinase inhibitors
- Modulators of the prostaglandin pathways, including inhibitors of H-PDGS and antagonists of DP-1 and CRTH2
- Antagonists of chemokine receptors CXCR1 and CXCR2
- Antagonists of chemokine receptors CCR3, CCR4 and CCR5
- Inhibitors of cytosolic and soluble phospholipase A_2 ($cPLA_2$ and $sPLA_2$)
- Prostaglandin D2 receptor antagonists (DP1 and CRTH2)
- Inhibitors of Prostaglandin D synthase (PGDS)
- Inhibitors of phosphoinositide-3-kinase,
- HDAC inhibitors,
- p38 inhibitors and/or
- CXCR2 antagonists.

[0108] According to the present invention, combination of the compounds of formula (I) with:

- Histamine H_1 receptor antagonists, in particular loratidine, desloratidine, fexofenadine and cetirizine,
- Histamine H_3 receptor antagonists,
- Histamine H_2 receptor antagonists,
- Leukotriene antagonists, including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4, for example Montelukast, and/or,
- Phosphodiesterase PDE4 inhibitors

form a further embodiment of the invention.

[0109] The compounds of formula (I) have the ability to interact with the H_4 receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role, which the H_4 receptor plays in the physiology of all mammals. According to this invention H_4 ligands are meant to include H_4 receptor antagonists, agonists and inverse agonists. For the preferred indications to be treated according to the invention, H_4 antagonists are believed to be most suitable.

[0110] Therefore, a further aspect of the present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts, derived forms or compositions thereof, for use as medicaments, more particularly in the treatment of diseases, disorders, and conditions in which the H_4 receptor is involved. More specifically, the present invention also concerns the compounds of the invention for use in the treatment of diseases, disorders, and conditions selected from the group consisting of:

- inflammatory diseases;
- respiratory diseases (e.g. adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis), allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion;
- female and male sexual dysfunction;
- skin diseases such as dermatitis and psoriasis;
- cardiac dysfunctions such as myocardial ischaemia and arrythmia;
- diseases of the gastrointestinal tract such as inflammatory bowel disease, Crohn's disease and colitis ulcerosa;
- cancer;
- rheumatoid arthritis;
- hypotension;
- inflammatory pain and
- overactive bladder conditions.

[0111] The compounds of formula (I) according to the present invention are particularly suitable for the treatment of asthma, allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion and allergic congestion.

[0112] A still further aspect of the present invention also relates to the use of the compounds of the invention for the manufacture of a drug being a H_4 ligand. In particular, the present inventions concerns the use of the compounds of formula (I), or pharmaceutically and/or veterinarily acceptable derivatives thereof, for the manufacture of a drug for the treatment of H_4 mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

[0113] As a consequence, the present invention provides a particularly interesting method to treat a mammal, including a human being, with an effective amount of a compound of formula (I), or a pharmaceutically and/or veterinarily acceptable derivative thereof. More precisely, the present invention provides a particularly interesting method for the treatment of a H_4 mediated diseases and/or conditions in a mammal, including a human being, in particular the diseases and/or conditions listed above, comprising administering to said mammal an effective amount of a compound of the invention.

[0114] The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, are easier and/or safer to prepare, have fewer side effects or are more selective, or have other more useful properties than the compounds of the prior art.

[0115] The following examples illustrate the preparation of compounds of formula (I) according to the present invention

[0116] ^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million (ppm) downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) and br (broad). The mass spectra (m/z) were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). Purfication by SCX indicates use of strong cation exchange resin.

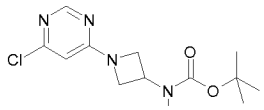
[0117] In the examples section, the following abbreviations are used:

DCM	dichloromethane
DIPEA	N-ethyl-N-isopropylpropan-2-amine
DMSO	dimethyl sulphoxide
IPA	2-propanol
NMP	1-methylpyrrolidin-2-one
SCX	strong cation exchange
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin-layer chromatography

Examples

Preparation 1: *tert*-Butyl [1-6-chloro-pyrimidin-4-yl-azetidin-3-yl]-methyl-carbamate

[0118]

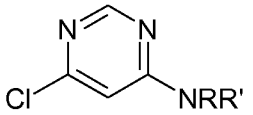


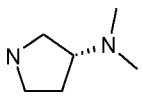
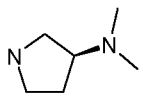
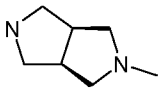
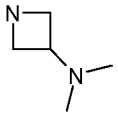
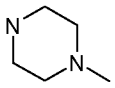
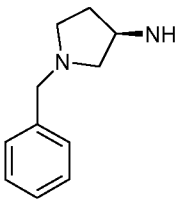
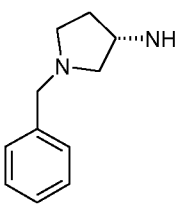
[0119] Azetidin-3-yl-methyl-carbamic acid *tert*-butyl ester (1.97 g, 11 mmol) in IPA (5 mL) was added dropwise to a stirred solution of 4,6-dichloropyrimidine (1.49 g, 10 mmol) in IPA (20 mL) followed by dropwise addition of TEA (2.11 mL, 15.1 mmol) at ambient temperature under N_2. The resulting milky yellow solution was heated to 80 °C and maintained at 80 °C for 2 hours. The solution was allowed to cool and evaporated to dryness to give a yellow oil. The crude material was partitioned between DCM (70 mL) and water (30 mL). The aqueous extract was re-extracted with DCM (70 mL). The combined organic extract was washed with saturated aqueous sodium bicarbonate (30 mL), dried ($MgSO_4$), filtered and evaporated to give a golden coloured oil. The crude oil was purified by flash column chromatography on silica gel eluting with DCM : MeOH (99 : 1 changing to 96 : 4 by volume) to yield the title compound as a solid (1.93 g, 64%).
^{1}H NMR (400MHz, CD_3OD): δ 8.25 (1H, d), 6.47 (1H, s), 4.9 (1H, br s), 4.31 (2H, t), 4.21 (2H, m), 2.94 (3H, s), 1.45

(9H, s) ppm.
MS (ESI) m/z 299 $[M+H]^+$

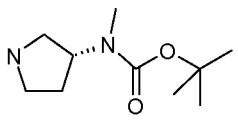
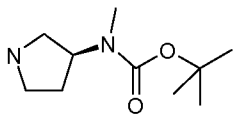
Preparations 2 to 11

[0120] The following compounds of the general formula shown below were prepared by a method similar to that described for preparation 1 using the appropriate starting material and 4,6-dichloropyrimidine. The reactions were monitored by TLC analysis and were heated to reflux for 3 to 18 hours.



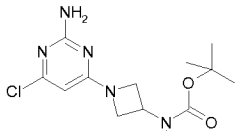
No.	NRR'	Name	Yield	LRMS m/z
2		(3R)-1-(6-Chloropyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine	66%	227
3		(3S)-1-(6-Chloropyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine	81%	227
4		(3aR*,6aS*)-2-(6-Chloropyrimidin-4-yl)-5-methyloctahydropyrrolo [3,4-c]pyrrole	77%	239
5		1-(6-Chloropyrimidin-4-yl)-N,N-dimethylazetidin-3-amine	55%	213
6		4-Chloro-6-(4-methylpiperazin-1-yl)pyrimidine	77%	213
7		(1S,4S)-2-(6-Chloropyrimidin-4-yl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane	97%	225
8		N-[(3R)-1-Benzylpyrrolidin-3-yl]-6-chloropyrimidin-4-amine	64%	289
9		N-[(3S)-1-Benzylpyrrolidin-3-yl]-6-chloropyrimidin-4-amine	49%	289

(continued)

No.	NRR'	Name	Yield	LRMS m/z
10		*tert*-Butyl [(3R)-1-(6-chloropyrimidin-4-yl)pyrrolidin-3-yl]methylcarbamate	86%	313
11		*tert*-Butyl [(3S)-1-(6-chloropyrimidin-4-yl)pyrrolidin-3-yl]methylcarbamate	95%	313

Preparation 12: *tert*-Butyl [1-(2-amino-6-chloro-pyrimidin-4-yl)-azetidin-3-yl]-methyl-carbamate

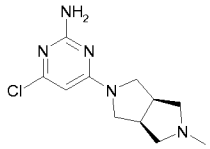
[0121]



[0122] 2-Amino-4,6-dichloropyrimidine (26.2 g, 160 mmol) was added portionwise to a stirred solution of azetidin-3-yl-methyl-carbamic acid *tert*-butyl ester HCl salt (37.4 g, 168 mmol) in absolute EtOH (400 mL) followed by TEA (55.6 mL, 400 mmol) dropwise at ambient temperature. The resulting suspension was warmed to reflux (initially a clear solution was observed on warming) which resulted in the gradual formation of a precipitate. The mixture was refluxed for a total of 2 hours. The mixture was allowed to cool and diluted with water (200 mL) dropwise over 30 min and stirring continued for 45 min. The resulting solid was filtered, washed with water (150 mL) and dried under suction to yield the title compound as a white solid (42.74 g, 85%).
^{1}H NMR (400MHz, $CDCl_3$): δ 5.66 (1 H, s), 5.02 (1 H, br s), 4.86 (2H, br s), 4.20 (2H, t), 4.04 (2H, m), 2.91 (3H, s), 1.47 (9H, s) ppm.
MS (APCI) m/z 314 $[M+H]^+$

Preparation 13: 4-Chloro-6-[(3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidin-2-amine

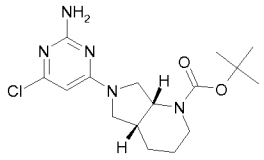
[0123]



[0124] 2-Amino-4,6-dichloropyrimidine (1.64 g, 10 mmol) was added portionwise to a stirred solution (3a*R*,6a*S*)-2-methyloctahydropyrrolo[3,4-c]pyrrole (1.6 g, 12.5 mmol) in absolute EtOH (10 mL) followed by TEA (1.8 mL, 12.5 mmol) dropwise at ambient temperature. The resulting suspension was warmed to reflux (initially a clear solution was observed on warming) and resulted in the gradual formation of a tan coloured precipitate. The mixture was refluxed for a total of 3 hours. The mixture was allowed to cool, EtOH (30 mL) was added to the mixture and heated to give a solution and was left to cool to ambient temperature. The resulting solid was collected by filtration, washed with cold EtOH (50 mL) and dried under suction to yield the title compound as a solid (2.07 g, 82%).
^{1}H NMR (400MHz, CD_3OD): δ 5.88 (1H, s), 3.62 (2H, m), 3.41(2H, m), 3.0 (2H, m), 2.78 (2H, m), 2.47 (2H, dd), 2.33 (3H, s) ppm.
MS (APCI) m/z 254, 256 $[M+H]^+$

Preparation 14: *tert*-Butyl (4aR*,7aR*)-6-(2-amino-6-chloropyrimidin-4-yl)octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate

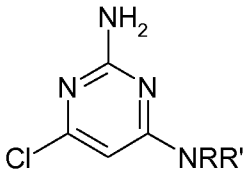
[0125]

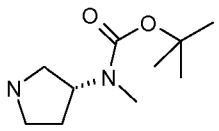
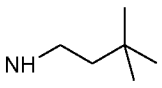
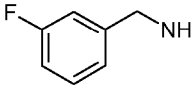
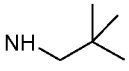


[0126] To a solution of racemic *tert*-butyl (4aR*,7aR*)-octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate (460 mg, 2.03 mmol) in EtOH (1 mL) containing DIPEA (590 μL, 3.39 mmol) was added a solution of 2-amino-4,6-dichloropyrimidine (277 mg, 169 mmol) in EtOH (9 mL) with stirring and the solution was heated to reflux for 24 hours. The solution was cooled and diluted with water (10 mL) and the resulting solid was collected by filtration, washed with water (20 mL) and dried *in vacuo* at 60 °C to yield the title compound as a white solid (558 mg, 93%).
^{1}H NMR (400MHz, CD_3OD): δ 5.85 (1H, s), 4.7 (1H, m), 3.98 (1H, m), 3.8 - 3.55 (1H, m), 3.47 (1H, m), 3.45 - 3.15 (1 H, m), 2.85 (1 H, m), 2.25 (1 H, m), 1.85 - 1.65 (2H, m), 1.5 - 1.15 (12H, m)
MS (APCI) m/z 354, 356 $[M+H]^+$

Preparations 15 to 19

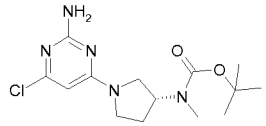
[0127] The following compounds of the general formula shown below were prepared by a method similar to that described for preparation 1 using the appropriate amine and 2-amino-4,6-dichloropyrimidine. The reactions were monitored by TLC analysis and were heated to reflux for 3 to 18 hours.



No.	NRR'	Name	Yield	LRMS m/z
15		*tert*-Butyl [(3R)-1-(2-amino-6-chloropyrimidin-4-yl)pyrrolidin-3-yl]methylcarbamate	100%	328
16		6-Chloro-N^4-(3,3-dimethylbutyl)pyrimidine-2,4-diamine	99%	229
17		6-Chloro-N^4-ethylpyrimidine-2,4-diamine	73%	173
18		6-Chloro-N^4-(3-fluorobenzyl)pyrimidine-2,4-diamine	75%	253
19		6-Chloro-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine	66%	213

Alternative method for preparation 15 *tert*-Butyl [(3R)-1-(2-amino-6-chloropyrimidin-4-yl)pyrrolidin-3-yl]methyl-carbamate

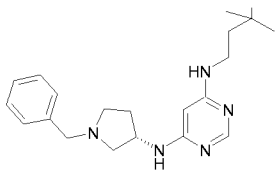
[0128]



[0129] A suspension of 2-amino-4,6-dichloropyrimidine (3.62g, 22.1mmol) and the amine of preparation 47 (5.40g, 27.0mmol) in ethanol (45ml) was treated with TEA (4.62ml, 33.1mmol) and the resulting mixture heated at 80°C for 1 hour. The reaction was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was separated and the aqueous extracted with further ethyl acteate. The combined organic extracts were dried (magnesium sulphate) and the solvent removed in vacuo to give an orange oil. Trituration with di-isopropyl ether gave a pale yellow solid which was filtered and dried in vacuo to give the title compound (7.0g, 87%).
^{1}H NMR (400MHz, $DMSO_{d6}$): δ 5.77 (1H, s), 4.60 (1H, br m), 3.27 (4H, br m), 2.70 (3H, s), 2.02 (2H, br m), 1.39 (9H, s) ppm.
MS (ESI) m/z 327 $[M+H]^+$

Preparation 20: *N*-[(3*S*)-1-Benzylpyrrolidin-3-yl]-*N'*-(3,3-dimethylbutyl)pyrimidine-4,6-diamine

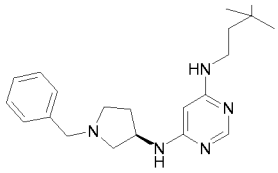
[0130]



[0131] A solution of the title compound of preparation 9 (2.7 g, 9.4 mmol), 3,3-dimethylbutan-1-amine (6.3 mL, 46 mmol) and DIPEA (1.63 mL, 9.4 mmol) in NMP (100 mL) was heated to 150 °C in a sealed vessel for 24 hours. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with water (2 x 400 mL) followed by saturated aqueous sodium chloride (500 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was triturated with diethyl ether and the resulting solid collected by filtration to yield the title compound as a white powder (2.15 g, 65%).
MS (APCI) m/z 354 $[M+H]^+$

Preparation 21: *N*-[(3R)-1-Benzylpyrrolidin-3-yl]-*N'*-(3,3-dimethylbutyl)pyrimidine-4,6-diamine

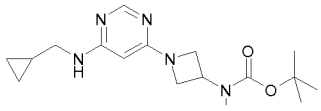
[0132]



[0133] The title compound was prepared by a method similar to that described for preparation 20, using the title compound of preparation 8, in 48% yield.
MS (APCI) m/z 354 $[M+H]^+$

Preparation 22: *tert*-Butyl {1-[6-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

[0134]



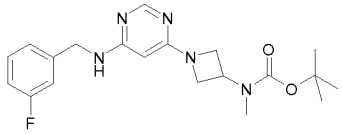
[0135] To a 5 mL reacti-vial™ containing the title compound of preparation 1 (100 mg, 0.33 mmol) and cyclopropylmethylamine (50 mg, 0.68 mmol) in DMSO (3 mL) was added TEA (94 μL, 0.68 mmol) and the solution was heated at 140 °C for 18 hours. The reaction was allowed to cool to ambient temperature, loaded onto a 5g SCX column, eluted with MeOH (100 mL) followed by 2M ammonia in MeOH (100 mL). Fractions containing product (as judged by TLC) were combined and evaporate to give a crude orange oil. The crude product was purified by flash column chromatography on silica gel eluting with DCM : MeOH (99 : 1 changing to 96 : 4 by volume) to yield the title compound as a colourless oil (75 mg, 67%).

^{1}H NMR (400MHz, $CDCl_3$): δ 8.13 (1H, s), 5.08 (1H, s), 4.79 (1H, br s), 4.20 (2H, t), 4.01 (2H, m), 3.04 (2H, t), 2.93 (3H, s), 1.46 (9H, s), 1.05 (1 H, m), 0.55 (2H, m), 0.24 (2H, m) ppm.

MS (APCI) m/z 334 $[M+H]^+$

Preparation 23: *tert*-Butyl {1-[6-(3-fluoro-benzylamino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

[0136]



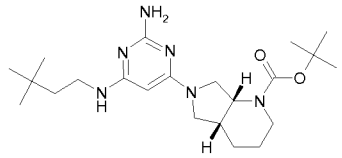
[0137] To a 5ml reacti-vial™ containing the title compound of preparation 1 (100 mg, 0.33 mmol) and 3-fluorobenzylamine (76 μL, 0.68 mmol) in DMSO (3 mL) was added TEA (9 μL, 0.68 mmol) and the solution was heated at 140 °C for 18 hours. The reaction was allowed to cool to ambient temperature and concentrated *in vacuo* to obtain crude product as a viscous orange oil. The crude product was purified by flash column chromatography on silica gel eluting with DCM : MeOH (99 : 1 changing to 97 : 3 by volume) to yield the title compound as a light beige coloured solid (49 mg, 38%).

^{1}H NMR (400MHz, $CDCl_3$): δ 8.18 (1H, s), 7.30 (1H, m), 7.09 (1H, m), 7.02 (1H, d), 6.97 (1H, m), 5.09 (1H, s), 5.0 (1H, br d), 4.46 (2H, d), 4.17 (2H, t), 3.98 (2H, m), 2.92 (3H, s), 1.47 (9H, s) ppm.

MS (APCI) m/z 388 $[M+H]^+$

Preparation 24: *tert*-Butyl (4aR*,7aR*)-6-{2-amino-6-[(3,3-dimethylbutyl)amino]pyrimidin-4-yl}octahydro-1H-pyrrolo[3,4-b]pyridine-1-carboxylate

[0138]



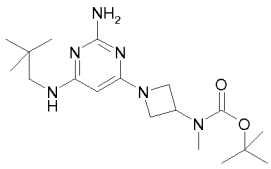
[0139] To a solution of the title compound of preparation 14 (60 mg, 0.17 mmol) in DMSO (150 μL) was added 3,3-dimethylbutan-1-amine (229 μL, 1.7 mmol) and the reaction mixture was heated to 120 °C in a sealed vessel for 48 hours. The reaction mixture was diluted with water (4 mL) and extracted with ethyl acetate (4 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo.* The residue was dissolved in MeOH (0.5 ml) and purified using a phenomomnex HPLC C-18 column eluting with acetonitrile:water (5 : 95 changing to 95 : 5 by volume containing 0.1% TFA by volume) to yield the title compound as a gum (45 mg, 63%).

^{1}H NMR (400MHz, $CDCl_3$): δ 8.41 - 8.33 (1H, m), 7.6 - 7.3 (1H, m), 6.15 (1H, br s), 4.92 - 4.69 (1H, m), 4.65 (1H, s), 4.05 (1H, d), 3.89 - 3.19 (5H, m), 3.17 - 3.09 (2H, m), 2.77 (1H, t), 2.39 - 2.19 (1H, m), 1.88 - 1.65 (2H, m), 1.62 - 1.51 (2H, m), 1.49 (9H, s), 1.44 - 1.17 (1H, m) 0.97 (9H, s) ppm.

MS (ESI) m/z 419 $[M+H]^+$

Preparation 25: *tert*-Butyl (1-{2-amino-6-[(2,2-dimethylpropyl)amino]pyrimidin-4-yl}azetidin-3-yl)methyl-carbamate

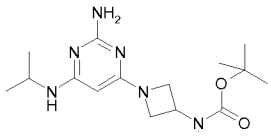
[0140]



[0141] To a solution of the title compound of preparation 12 (40 mg, 0.13 mmol) in DMSO (150 μL) was added isopropylamine (150 μL, 1.7 mmol) and the resulting mixture was heated to 120 °C in a sealed vessel for 48 hours. The reaction mixture was concentrated *in vacuo* to give a brown gum. The residual gum was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (990 : 10 : 1 changing to 190 : 10 : 1 by volume) to yield the title compound as a gum (20 mg, 42%).
^{1}H NMR (400MHz, CD_3OD): δ 4.83 (1H, s), 4.13 (2H, t), 3.97 (2H, dd), 3.01 (2H, s), 2.93 (3H, s), 1.46 (9H, s), 0.94 (9H, s) ppm.
MS (ESI) m/z 365 $[M+H]^+$

Preparation 26: *tert*-Butyl [1-(2-amino-6-isopropylamino-pyrimidin-4-yl)-azetidin-3-yl]-methyl-carbamate

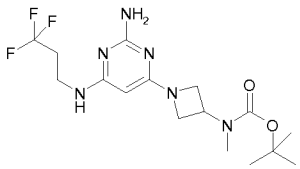
[0142]



[0143] To a solution of the title compound of preparation 12 (40 mg, 0.13 mmol) in DMSO (150 μL) was added isopropylamine (150 μL, 1.7 mmol) and the resulting mixture was heated to 120 °C in a sealed vessel for 48 hours. The reaction mixture was concentrated *in vacuo* to give a brown gum. The residual gum was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (990 : 10 : 1 changing to 190 : 10 : 1 by volume) to yield the title compound as a gum (22 mg, 50%).
^{1}H NMR (400MHz, $CDCl_3$): δ 4.95 (1 H, br s), 4.67 (1 H, s), 4.48 (2H, br s), 4.33 (1 H, br d), 4.16 (2H, br t), 3.95 (2H, dd), 3.72 (1H, m), 2.92 (3H, s), 1.46 (9H, s) 1.19 (6H, d) ppm.
MS (APCI) m/z 337 $[M+H]^+$

Preparation 27: *tert*-Butyl {1-[2-amino-6-(3,3,3-trifluoro-propylamino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

[0144]

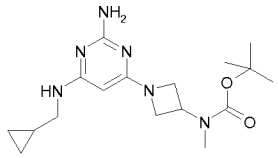


[0145] To a solution of the title compound of preparation 12 (30 mg, 0.1 mmol) in EtOH (200 μL) was added 3,3,3 trifluoropropylamine hydrochloride (48 mg, 0.3 mmol) followed by TEA (100 μL, 0.7 mmol) and the resulting mixture was heated under microwave irradiation to 130 °C in a sealed vessel for 90 min. The reaction mixture was concentrated *in vacuo* to give a brown gum. The residual gum was purified by flash column chromatography eluting with DCM : MeOH : 880 ammonia (99 : 1 : 0.1 changing to 95 : 5 : 0.5, by volume) to yield the title compound as a gum (15 mg, 38%).
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.71 (1 H, br t), 5.13 (2H, br s), 4.87 (1 H, br s), 4.84 (1 H, s), 4.04 (2H, t), 3.88 (2H,

dd), 3.54 (2H, q), 2.91 (3H, s), 2.52 (2H, m), 1.44 (9H, s) ppm.
MS (APCI) m/z 391 $[M+H]^+$

Preparation 28: *tert*-Butyl {1-[2-amino-6-(cyclopropylmethyl-amino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

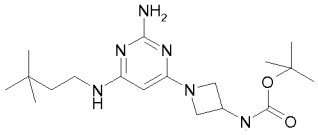
[0146]



[0147] The title compound was prepared by a method similar to that described for preparation 26, using the title compound of preparation 12 and cyclopropylmethylamine, in 48% yield.
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.51 (1H, m), 5.08 (2H, br s), 4.87 (1H, br s), 4.79 (1H, s), 4.03 (2H, t), 3.87 (2H, dd), 3.08 (2H, t), 2.90 (3H, s), 1.43 (9H, s), 1.02 (1H, m), 0.42 (2H, m), 0.19 (2H, m) ppm.
MS (APCI) m/z 349 $[M+H]^+$

Preparation 29: *tert*-Butyl {1-[2-amino-6-(3,3-dimethyl-butylamino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

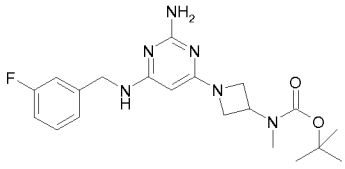
[0148]



[0149] The title compound was prepared by a method similar to that described for preparation 26, using the title compound of preparation 12 and 3,3-dimethylbutan-1-amine, in 58% yield.
^{1}H NMR (400MHz, $CDCl_3$): δ 5.0 (1H, br s), 4.67 (1H, s), 4.52 (2H, br s), 4.36 (1H br t), 4.16 (2H, t), 3.96 (2H, m), 3.13 (2H, m), 2.92 (3H, s), 1.50 - 1.45 (11 H, m), 0.95 (9H, s) ppm.
MS (APCI) m/z 379 $[M+H]^+$

Preparation 30: *tert*-Butyl {1-[2-amino-6-(3-fluoro-benzylamino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

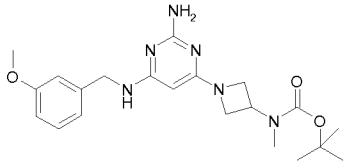
[0150]



[0151] The title compound was prepared by a method similar to that described for preparation 26, using the title compound of preparation 12 and 3-fluorobenzylamine using 1,2-diethoxy-ethane as reaction solvent, in 53% yield.
^{1}H NMR (400MHz, $CDCl_3$): δ 7.28 (1H, m), 7.08 (1H, d), 7.01(1H, br d), 6.95 (1H, br t), 5.15 (1H, br t), 5.00 (1H, br s), 4.80 (2H, br s), 4.64 (1 H, s), 4.41 (2H, br d), 4.13 (2H, t), 3.96 (2H, dd), 2.90 (3H, s), 1.45 (9H, s) ppm.
MS (ESI) m/z 403 $[M+H]^+$

Preparation 31: *tert*-Butyl {1-[2-amino-6-(3-methoxy-benzylamino)-pyrimidin-4-yl]-azetidin-3-yl-methyl-carbamate

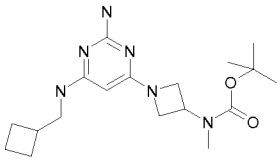
[0152]



[0153] The title compound was prepared by a method similar to that described for preparation 26, using the title compound of preparation 12 and 3-methoxy-benzylamine, in 17% yield.
^{1}H NMR (400MHz, CD_3COCD_3): δ 7.20 (1 H, t), 6.93 - 6.89 (2H, m), 6.78 (1 H, dd), 5.96 (1 H, br t), 5.12 (2H, br s), 5.00 - 4.70 (2H, m), 4.46 (2H, d), 4.01 (2H, t), 3.86 (2H, m), 3.76 (3H, s), 2.90 (3H, s), 1.44 (9H, s) ppm.

Preparation 32: *tert*-Butyl {1-[2-amino-6-(cyclobutylmethyl-amino)-pyrimidin-4-yl]-azetidin-3-yl-methyl-carbamate

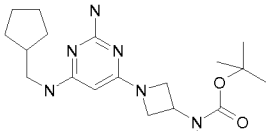
[0154]



[0155] To a solution of the title compound of preparation 1 (30 mg, 0.10 mmol) in DMSO (150 μL) was added cyclobutylmethylamine hydrogen chloride (127 mg, 1 mmol) followed by DIPEA (300 μL, 1.76 mmol) and the resulting mixture was heated to 120 °C in a sealed vessel for 48 hours. The reaction mixture was concentrated *in vacuo* to give a gum. The residual gum was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (990 : 10 : 1 changing to 190 : 10 : 1 by volume) to yield the title compound as a gum (12 mg, 33%).
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.52 (1H, m), 5.13 (2H, br s), 4.87 (1H, br s), 4.79 (1H, s), 4.05 (2H, t), 3.86 (2H, dd), 3.25 (2H, t), 2.91 (3H, s), 2.56 (1H, m), 2.05 - 1.97 (H, m), 1.89 - 1.80 (2H, m), 1.77 - 1.69 (2H, m), 1.44 (9H, s) ppm.
MS (ESI) m/z 363 $[M+H]^+$

Preparation 33: *tert*-Butyl {1-[2-amino-6-(cyclopentylmethyl-amino)-pyrimidin-4-yl]-azetidin-3-yl}-methyl-carbamate

[0156]

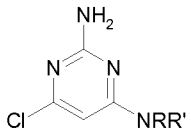


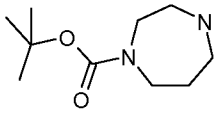
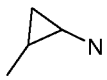
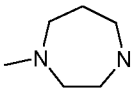
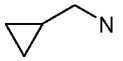
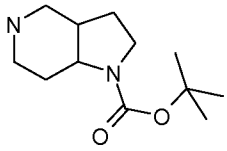
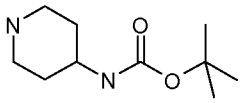
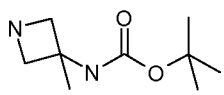
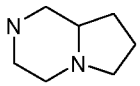
[0157] The title compound was prepared by a method similar to that described for preparation 26, using the title compound of preparation 12 and cyclopentylmethylamine hydrogen chloride, in 16% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.79 (1H, s), 4.15 (2H, t), 4.00 (2H, dd), 3.10 (2H, d), 2.93 (3H, s), 2.14 (1 H, m), 1.83 - 1.75 (2H, m), 1.69 - 1.53 (4H, m), 1.46 (9H, s), 1.30 - 1.22 (2H, m) ppm.
MS (APCI) m/z 377 $[M+H]^+$

Preparations 34 to 42

[0158] The following compounds of the general formula shown below were prepared by a method similar to that

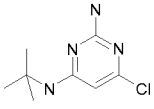
described for preparation 1 using the appropriate amine and 2-amino-4,6-dichloropyrimidine. Reactions were monitored by TLC analysis.



No.	NRR'	Name	LRMS m/z
34		*tert*-Butyl 4-(2-amino-6-chloropyrimidin-4-yl)-1,4-diazepane-1-carboxylate	328
35		6-Chloro-N^4-(2-methylcyclopropyl)pyrimidine-2,4-diamine	199
36		4-Chloro-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-2-amine	242
37		6-Chloro-N^4-(cyclopropylmethyl)pyrimidine-2,4-diamine	254
38		tert-Butyl (3aR*,7aS*)-5-(2-amino-6-chloropyrimidin-4-yl)octahydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate	354
39		N^4-Bicyclo[1.1.1]pent-1-yl-6-chloropyrimidine-2,4-diamine	211
40		*tert*-Butyl [1-(2-amino-6-chloropyrimidin-4-yl)piperidin-4-yl]carbamate	328
41		*tert*-Butyl [1-(2-amino-6-chloropyrimidin-4-yl)-3-methylazetidin-3-yl]methylcarbamate	328
42		4-Chloro-6-(hexahydropyrrolo[12-a]pyrazin-2(1H)-yl)pyrimidin-2-amine	254

Preparation 43: N^4-(*tert*-Butyl)-6-chloropyrimidine-2,4-diamine

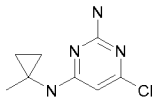
[0159]



[0160] A solution of 2-amino-4,6-dichloropyrimidine (400mg, 2.44mmol) and t-butylamine (2.6ml, 25.0mmol) in NMP (1ml) was heated in a microwave at 150°C for 60 minutes. The reaction mixture was partitioned between water (10ml) and ethyl acetate (10ml), the organic phase separated, dried and reduced in vacuo. Purification by flash column chromatography on silica gel eluting with ethyl acetate:pentane (30:70 changing to 80:20 by volume) to yield the title compound as a colourless solid (494mg, 100%).
^{1}H NMR (400MHz, $CDCl_3$): δ 5.80 (1H, s), 4.78 (2H, bs), 1.42 (9H, s) ppm.
MS (ESI) m/z 201 $[M+H]^+$

Preparation 44: 6-Chloro-N^4-(1-methylcyclopropyl)pyrimidine-24-diamine

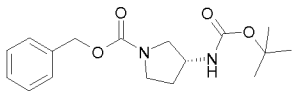
[0161]



[0162] 2-amino-4,6-dichloropyrimidine (508mg, 3.1mmol) was added to a suspension of 1-methylcyclopropylamine hydrochloride (1.0g, 9.3mmol) and sodium methoxide (502mg, 9.30mmol) in NMP (3ml). The resulting mixture was heated at 90°C for 16 hours and then cooled to room temperature. The reaction mixture was diluted with water (20ml) and the resulting precipitate filtered off, washed with further water (20ml) and dried in vacuo to give the title compound as a colourless solid (280mg, 15%).
^{1}H NMR (400MHz, $CDCl_3$): δ 6.71 (1 H, s), 1.37 (3H, s), 0.83-0.79 (2H, m), 0.72-0.65 (2H, m) ppm.
MS (ESI) m/z 199 $[M+H]^+$

Preparation 45 : **Benzyl (3R)-3-[(*tert*-butoxycarbonyl)amino]pyrrolidine-1-carboxylate**

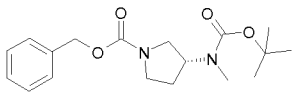
[0163]



[0164] A solution of *tert*-Butyl (3S)-pyrrolidin-3-ylcarbamate (10.0g, 53.7mmol) in DCM (40ml) was treated with TEA (14.9ml, 107mmol) and cooled to 0°C. Benzyl chloroformate (7.6ml, 53.7mmol) was added dropwise and the resulting suspension was allowed to warm gradually to room temperature over a period of 18 hours. The reaction mixture was diluted with water (100ml) and the organic phase separated. The aqueous phase was extracted with further DCM (2 x 50ml) and the combined organic extracts dried (sodium sulphate) and concentrated in vacuo to give a pale yellow solid (14.6g, 85%)
^{1}H NMR (400MHz, $CDCl_3$): δ 7.39-7.29 (5H, m), 5.13 (2H, s), 4.58 (1H, m), 4.19 (1H, m), 3.66 (1H, m), 3.49 (1H, m), 3.25 (1H, m), 2.14 (1H, m), 1.82 (1H, m), 1.44 (9H, s) ppm.
MS (ESI) m/z 321 $[M+H]^+$

Preparation 46 : Benzyl (3R)-3-[(*tert*-butoxycarbonyl)amino]pyrrolidine-1-carboxylate

[0165]



[0166] A solution of the carbamate of preparation 45 (14.6g, 45.6mmol) in THF (85ml) was cooled to 0°C and treated with potassium *tert*-butoxide (4.38g, 59.27mmol). The reaction was left to stir for 30 minutes prior to the addition of methyl iodide (4.26ml, 59.3mmol) and then allowed to warm gradually to room temperature. The reaction mixture was partitioned between ethyl acetate (200ml) and water (100ml). The aqueous phase was separated and extracted with further ethyl acetate (100ml). The combined organic extracts were washed with saturated aqueous sodium chloride

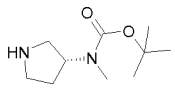
(100ml), dried (magnesium sulphate) and reduced in vacuo to give an orange oil. The oil was re-dissolved in THF (85ml), cooled to 0°C and treated with potassium *tert*-butoxide (3.00g, 40.6mmol). The reaction was left to stir for 30 minutes prior to the addition of methyl iodide (3.0ml, 41.7mmol) and then allowed to warm gradually to room temperature. The reaction mixture was partitioned between ethyl acetate (200ml) and water (100ml). The aqueous phase was separated and extracted with further ethyl acetate (100ml). The combined organic extracts were washed with saturated aqueous sodium chloride (100ml), dried (magnesium sulphate) and reduced in vacuo to give the title compound as an orange oil (15.3g, 100%).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.35-7.26 (5H, m), 5.11 (2H, s), 4.70 (1H, m), 3.58 (2H, m), 3.34 (1H, m), 3.29 (1H, m), 2.74 (3H, s), 1.98 (2H, m), 1.43 (9H, s) ppm.

MS (ESI) m/z 335 $[M+H]^+$

Preparation 47 : *tert*-Butyl methyl[(3R)-pyrrolidin-3-yl]carbamate

[0167]



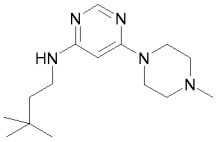
[0168] A solution of the carbamate of preparation 46 (15.58g, 46.6mmol) in ethanol (150ml) was hydrogenated in the presence of 5%Pd/C (1g) at 50psi at room temperature for a period of 18 hours. Further Pd/C (500mg) was added and the resulting mixture hydrogenated under the same conditions for a further 26 hours. The catalyst was filtered off and the filtrate concentrated in vacuo. Purification by chromatography (DCM:MeOH:0.880 ammonia (100:0:0 changing to 90:10:1 by volume) gave the title compounds as a pale yellow oil (5.85g, 62%).

^{1}H NMR (400MHz, $CDCl_3$): δ 4.56 (1H, m), 3.06 (2H, m), 2.87 (1H, m), 2.79 (1H, m), 2.78 (3H, s), 2.54 (1H, s), 1.95 (1H, m), 1.73 (1H, m), 1.43 (9H, s) ppm.

MS (ESI) m/z 201 $[M+H]^+$

Example 1: *N*-(3,3-Dimethylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine

[0169]



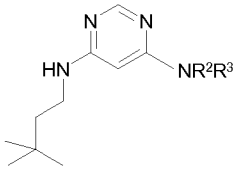
[0170] A solution of the title compound (110 mg, 0.52 mmol) of preparation 6 in NMP (2 mL) was treated with DIPEA (135 μL, 0.78 mmol) and 3,3-dimethylbutan-1-amine (347 μL, 2.6 mmol) and heated to 150 °C for 18 hours in a sealed vessel. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate (20 mL) and water (20 mL). The organic fraction was washed with saturated aqueous sodium chloride (20 mL) dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (90 : 10 : 1 by volume) to yield the title compound as a gum (57mg, 40%).

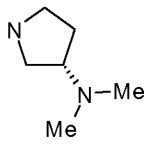
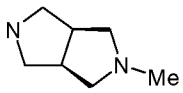
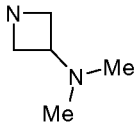
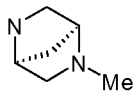
^{1}H NMR (400MHz, CD_3OD): δ 7.95 (1H, s), 5.56 (1H, s), 3.51 (4H, m), 3.23 (2H, m), 2.47 (4H, m), 2.30 (3H, s), 1.49 (2H, m), 0.95 (9H, s) ppm.

MS (APCI) m/z 278 $[M+H]^+$

Examples 2 to 5

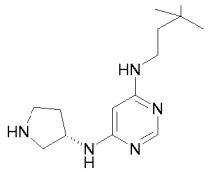
[0171] The following compounds were prepared by a method similar to that described for example 1 using the appropriate starting material.



No.	Preparation No. of Starting material.	NR^2R^3	Name	Yield	LRMS m/z
2	3		6-[(3S)-3-(Dimethylamino)pyrrolidin-1-yl]-N-(3,3-dimethylbutyl)pyrimidin-4-amine	20%	292
3	4		N-(3,3-Dimethylbutyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidin-4-amine	24%	304
4	5		6-[3-(Dimethylamino)azetidin-1-yl]-N-(3,3-dimethylbutyl)pyrimidin-4-amine	41%	278
5	7		N-(3,3-Dimethylbutyl)-6-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidin-4-amine	3%	290

Example 6: *N*-(3,3-Dimethylbutyl)-*N'*-[(3*S*)-pyrrolidin-3-yl]pyrimidine-4,6-diamine

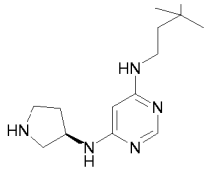
[0172]



[0173] A solution of the compound of preparation 20 (2.15 g, 6.1 mmol) in EtOH (40 mL) and MeOH (20 mL) was cooled to 0 °C and treated with palladium hydroxide (20% on carbon 100 mg) followed by ammonium formate (5.8 g, 91 mmol) and heated to reflux for 2 hours. The reaction mixture was cooled to ambient temperature filtered and the filtrate concentrated *in vacuo.* The residue was purified directly by SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 1N ammonia in MeOH. The basic washings were concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (1 : 0 : 0 changing to 80 : 20 : 1, by volume) to yield the title compound as a white powdery solid (1.2 g, 75%).
^{1}H NMR (400MHz, CD_3OD): δ 7.9 (1H, s), 5.4 (1H, s), 4.1 (1H, m), 3.2 (2H m), 3.1 (1H, m), 3.0 (1H, m), 2.9 (1 H, m), 2.7 (1 H, m), 2.1 (1 H, m), 1.7 (1 H, m), 1.5 (2H, m), 1.0 (9H, s) ppm.
Accurate mass: found 264.2181, $C_{14}H_{26}N_5$ requires 264.2183.

Example 7: N-(3,3-Dimethylbutyl)-*N'*-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine

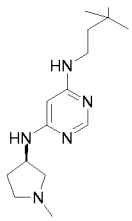
[0174]



[0175] The title compound was prepared by a similar method to that described for example 6, using the title compound of preparation 21, in 70% yield.
^{1}H NMR (400MHz, CD_3OD): δ 7.9 (1H, s), 5.4 (1H, s), 4.1 (1H, m), 3.2 (2H m), 3.1 (1H, m), 3.0 (1H, m), 2.9 (1 H, m), 2.7 (1 H, m), 2.1 (1 H, m), 1.7 (1 H, m), 1.5 (2H, m), 1.0 (9H, s) ppm.
MS (APCI) m/z 264 $[M+H]^+$

Example 8: *N*-(3,3-Dimethylbutyl)-*N'*-[(3*R*)-1-methylpyrrolidin-3-yl]pyrimidine-4,6-diamine

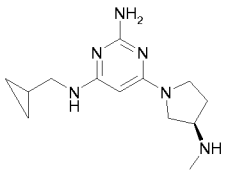
[0176]



[0177] A suspension of the compound of example 7 (38 mg, 0.144 mmol) in THF (1.5 mL) containing aqueous formaldehyde (11 μL, 0.144 mmol, 37% in water) and acetic acid (8.3 μL, 0.144 mmol) was treated with sodium triacetoxyborohydride (37 mg, 0.173 mmol) and stirred at ambient temperature for 10 min. The reaction mixture was applied directly to SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 1N ammonia in MeOH. The basic washings were concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (1 : 0 : 0 changing to 40 : 10 : 1, by volume) further purification on reverse phase silica eluting with water : acetonitrile (1 : 0 changing to 19 : 1 by volume) gave the title compound as a white solid (14 mg, 35%).
^{1}H NMR (400MHz, CD_3OD) δ 7.9 (1H, s), 5.4 1H, s), 4.2 (1H, m), 3.2 (2H, m), 2.9 (1H, m), 2.8 (1H, m), 2.5 (2H, m), 2.4 (4H, m), 1.7 (1H, m), 1.5 (2H, m) 1.1 (9H, s) ppm.
MS (APCI) m/z 278 $[M+H]^+$, 276 $[M-H]^-$

Example 9: N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine

[0178]

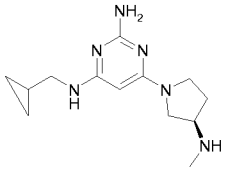


[0179] A solution of the compound of preparation 15 (120 mg, 0.38 mmol) in NMP (2 mL) was treated with DIPEA (191 uL, 1.1 mmol) and 1-cyclopropylmethylamine (99 uL, 1.15 mmol) and heated to 150 °C in a sealed vessel for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (4 x 50 mL) and saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude intermediate *tert*-butyloxycarbonyl-protected compound. This crude material was dissolved in DCM (2 mL), treated with trifluoroacetic acid (2 mL) and stirred at ambient temperature for 3 h after which time the reaction mixture was concentrated *in vacuo.* The residue was purified directly by SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 2 N ammonia in MeOH. The basic washings were concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (1 : 0 : 0 changing to 170 : 30 : 3, by volume) to yield the title compound as a white foam (16 mg, 17%).
^{1}H NMR (400MHz, CD_3OD): δ 4.89 (1H, s), 3.63 (1H, m), 3.55 (1H, m), 3.47 (1H, m), 3.39 (1H, m), 3.23 (1H, m), 3.05

(2H, d), 2.42 (3H, s), 2.21 (1H, m), 1.88 (1H, m), 1.06 (1H, m), 0.52 (2H, q), 0.23 (2H, q) ppm.
MS (APCI) m/z 248 $[M+H]^+$

Alternative method for example 9: N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine

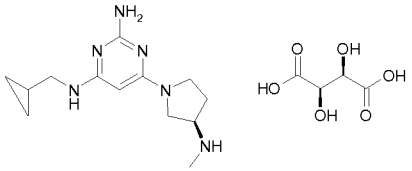
[0180]



[0181] A suspension of the compound of preparation 15 (1.8g, 5.5mmol) in cyclopropylmethanamine (5.4ml, 62.3mmol) and TEA (1.53ml, 11mmol) was heated in a sealed pressure vessel at 120°C for 24 hours. The excess amine was removed in vacuo and the residue partitioned between water (100ml) and DCM (100ml). The aqueous phase was separated and extracted with further DCM (100ml). The combined organic extracts were washed with saturated aqueous sodium chloride (100ml) and the solvent removed in vacuo. Purification by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (98 : 2 : 0 changing to 95 : 5 : 0.2, by volume) gave the to give the intermediate *tert*-butyloxycarbonyl-protected compound (1.55g, 77%).
^{1}H NMR (400MHz, CD_3OD): δ 4.89 (1H, s), 4.71 (1H, m), 3.64 (2H, m), 3.32 (2H, m), 3.07 (2H, d), 2.80 (3H, s), 2.13 (2H, m), 1.46 (9H, s), 1.05 (1H, m), 0.52 (2H, m), 0.23 (2H, m) ppm.
MS (APCI) m/z 363 $[M+H]^+$
[0182] A solution of the intermediate *tert*-butyloxycarbonyl-protected compound (6.18g, 16.6mmol) in methanol (15ml) was treated with 4M HCl in 1,4-dioxan (42ml, 168mmol) and the resulting solution was left to stir at room temperature (exotherm observed on addition of the HCl) for 18 hours. The solvent was removed in vacuo and the residue partitioned between 0.880 ammonia (50ml) and DCM (400ml). The aqueous phase was separated and extracted with further DCM (200ml). The combined organic extracts were dried (sodium sulphate) and the solvent removed in vacuo to give a pale yellow oil (4.00g, 92%).

Example 9a : N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine L-tartrate

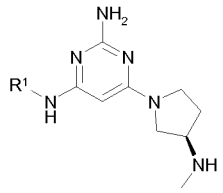
[0183]

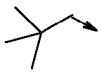


[0184] A solution of the compound of example 9 (10.14g, 38.65mmol) in methanol (340ml) was treated with a solution of L(+) tartaric acid in (5.8g, 38.65mmol) in methanol (50ml). The resulting suspension was stirred at room temperature for 30 minutes and the resulting solid filtered off and dried in vacuo. The solid was dissolved in the minimum volume of boiling water (22ml) and then methanol was added until a permanent ppt was observed (102ml). The resulting suspension was allowed to cool gradually to room temperature and the solid filtered and dried in vacuo for 50°C for 3 days and then allowed to equilibrate at room temperature in air for a further 2 days to give the title compounds as a colourless solid (14.15g, 89%)
^{1}H NMR (400MHz, CD_3OD): δ 6.41 (1H, br s), 5.72 (2H, br s), 4.81 (1H, s), 3.92 (2H, s), 3.58 (2H, m), 3.40 (1H, m), 3.32 (2H, m), 3.03 (2H, m), 2.48 (3H, s), 2.18 (1H, m), 1.95 (1H, m), 0.96 (1H, m), 0.39 (2H, m), 0.12 (2H, m) ppm.
MS (APCI) m/z 263 $[M+H]^+$

Examples 10 to 12

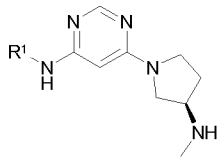
[0185] The following compounds were prepared by a method similar to that described for example 9 using the title compound of preparation 15 and the appropriate amine starting material.

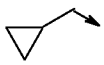


No.	R^1	Name	Yield	LRMS m/z
10		N^4-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine	24%	265
11		N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine	34%	279
12	Et	N^4-Ethyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine	27%	237

Examples 13 to 15

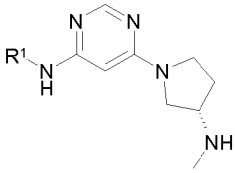
[0186] The following compounds were prepared by a method similar to that described for example 9, using the compound of preparation 10 and the appropriate amine starting material.

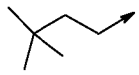


No.	R^1	Name	Yield	LRMS m/z
13	Et	N-Ethyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	64%	222
14		N-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	32%	250
15		N-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	17%	248

Examples 16 to 17

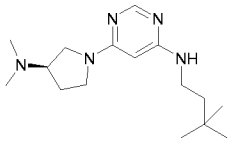
[0187] The following compounds were prepared by a method similar to that described for example 9 using the compound of preparation 11 and the appropriate amine starting material.



No.	R^1	Name	Yield	LRMS m/z
16	Et	N-Ethyl-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	28%	222
17		N-(3,3-Dimethylbutyl)-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	26%	278

Example 18: 6-[(3R)-3-(Dimethylamino)pyrrolidin-1-yl]-N-(3,3-dimethylbutyl)pyrimidin-4-amine

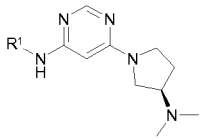
[0188]

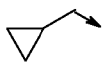
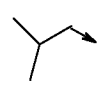


[0189] A solution of the title compound of preparation 2 (120 mg, 0.53 mmol) in NMP (2 mL) was treated with DIPEA (276 μL 1.59 mmol) 3,3-dimethylbutan-1-amine (213 μL, 1.59 mmol) and heated to 150 °C in a sealed vessel for 72 hours. The reaction mixture was cooled and purified directly by SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 2 N ammonia in MeOH. The basic washings were concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (1 : 0 : 0 changing to 40 : 10 : 1, by volume) to yield the title compound as a gum (72 mg, 47%).
^{1}H NMR (400MHz, CD_3OD): δ 7.92 (1H, s), 5.30 (1H, s), 3.72 (1H, m), 3.61 (1H, m), 3.37 (1H, m), 3.24 (2H, m), 3.17 (1H, m), 2.89 (1H, m), 2.32 (6H, s), 2.25 (1H, m), 1.87 (1H, m), 1.52 (2H, m), 0.98 (9H, s) ppm.
MS (APCI) m/z 292 $[M+H]^+$

Examples 19 to 22

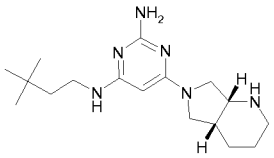
[0190] The following compounds were prepared by a method similar to that described for example 18 using the title compound of preparation 2.



No.	R^1	Name	Yield	LRMS m/z
19		N-(Cyclopropylmethyl)-6-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]pyrimidin-4-amine	64%	262
20		6-[(3R)-3-(Dimethylamino)pyrrolidin-1-yl]-N-isobutylpyrimidin-4-amine	60%	264
21	Et	6-[(3R)-3-(Dimethylamino)pyrrolidin-1-yl]-N-ethylpyrimidin-4-amine	55%	236
22		6-[(3R)-3-(Dimethylamino)pyrrolidin-1-yl]-N-(2,2-dimethylpropyl)pyrimidin-4-amine	41%	278

Example 23: N^4-(3,3-Dimethylbutyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine

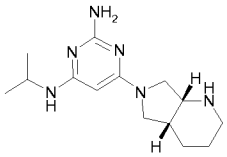
[0191]



[0192] The title compound of preparation 24 (45 mg, 0.11 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred at ambient temperature for 1 hour after which time the reaction mixture was concentrated *in vacuo*. The residue was purified directly by SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 1 N ammonia in MeOH taking 4 mL fractions to yield the title compound as a solid (25 mg, 71 %).
^{1}H NMR (400MHz, CD_3OD): δ 3.52 - 3.33 (5H, m), 3.22 - 3.14 (2H, m), 2.97 - 2.86 (1H, m), 2.66 - 2.57 (1H, m), 2.40 - 2.29 (1H, m), 1.80 - 1.72 (2H, m), 1.70 - 1.55 (1H, m), 1.53 - 1.43 (3H, m), 0.97 (9H, s) ppm.
MS (ESI) m/z 319 $[M+H]^+$

Example 24: N^4-Isopropyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine

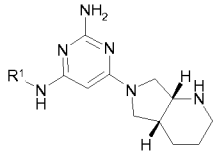
[0193]



[0194] The title compound was prepared by a method similar to that described for example 23 and preparation 24, by reaction of the compound of preparation 14 with isopropyl amine and subsequent deprotection, in 28% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.77 (1H, s), 3.86 - 3.74 (1H, m), 3.51 - 3.34 (5H, m) 2.96 - 2.86 (1H, m), 2.66 - 2.56 (1H, m), 2.40 - 2.26 (1H, m), 1.81 - 1.72 (2H, m), 1.70 - 1.57 (1H, m), 1.54 - 1.41 (1H, m), 1.18 (6H, d) ppm
MS (ESI) m/z 277 $[M+H]^+$

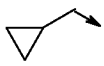
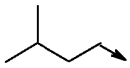
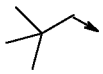
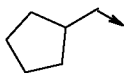
Examples 25 to 33

[0195] The following compounds were prepared by a method similar to that described for example 23 and preparation 24 by reaction of the compound of preparation 14 with an appropriate amine and subsequent deprotection.



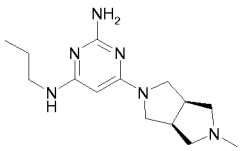
No.	R^1	Name	Yield	LRMS m/z
25	Me	N^4-Methyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	36%	249
26	Et	N^4-Ethyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	11%	263

(continued)

No.	R^1	Name	Yield	LRMS m/z
27		N^4-Isobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	32%	291
28		N^4-(Cyclopropylmethyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	39%	289
29		N^4-(3-Methylbutyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	62%	305
30		N^4-(2,2-Dimethylpropyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	29%	305
31		N^4-Cyclopropyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	19%	275
32		N^4-Cyclobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	43%	289
33		N^4-(Cyclopentylmethyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	11%	317

Example 34: 6-[(3aR*,6aS*)-5-Methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-N^4-propylpyrimidine-2,4-diamine

[0196]



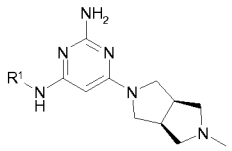
[0197] To a solution of the title compound of preparation 13 (20 mg, 0.08 mmol) in DMSO (75 μL) was added propylamine (75 μL, 1 mmol) and the mixture was heated to 120 °C in a sealed vessel for 48 hours. The reaction mixture was concentrated *in vacuo* to give a brown gum. The residual gum was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (990 : 10 : 1 changing to 90 :10 : 1, by volume) to yield the title compound as a gum (10 mg, 45%).

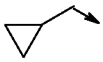
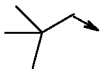
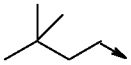
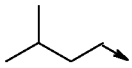
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.28 (1H, br t), 4.97 (3H, m), 3.51 (2H, m), 3.20 (4H, m), 2.83 (H, m), 2.51 (2H, m), 2.41 (2H, m), 2.22 (3H, s) 1.56 (2H, m), 0.92 (3H, t) ppm

MS (ESI) m/z 277 $[M+H]^+$

Examples 35 to 43

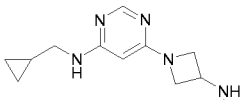
[0198] The following compounds were prepared by a method similar to that described for example 34 using the compound of preparation 13 and the appropriate amine starting material.



No.	R^1	Name	Yield	LRMS m/z
35	Me	N^4-Methyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	30%	249
36	Et	N^4-Ethyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	62%	263
37		N^4-Isobutyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	52%	291
38		N^4-(Cyclopropylmethyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	78%	289
39		N^4-(2,2-Dimethylpropyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	46%	305
40		N^4-(3,3-Dimethylbutyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	48%	319
41		N^4-(3-Methylbutyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	54%	305
42		N^4-Cyclopropyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	27%	275
43		N^4-Cyclobutyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	48%	289

Example 44: Cyclopropylmethyl-[6-(3-methylamino-azetidin-1-yl]-pyrimidin-4-yl]-amine

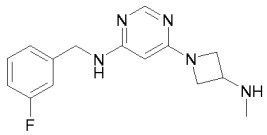
[0199]



[0200] A solution of the title compound of preparation 22 (70 mg, 0.21 mmol) in DCM (5 mL) was treated with trifluoroacetic acid (0.5 mL) and stirred at ambient temperature for 2 hours after which time the reaction mixture was concentrated *in vacuo.* The residue was purified directly by SCX resin, eluting non-basic compounds with MeOH and the basic compounds with 2 N ammonia in MeOH taking 20 mL fractions to yield the title compound (45 mg, 92%).
^{1}H NMR (400MHz, $CDCl_3$): δ 8.12 (1H, s), 5.06 (1H, s), 4.89 (1H, br s), 4.20 (2H, m) 3.71 (3H, m), 3.03 (2H, m), 2.42 (3H, s), 1.05 (1H, m), 0.54 (2H, m), 0.24 (2H, m) ppm.
Accurate mass: found 234.1709, $C_{12}H_{20}N_5$ requires 234.1719.

Example 45: (3-Fluoro-benzyl)-[6-(3-methylamino-azetidin-1-yl)-pyrimidin-4-yl]-amine

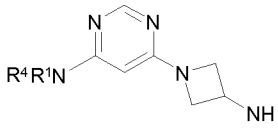
[0201]

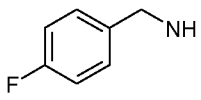
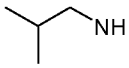
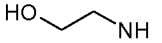
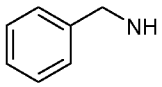
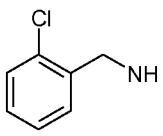


[0202] A solution of the title compound of preparation 23 (42 mg, 0.11 mmol) in DCM (5 mL) was treated with trifluoroacetic acid (0.5 mL) and stirred at ambient temperature for 2 hours after which time the reaction mixture was concentrated *in vacuo.* The residual oil was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (1 : 0 : 0 changing to 182 : 15 : 3, by volume) to yield the title compound as a solid (29 mg, 94%).
^{1}H NMR (400MHz, $CDCl_3$): δ 8.17 (1H, s), 7.29 (1H, m), 7.09 (1H, d), 7.02 (1H, d), 6.97 (1H, m), 5.07 (1H, d), 5.02 (1H, br s), 4.45 (2H, d), 4.16 (2H, m), 3.69 (3H, m), 2.42 (3H, s) ppm.
MS (APCI) m/z 288 $[M+H]^+$

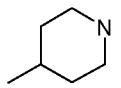
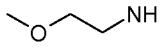
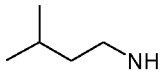
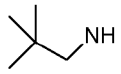
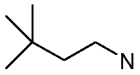
Examples 46 to 59

[0203] The following compounds were prepared by a method similar to that described for example 44 and preparation 22, by reaction of the compound of preparation 1 with an appropriate amine and subsequent deprotection.



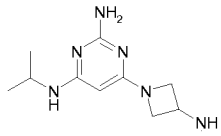
No.	R^4R^1N	Name	Yield	LRMS m/z
46	iPrNH	N-Isopropyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	74%	222
47		N-(4-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	38%	288
48	EtNH	N-Ethyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	92%	208
49		N-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	12%	236
50		2-({6-[3-(Methylamino)azetidin-1-yl]pyrimidin-4-yl}amino)ethanol	41%	224
51		N-Benzyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	27%	270
52		N-(2-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	42%	304

(continued)

No.	R^4R^1N	Name	Yield	LRMS m/z
53		N-Methyl-1-[6-(4-methylpiperidin-1-yl)pyrimidin-4-yl]azetidin-3-amine	46%	262
54		N-(2-Methoxyethyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	77%	238
55		6-[3-(Methylamino)azetidin-1-yl]-N-(3-methylbutyl)pyrimidin-4-amine	85%	250
56		N-Methyl-1-(6-piperidin-1-ylpyrimidin-4-yl)azetidin-3-amine	45%	248
57		N-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	84%	250
58	MeNH	N-Methyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	88%	195
59		N-(3,3-Dimethylbutyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	81%	264

Example 60: N^4-Isopropyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

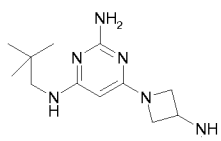
[0204]



[0205] The title compound of preparation 26 (22 mg, 0.07 mmol) was dissolved in trifluoroacetic acid (1 mL) and stirred at ambient temperature for 2 hours after which time the reaction mixture was concentrated *in vacuo.* The residual gum was purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (98 : 2 : 0.2 changing to 90 : 10 : 1, by volume) to yield the title compound as a gum (12mg, 73%).
^{1}H NMR (400MHz, CD_3OD): δ 4.74 (1H, s), 4.1 (2H, dd), 3.82 (1H, m), 3.67 (2H, m), 3.61 (1H, m), 2.33 (3H, s), 1.16 (6H, d) ppm.
MS (APCI) m/z 237 $[M+H]^+$

Example 61: N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine

[0206]

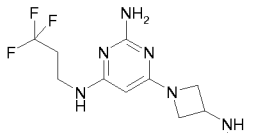


[0207] The title compound was prepared by a method similar to that described for example 60, using the compound

of preparation 25, in 91 % yield.
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.29 (1H, br t), 4.97 (2H, br s), 4.79 (1H, s), 3.97 (2H, t), 3.56 - 3.49 (3H, m), 3.08 (2H, br d), 2.32 (3H, s), 0.93 (9H, s) ppm
MS (ESI) m/z 265 $[M+H]^+$

Example 62: 6-(3-Methylamino-azetidin-1-yl)-N^4-(3,3,3-trifluoro-propyl)-pyrimidine-2,4-diamine

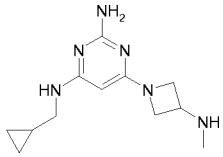
[0208]



[0209] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 27, in 92% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.78 (1H, s), 4.11 (2H, m), 3.68 (2H, dd), 3.62 (1H, m), 3.48 (2H, t), 2.42 (2H, m), 2.34 (3H, s) ppm
MS (ESI) m/z 291 $[M+H]^+$

Example 63: N^4-Cyclopropylmethyl-6-(3-methylamino-azetidin-1-yl]-pyrimidine-2,4-diamine

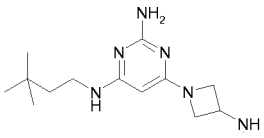
[0210]



[0211] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 28, in 85% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.17 (2H, m), 3.76 (2H, m), 3.70 (1H, m), 3.06 (2H, d), 2.39 (3H, s), 1.01 (1H, m), 0.52 (2H, m), 0.22 (2H, m) ppm.
MS (APCI) m/z 249 $[M+H]^+$

Example 64: N^4-(3,3-Dimethyl-butyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

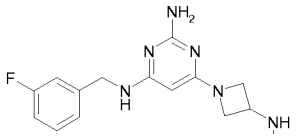
[0212]



[0213] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 29, in 87% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.73 (1H, s) 4.11 (2H, m), 3.68 (2H, m), 3.62 (1H, m), 3.18 (2H, m), 2.33 (3H, s), 1.48 (2H, m), 0.96 (9H, s) ppm.
MS (APCI) m/z 279 $[M+H]^+$

Example 65: N^4-(3-Fluoro-benzyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

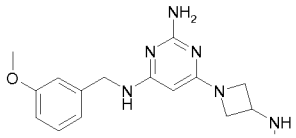
[0214]



[0215] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 30, in 84% yield.
^{1}H NMR (400MHz, CD_3COCD_3): δ 7.32 (1H, m), 7.16 (1H, d), 7.10 (1H, br d), 6.96 (1H, m), 6.01 (1H, m), 5.06 (2H, br s), 4.79 (1 H, s), 4.51 (2H, d), 3.96 (2H, t), 3.57 - 3.48 (3H, m), 2.31 (3H, s) ppm.
MS (APCI) m/z 303 $[M+H]^+$

Example 66: N^4-(3-Methoxy-benzyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

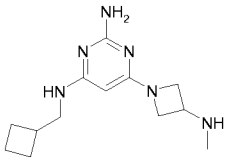
[0216]



[0217] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 31, in 72% yield.
^{1}H NMR (400MHz, CD_3OD): δ 7.20 (1H, t), 6.89 - 6.85 (2H, m), 6.78 (1H, dd), 4.73 (1H, s), 4.37 (2H, s), 4.07 (2H, t), 3.76 (3H, s), 3.65 - 3.55 (3H, m), 2.31 (3H, s) ppm.
MS (APCI) m/z 315 $[M+H]^+$

Example 67: N^4-Cyclobutylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

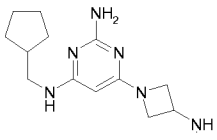
[0218]



[0219] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 32, in 86% yield.
^{1}H NMR (400MHz, CD_3COCD_3): δ 5.31 (1H, m), 4.99 (2H, br s), 4.73 (1H, s), 3.96 (2H, t), 3.58 - 3.50 (3H, m), 3.23 (2H, t), 2.55 (1H, m), 2.32 (3H, s), 2.05 - 1.97(H, m), 1.90 - 1.82 (2H, m), 1.77 - 1.68 (2H, m) ppm.
MS (APCI) m/z 263 $[M+H]^+$

Example 68: N^4-Cyclopentylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine

[0220]

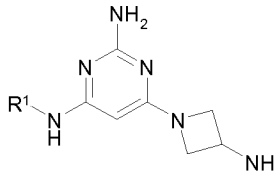


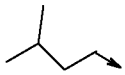
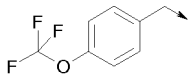
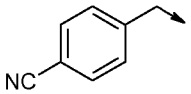
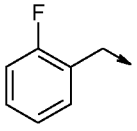
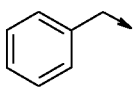
[0221] The title compound was prepared by a method similar to that described for example 60, using the compound of preparation 33, in 81% yield.
^{1}H NMR (400MHz, CD_3OD): δ 4.75 (1H, s), 4.11 (2H, dd), 3.68 (2H, dd), 3.61 (1H, m), 3.09 (2H, d), 2.33 (3H, s), 2.13

(1H, m), 1.83 - 1.75 (2H, m), 1.70 -1.53 (4H, m), 1.29 - 1.21 (2H, m) ppm.
MS (APCI) m/z 277 $[M+H]^+$

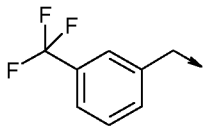
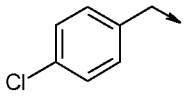
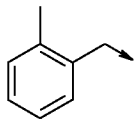
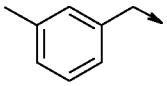
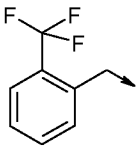
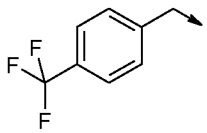
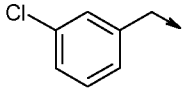
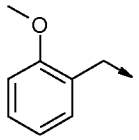
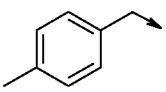
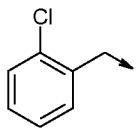
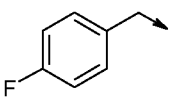
Examples 69 to 90

[0222] The following compounds were prepared by a method similar to that described for example 60 and preparation 26 by reaction of the compound of preparation 12 with an appropriate amine and subsequent deprotection.



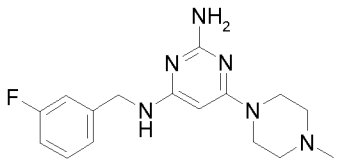
No .	R^1	Name	Yield	LRMS m/z
69	Me	N^4-Methyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	78%	209
70	Et	N^4-Ethyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	83%	223
71		N^4-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	87%	251
72		N^4-Cyclopropyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	74%	235
73		6-[3-(Methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine	85%	237
74		6-[3-(Methylamino)azetidin-1-yl]-N^4-(3-methylbutyl)pyrimidine-2,4-diamine	81%	265
75		N^4-Cyclobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	72%	249
76		6-[3-(Methylamino)azetidin-1-yl]-N^4-[4-(trifluoromethoxy)benzyl]pyrimidine-2,4-diamine	76%	369
77		4-[({2-Amino-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-yl}amino)methyl]benzonitrile	79%	310
78		N^4-(2-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	77%	303
79		N^4-Benzyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	65%	285

(continued)

No .	R^1	Name	Yield	LRMS m/z
80		6-[3-(Methylamino)azetidin-1-yl]-N^4-[3-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine	81%	353
81		N^4-(4-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	73%	319
82		6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbenzyl)pyrimidine-2,4-diamine	68%	299
83		6-[3-(Methylamino)azetidin-1-yl]-N^4-(3-methylbenzyl)pyrimidine-2,4-diamine	79%	299
84		6-[3-(Methylamino)azetidin-1-yl]-N^4-[2-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine	74%	353
85		6-[3-(Methylamino)azetidin-1-yl]-N^4-[4-(trifluoromethyl)benzyl]pyrimidine-2,4-diamine	77%	353
86		N^4-(3-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	71%	319
87		N^4-(2-Methoxybenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	68%	315
88		6-[3-(Methylamino)azetidin-1-yl]-N^4-(4-methylbenzyl)pyrimidine-2,4-diamine	70%	299
89		N^4-(2-Chlorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	72%	319
90		N^4-(4-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	83%	303

Example 91: N^4-(3-Fluorobenzyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine

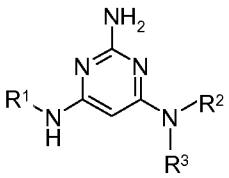
[0223]

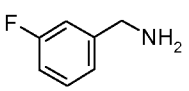
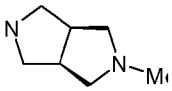
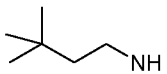
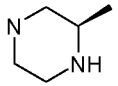
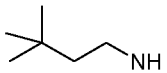
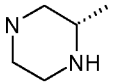
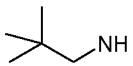
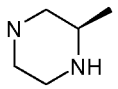
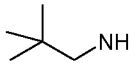
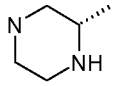
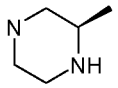
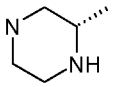


[0224] The title compound of preparation 18 (20 mg, 0.08 mmol) was treated with DMSO (150 μL) and N-methylpiperazine (88 μL, 0.79 mmol) and heated to 120 °C in a sealed vessel for 16 hours. The reaction mixture was cooled to ambient temperature, partitioned between water (2 mL) and ethyl acetate (2 mL) and filtered through diatomaceous earth, washing with further ethyl acetate (15 mL). The organic fraction of the filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with DCM : MeOH : 0.880 ammonia (90 : 10 : 1 changing to 90 : 10 : 1, by volume) to yield the title compound as a gum (20 mg, 79%).
^{1}H NMR (400MHz, CD_3OD): δ 7.34 - 7.27 (1H, m), 7.14 - 7.10 (1H, m), 7.08 - 7.01 (1H, m), 6.98 - 6.89 (1H, m), 5.11 (1H, s), 4.45 (2H, s), 3.51 - 3.42 (4H, m), 2.48 - 2.41 (4H, m), (2.30 (3H, s) ppm.
MS (APCI) m/z 208 $[M\text{-}C_7H_6F_1+2H]^+$

Examples 92 to 98

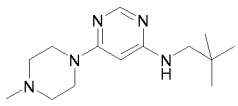
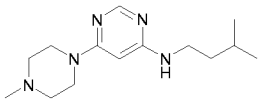
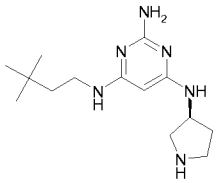
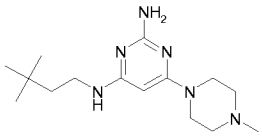
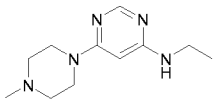
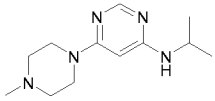
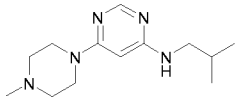
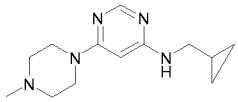
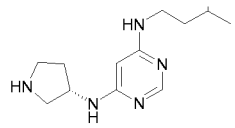
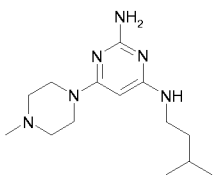
[0225] The following compounds were prepared by a method similar to that described for example 91 using the appropriate pyrimidine starting material and the appropriate amine starting material.



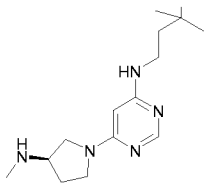
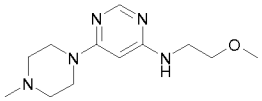
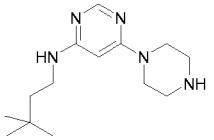
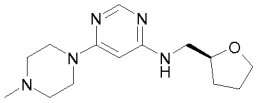
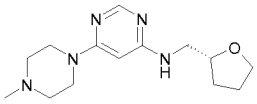
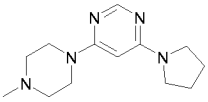
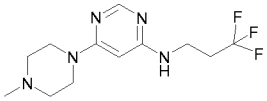
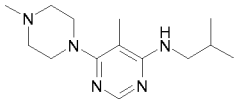
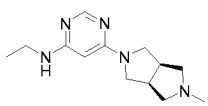
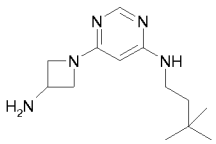
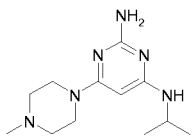
No.	R^1NH	NR^2R^3	Name	Yield	Preparation No. of Starting material	LR MS m/z
92			N^4-(3-Fluorobenzyl)-6-[(3aR*,6aS*)-5-methylhexahydropyrrol o[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine	73%	18	343
93			N^4-(3,3-Dimethylbutyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	92%	16	293
94			N^4-(3,3-Dimethylbutyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	89%	16	293
95			N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	85%	19	279
96			N^4-(2,2-Dimethylpropyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	77%	19	279
97	EtNH		N^4-Ethyl-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	85%	17	237
98	EtNH		N^4-Ethyl-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine	73%	17	237

Examples 99 to 127

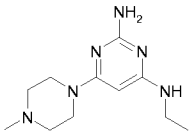
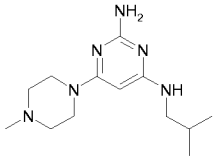
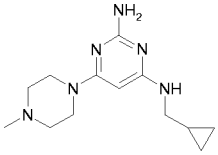
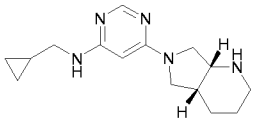
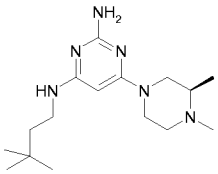
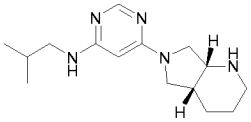
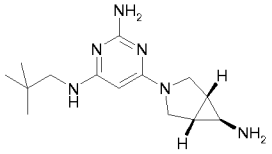
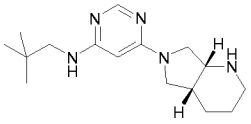
[0226] The following compounds were prepared by similar method to those used to prepare the compounds above.

No.	Structure	Name	LRMS m/z
99		N-(2,2-Dimethylpropyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	264
100		N-(3-Methylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	264
101		N^4-(3,3-Dimethylbutyl)-N^6-[(3S)-pyrrolidin-3-yl]pyrimidine-2,4,6-triamine	279
102		N^4-(3,3-Dimethylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	293
103		N-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	222
104		N-Isopropyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	236
105		N-Isobutyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	250
106		N-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	248
107		N-(3-Methylbutyl)-N'-[(3S)-pyrrolidin-3-yl]pyrimidine-4,6-diamine	250
108		N^4-(3-Methylbutyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	279

(continued)

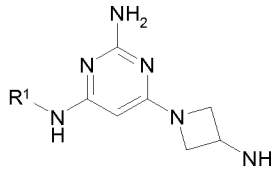
No.	Structure	Name	LRMS m/z
109		N-(3,3-Dimethylbutyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	278
110		N-(2-Methoxyethyl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	252
111		N-(3,3-Dimethylbutyl)-6-piperazin-1-ylpyrimidin-4-amine	264
112		6-(4-Methylpiperazin-1-yl)-N-[(2S)-tetrahydrofuran-2-ylmethyl]pyrimidin-4-amine	278
113		6-(4-Methylpiperazin-1-yl)-N-[(2R)-tetrahydrofuran-2-ylmethyl]pyrimidin-4-amine	278
114		4-(4-Methylpiperazin-1-yl)-6-pyrrolidin-1-ylpyrimidine	248
115		6-(4-Methylpiperazin-1-yl)-N-(3,3,3-trifluoropropyl)pyrimidin-4-amine	290
116		N-Isobutyl-5-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine	263
117		N-Ethyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidin-4-amine	248
118		6-(3-Aminoazetidin-1-yl)-N-(3,3-dimethylbutyl)pyrimidin-4-amine	250
119		N^4-Isopropyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	251

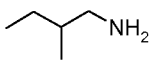
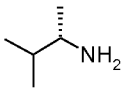
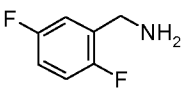
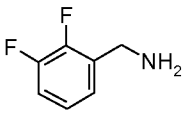
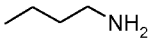
(continued)

No.	Structure	Name	LRMS m/z
120		N^4-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	237
121		N^4-Isobutyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	265
122		N^4-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine	263
123		N-(Cyclopropylmethyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine	274
124		N^4-(3,3-Dimethylbutyl)-6-[(3R)-3,4-dimethylpiperazin-1-yl]pyrimidine-2,4-diamine	307
125		N-Isobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine	276
126		6-[(1R*,5S*,6s*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine	277
127		N-(2,2-Dimethylpropyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine	290

Examples 128 to 132

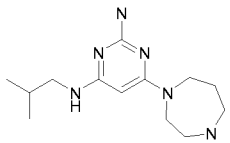
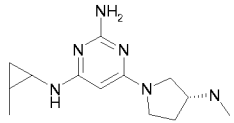
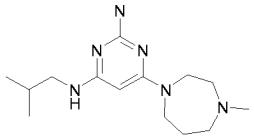
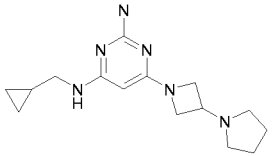
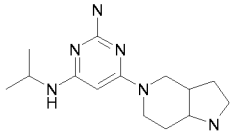
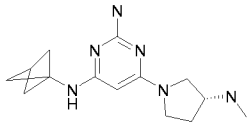
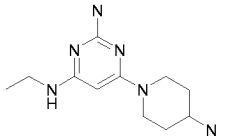
[0227] The following compounds were prepared by a method similar to that described for example 60 and preparation 26 by reaction of the compound of preparation 12 with an appropriate amine and subsequent deprotection.



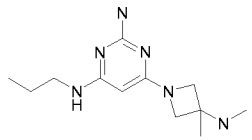
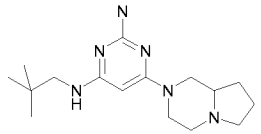
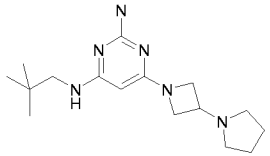
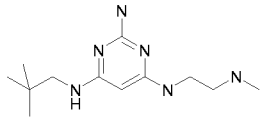
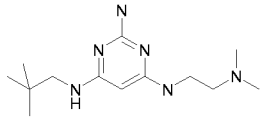
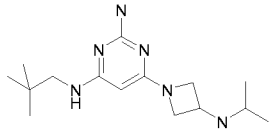
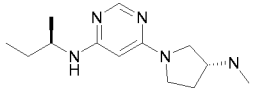
No.	R^1	Name	LRMS m/z
128		6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbutyl)pyrimidine-2,4-diamine	265
129		N^4-[(1*S*)-1,2-Dimethylpropyl]-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	265
130		N^4-(2,5-Difluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	321
131		N^4-(2,3-Difluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	321
132		N^4-Butyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine	251

Examples 133 to 153

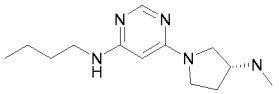
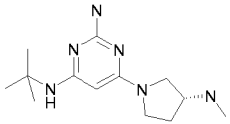
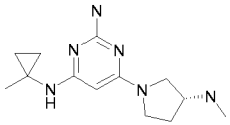
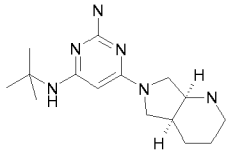
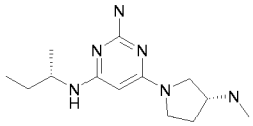
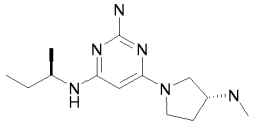
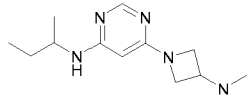
[0228] The following compounds were prepared by a method similar to that described for preparation 26 (solvent and temperature indicated in the table for a period between 10 and 72 hours) using the appropriate pyrimidine starting material and the appropriate amine. Deprotection (if necessary) was carried out using conditions described for example 60.

No.	Structure	Name	Cond.	Prep.	Depr.	LRMS m/z
133		6-(1,4-Diazepan-1-yl)-N^4-isobutylpyrimidine-2,4-diamine	Neat / 120°C	34	Y	265
134		6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(2-methylcyclopropyl)pyrimidine-2,4-diamine	DMSO / 130°C	35	Y	263
135		N^4-Isobutyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine	Neat / 120°C	36	N	279
136		N^4-(Cyclopropylmethyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine	NMP / 150°C	37	N	289
137		N^4-Isopropyl-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine	DMSO / 120°C	38	Y	277
138		N^4-Bicyclo[1.1.1]pent-1-yl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine	DMSO / 120°C	39	Y	275
139		6-(4-Aminopiperidin-1-yl)-N^4-ethylpyrimidine-2,4-diamine	Neat / 120°C	40	Y	237

(continued)

No.	Structure	Name	Cond.	Prep.	Depr.	LRMS m/z
140		6-[3-Methyl-3-(methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine	DMSO / 120°C	41	Y	251
141		N^4-(2,2-Dimethylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1 H)-yl)pyrimidine-2,4-diamine	NMP / 145°C	42	N	305
142		N^4-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine	NMP / 150°C	19	N	305
143		N^4-(2,2-Dimethylpropyl)-N^6-[2-(methylamino)ethyl]pyrimidine-2,4,6-triamine	Neat / 120°C	19	Y	253
144		N^4-[2-(Dimethylamino)ethyl]-N^6-(2,2-dimethylpropyl)pyrimidine-2,4,6-triamine	Neat / 120°C	19	N	267
145		N^4-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidine-2,4-diamine	NMP / 150°C	19	Y	293
146		6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N-[(1R)-1-methylpropyl]pyrimidin-4-amine	Neat / 120°C	10	Y	250

(continued)

No.	Structure	Name	Cond.	Prep.	Depr.	LRMS m/z
147		N-Butyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine	Neat / 120°C	10	Y	250
148		N^4-(*tert*-Butyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine	NMP / 160°C	43	Y	265
149		6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(1-methylcyclopropyl)pyrimidine-2,4-diamine	DMSO / 130°C	44	Y	263
150		N^4-(*tert*-Butyl)-6-[(4aS*,7aS*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine	NMP / 170°C	43	Y	291
151		6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-[(1S)-1-methylpropyl]pyrimidine-2,4-diamine	DMSO / 120°C	15	Y	265
152		6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-[(1R)-1-methylpropyl]pyrimidine-2,4-diamine	DMSO / 120°C	15	Y	265
153		N-(*sec*-Butyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine	Neat / 120°C	1	Y	235

[0229] The following compounds were prepared by similar method to those used to prepare the compounds above, using the appropriate pyrimidine starting material and the appropriate amine:

Example	Name
154	N^4-(Cyclopropylmethyl)-6-piperazin-1-ylpyrimidine-2,4-diamine
155	N^4-(4-Fluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
156	N^4-(2,2-Dimethylpropyl)-6-piperazin-1-ylpyrimidine-2,4-diamine
157	N4-(2,4-Difluorobenzyl)6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
158	6-[3-(Methylamino)azetidin-1-yl]-N^4-(1-methylbutyl)pyrimidine-2,4-diamine
159	N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine hydrochloride
160	N^4-[(1R)-1,2-Dimethylpropyl]-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
161	6-[3-(Methylamino)azetidin-1-yl]-N^4-[(1S)-1-methylpropyl]pyrimidine-2,4-diamine
162	N^4-(2,2-Dimethylpropyl)-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine
163	6-Piperazin-1-yl-N^4-propylpyrimidine-2,4-diamine
164	N^4-Ethyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
165	N^4-(Cyclopropylmethyl)-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
166	N^4-(2,2-Dimethylpropyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
167	N^4-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
168	N^4-(*tert*-Butyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
169	N^4-Isopropyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
170	6-(3-Aminoazetidin-1-yl)-N^4-ethylpyrimidine-2,4-diamine
171	6-(3-Aminoazetidin-1-yl)-N^4-(cyclopropylmethyl)pyrimidine-2,4-diamine
172	N^4-Cyclopropyl-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine
173	4-[3-(Methylamino)azetidin-1-yl]-6-(4-methylpiperidin-1-yl)pyrimidin-2-amine
174	N^4-(Cyclopentylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
175	6-(1,4-Diazepan-1-yl)-N^4-ethylpyrimidine-2,4-diamine
176	N^4-(Cyclopropylmethyl)-N^6-[2-(dimethylamino)ethyl]pyrimidine-2,4,6-triamine
177	N^4-(2,2-Dimethylpropyl)-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
178	N^4-Cyclobutyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
179	N-Cyclobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine
180	6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-propylpyrimidine-2,4-diamine
181	N-Cyclobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
182	N^4-(2-Methoxyethyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
183	N-(2,2-Dimethylpropyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
184	N^4-(Cyclopropylmethyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
185	N^4-Ethyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine
186	N^4-(2,2-Dimethylpropyl)-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
187	N^4-Isopropyl-6-piperazin-1-ylpyrimidine-2,4-diamine
188	N^4-(Cyclopropylmethyl)-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine
189	N-Cyclopropyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-amine
190	6-(3-Aminoazetidin-1-yl)-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine
191	N^4-(2,2-Dimethylpropyl)-6-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine
192	N-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidin-4-amine
193	N^4-Ethyl-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine
194	N-(Cyclopropylmethyl)-N'-[2-(dimethylamino)ethyl]pyrimidine-4,6-diamine
195	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(2-methylbutyl)pyrimidine-2,4-diamine
196	N^4-(Cyclopropylmethyl)-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
197	N^4-Ethyl-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine
198	N^4-isoPropyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine
199	N^4-Cyclobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
200	N^4-Methyl-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine
201	6-(4-Aminopiperidin-1-yl)-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine

(continued)

Example	Name
202	N-Isopropyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
203	N-Cyclopropyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
204	N^4-(Cyclopropylmethyl)-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
205	N^4-Ethyl-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
206	6-[3-(Methylamino)azetidin-1-yl]-N-propylpyrimidin-4-amine
207	N^4-(*tert*-Butyl)-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
208	N^4-Methyl-6-piperazin-1-ylpyrimidine-2,4-diamine
209	N^4-(2,2-Dimethylpropyl)-6-{3-[(methylamino)methyl]azetidin-1-yl}pyrimidine-2,4-diamine
210	N^4-(Cyclopropylmethyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
211	N^4-(3,3-Dimethylbutyl)-6-[(3S)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
212	N^4-(2-Aminoethyl)-N^6-(cyclopropylmethyl)pyrimidine-2,4,6-triamine
213	N^4-(2-Fluorobenzyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
214	N^4-Ethyl-6-piperazin-1-ylpyrimidine-2,4-diamine
215	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(cyclopropylmethyl)pyrimidine-2,4-diamine
216	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-isobutylpyrimidine-2,4-diamine
217	6-[(3aR*,6aS*)-Hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-N^4-isobutylpyrimidine-2,4-diamine
218	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(cyclopentylmethyl)pyrimidine-2,4-diamine
219	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-propylpyrimidine-2,4-diamine
220	N-(2-Aminoethyl)-N'-(cyclopropylmethyl)pyrimidine-4,6-diamine
221	N^4-Methyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
222	N^4-[(1R*,5S*,6s*)-3-Azabicyclo[3.1.0]hex-6-yl]-N^6-(2,2-dimethylpropyl)pyrimidine-2,4,6-triamine
223	N^4-(*tert*-Butyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
224	N-Cyclopropyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-amine
225	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(3,3-dimethylbutyl)pyrimidine-2,4-diamine
226	N-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidin-4-amine
227	N^4-(Cyclopropylmethyl)-6-{3-[(methylamino)methyl]azetidin-1-yl}pyrimidine-2,4-diamine
228	N^4-(3-Fluorobenzyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
229	6-(4-Aminopiperidin-1-yl)-N^4-isobutylpyrimidine-2,4-diamine
230	N^4-Cyclobutyl-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
231	N^4-Isopropyl-6-(octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl)pyrimidine-2,4-diamine
232	6-(3-Aminoazetidin-1-yl)-N^4-propylpyrimidine-2,4-diamine
233	N^4-(3,4-Difluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
234	6-(4-Aminopiperidin-1-yl)-N^4-isopropylpyrimidine-2,4-diamine
235	6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(3,3,3-trifluoropropyl)pyrimidine-2,4-diamine
236	4-(3,3-Difluoroazetidin-1-yl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-2-amine
237	N^4-(2-Fluorobenzyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
238	6-[(3aR*,6aS*)-Hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-N^4-isopropylpyrimidine-2,4-diamine
239	N-(2,2-Dimethylpropyl)-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-amine
240	N^4-(4-Fluorobenzyl)-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
241	N^4-Isopropyl-6-[(3aR*,6aS*)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]pyrimidine-2,4-diamine
242	4-[3-(Methylamino)azetidin-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-amine
243	N^4-(Cyclobutylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
244	N-(3,3-Dimethylbutyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidin-4-amine
245	N^4-(2,5-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
246	6-(3-Amino-3-methylpyrrolidin-1-yl)-N^4-(cyclopropylmethyl)pyrimidine-2,4-diamine
247	N^4-(4-Fluorobenzyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
248	N^4-Methyl-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
249	N^4-(3-Fluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
250	N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)piperidin-1-yl]pyrimidine-2,4-diamine
251	N^4-Benzyl-6-[(3S)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine

(continued)

Example	Name
252	N-Cyclopropyl-6-[(3S)-3-methylpiperazin-1-yl]pyrimidin-4-amine
253	N^4-(2-Fluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
254	N^4-Benzyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
255	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(2,3-difluorobenzyl)pyrimidine-2,4-diamine
256	N^4-Cyclopropyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
257	N^4-Ethyl-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
258	6-[(3S)-3-Methylpiperazin-1-yl]-N-propylpyrimidin-4-amine
259	N^4-Benzyl-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
260	6-(4-Cyclohexylpiperazin-1-yl)-N-(2,2-dimethylpropyl)pyrimidin-4-amine
261	N-Isopropyl-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidin-4-amine
262	N-Methyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
263	4-[3-(Methylamino)azetidin-1-yl]-6-[(3R)-3-methylmorpholin-4-yl]pyrimidin-2-amine
264	6-(3-Amino-3-methylpyrrolidin-1-yl)-N^4-propylpyrimidine-2,4-diamine
265	6-(3-Amino-3-methylpyrrolidin-1-yl)-N^4-ethylpyrimidine-2,4-diamine
266	6-(4-Aminopiperidin-1-yl)-N^4-propylpyrimidine-2,4-diamine
267	N^4-(3-Fluorobenzyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
268	4-[3-(Methylamino)azetidin-1-yl]-6-morpholin-4-ylpyrimidin-2-amine
269	6-(4-Aminopiperidin-1-yl)-N4-cyclopropylpyrimidine-2,4-diamine
270	N-(3,3-Dimethylbutyl)-6-(4-ethylpiperazin-1-yl)pyrimidin-4-amine
271	N^4-(2,6-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
272	N^4-(2,3-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
273	N^4-(3,5-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
274	(5-{[(3S)-3-({6-[(3,3-Dimethylbutyl)amino]pyrimidin-4-yl}amino)pyrrolidin-1-yl]methyl}-2-furyl)methanol
275	4-(3,3-Difluoroazetidin-1-yl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2-amine
276	N,N'-Bis(cyclopropylmethyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
277	N^4-(3,4-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
278	N^4-Isobutyl-6-[3-(methylamino)piperidin-1-yl]pyrimidine-2,4-diamine
279	N'-(3,3-Dimethylbutyl)-N-methyl-N-(1-methylpiperidin-4-yl)pyrimidine-4,6-diamine
280	6-(1,4-Diazepan-1-yl)-N-(3,3-dimethylbutyl)pyrimidin-4-amine
281	N-Benzyl-N'-[(3S)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
282	4-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-6-morpholin-4-ylpyrimidin-2-amine
283	6-(4-Aminopiperidin-1-yl)-N^4-(cyclopropylmethyl)pyrimidine-2,4-diamine
284	6-(4-Aminopiperidin-1-yl)-N^4-methylpyrimidine-2,4-diamine
285	N-(Cyclopropylmethyl)-6-piperazin-1-ylpyrimidin-4-amine
286	N^4-Isopropyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
287	N^4-(2,2-Dimethylpropyl)-6-(3-morpholin-4-ylazetidin-1-yl)pyrimidine-2,4-diamine
288	N-(3,3-Dimethylbutyl)-N'-(1-methylpiperidin-3-yl)pyrimidine-4,6-diamine
289	N-[(3S)-1-Benzylpyrrolidin-3-yl]-N'-(3,3-dimethylbutyl)pyrimidine-4,6-diamine
290	N-[(3S)-Pyrrolidin-3-yl]-N'-[(2S)-tetrahydrofuran-2-ylmethyl]pyrimidine-4,6-diamine
291	N-(Cyclopropylmethyl)-5-methyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
292	6-(3-Aminopyrrolidin-1-yl)-N-(3,3-dimethylbutyl)pyrimidin-4-amine
293	4-[6-(4-Methylpiperazin-1-yl)pyrimidin-4-yl]morpholine
294	N^4-(Cyclopropylmethyl)-6-[3-(methylamino)piperidin-1-yl]pyrimidine-2,4-diamine
295	4-[3-(Methylamino)azetidin-1-yl]-6-piperidin-1-ylpyrimidin-2-amine
296	N-(3,3-Dimethylbutyl)-N'-[(3S)-1-methylpyrrolidin-3-yl]pyrimidine-4,6-diamine
297	(1S,5R)-3-{6-[(2,2-Dimethylpropyl)amino]pyrimidin-4-yl}-3-azabicyclo[3.1.0]hexan-1-amine
298	N^4-(3,3-Dimethylbutyl)-6-[3-methyl-3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
299	N-(3,3-Dimethylbutyl)-6-{4-[(1-methyl-1H-imidazol-2-yl)methyl]piperazin-1-yl}pyrimidin-4-amine
300	(1R*,5S*,6s*)-3-{6-[(3,3-Dimethylbutyl)amino]pyrimidin-4-yl}-N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine

(continued)

Example	Name
301	N-(3,3-Dimethylbutyl)-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidin-4-amine
302	6-[3-(Diethylamino)pyrrolidin-1-yl]-N-(2,2-dimethylpropyl)pyrimidin-4-amine
303	6-(4-Azetidin-3-ylpiperazin-1-yl)-N-(2,2-dimethylpropyl)pyrimidin-4-amine
304	(1S*,5R*)-3-{6-[(Cyclopropylmethyl)amino]pyrimidin-4-yl}-3-azabicyclo[3.1.0]hexan-1-amine
305	6-(4-Cyclohexylpiperazin-1-yl)-N-(cyclopropylmethyl)pyrimidin-4-amine
306	N'-(Cyclopropylmethyl)-N-[2-(diethylamino)ethyl]-N-methylpyrimidine-4,6-diamine
307	2-(4-{6-[(3,3-Dimethylbutyl)amino]pyrimidin-4-yl}piperazin-1-yl)ethanol
308	6-(4-Azetidin-3-ylpiperazin-1-yl)-N-(cyclopropylmethyl)pyrimidin-4-amine
309	N^4-(3,3-Dimethylbutyl)-6-[(1R,5S,6s)-6-(methylamino)-3-azabicyclo[3.1.0]hex-3-yl]pyrimidine-2,4-diamine
310	N^4-(Cyclopropylmethyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
311	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(2,5-difluorobenzyl)pyrimidine-2,4-diamine
312	N-(3,3-Dimethylbutyl)-6-(3-morpholin-4-ylazetidin-1-yl)pyrimidin-4-amine
313	6-[(3R)-3-Methylpiperazin-1-yl]-N-propylpyrimidin-4-amine
314	N-Cyclopropyl-6-(1,4-diazepan-1-yl)pyrimidin-4-amine
315	N-(2-Phenylethyl)-N'-[(3S)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
316	N^4-(3,5-Difluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
317	N^4-(2,6-Difluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
318	N^4-(2,2-Dimethylpropyl)-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
319	N-[(3S)-Pyrrolidin-3-yl]-N'-[(2R)-tetrahydrofuran-2-ylmethyl]pyrimidine-4,6-diamine
320	6-(3-Amino-3-methylpyrrolidin-1-yl)-N^4-methylpyrimidine-2,4-diamine
321	N^4-Methyl-6-[3-(methylamino)piperidin-1-yl]pyrimidine-2,4-diamine
322	N^4-(Cyclopropylmethyl)-6-(3-morpholin-4-ylazetidin-1-yl)pyrimidine-2,4-diamine
323	6-[3-(Methylamino)piperidin-1-yl]-N^4-propylpyrimidine-2,4-diamine
324	N^4-Ethyl-6-[3-(methylamino)piperidin-1-yl]pyrimidine-2,4-diamine
325	N^4-(2,4-Difluorobenzyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
326	N-(2,2-Dimethylpropyl)-5-methyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine
327	6-[(3'S)-1,3'-Bipyrrolidin-1'-yl]-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine
328	N-(3,3-Dimethylbutyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-4-amine
329	N-(3-Methylbutyl)-N'-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
330	N^4-(3,3-Dimethylbutyl)-N^2,N^2-dimethyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
331	N-isoPropyl-5-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine
332	6-[(3'S)-1,3'-Bipyrrolidin-1'-yl]-N^4-(3,3-dimethylbutyl)pyrimidine-2,4-diamine
333	6-[(1R*,5S*,6s*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-N^4-(3,3-dimethylbutyl)pyrimidine-2,4-diamine
334	N-(Cyclopropylmethyl)-N-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-amine
335	N-(2-Methoxyethyl)-N'-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
336	N-Methyl-1-(6-pyrrolidin-1-ylpyrimidin-4-yl)azetidin-3-amine
337	N-Benzyl-N'-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
338	N^4-[(3S)-1-Benzylpyrrolidin-3-yl]-N^6-(3,3-dimethylbutyl)pyrimidine-2,4,6-triamine
339	N^4-(3,3-Dimethylbutyl)-N^2-methyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
340	6-(4-Aminopiperidin-1-yl)-N-(3,3-dimethylbutyl)pyrimidin-4-amine
341	N-[(3R)-Pyrrolidin-3-yl]-N'-[(2S)-tetrahydrofuran-2-ylmethyl]pyrimidine-4,6-diamine
342	6-[(3'S)-1,3'-Bipyrrolidin-1'-yl]-N-(3,3-dimethylbutyl)pyrimidin-4-amine
343	N-(3,3-Dimethylbutyl)-N'-(1-methylpiperidin-4-yl)pyrimidine-4,6-diamine
344	N-(2-Methoxyethyl)-N'-[(3S)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
345	N-[(3R)-Pyrrolidin-3-yl]-N'-[(2R)-tetrahydrofuran-2-ylmethyl]pyrimidine-4,6-diamine
346	N-(2-Phenylethyl)-N'-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
347	N-(Cyclopropylmethyl)-N'-[2-(methylamino)ethyl]pyrimidine-4,6-diamine
348	N-[(3R)-1-Benzylpyrrolidin-3-yl]-N'-(3,3-dimethylbutyl)pyrimidine-4,6-diamine
349	(5-{[(3R)-3-({6-[(3,3-Dimethylbutyl)amino]pyrimidin-4-yl}amino)pyrrolidin-1-yl]methyl}-2-furyl)methanol

(continued)

Example	Name
350	N-(2,3-Dihydro-1H-inden-2-yl)-N'-[(3R)-pyrrolidin-3-yl]pyrimidine-4,6-diamine
351	6-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-[(3R)-pyrrolidin-3-yl]pyrimidin-4-amine
352	N^4-(3-Fluorobenzyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine
353	N-(2,2-Dimethylpropyl)-6-[(1R,5S)-1,2,4,5-tetrahydro-3H-1,5-epimino-3-benzazepin-3-yl]pyrimidin-4-amine
354	N^4-Cyclobutyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
355	N^4-(Cyclopropylmethyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
356	N^4-(*tert*-Butyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
357	N^4-(*tert*-Butyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
358	N^4-(2,2-Dimethylpropyl)-6-[(1R*,5S*,6s*)-6-(methylamino)-3-azabicyclo[3.1.0]hex-3-yl]pyrimidine-2,4-diamine
359	N^4-Cyclopropyl-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine
360	2-({2-Amino-6-[3-(methylamino)azetidin-1-yl]pyrimidin-4-yl}amino)ethanol
361	6-(1,4-Diazepan-1-yl)-N^4-isopropylpyrimidine-2,4-diamine
362	6-[(1R,4R)-2,5-Diazabicyclo[2.2.1]hept-2-yl]-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine
363	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(2,2-dimethylpropyl)pyrimidine-2,4-diamine
364	4-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-6-(2-methyl-1H-imidazol-1-yl)pyrimidin-2-amine
365	6-[3-(Methylamino)azetidin-1-yl]-N^4-[(1R)-1-methylpropyl]pyrimidine-2,4-diamine
366	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-ethylpyrimidine-2,4-diamine
367	6-[(3R)-3-Aminopyrrolidin-1-yl]-N^4-(3,3,3-trifluoropropyl)pyrimidine-2,4-diamine
368	6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N-[(1S)-1-methylpropyl]pyrimidin-4-amine
369	6-[3-(Methylamino)azetidin-1-yl]-N-[(1R)-1-methylpropyl]pyrimidin-4-amine
370	6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N-propylpyrimidin-4-amine
371	6-(3-Aminoazetidin-1-yl)-N-(2,2-dimethylpropyl)pyrimidin-4-amine
372	N^4-(Cyclopropylmethyl)-5-methyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine
373	N^4-(Cyclopropylmethyl)-6-(2,8-diazaspiro[4.5]dec-2-yl)pyrimidine-2,4-diamine
374	6-(2,8-Diazaspiro[4.5]dec-2-yl)-N^4-isobutylpyrimidine-2,4-diamine
375	N^4-(Cyclopropylmethyl)-6-(2,7-diazaspiro[4.4]non-2-yl)pyrimidine-2,4-diamine
376	6-(2,7-Diazaspiro[4.4]non-2-yl)-N^4-isobutylpyrimidine-2,4-diamine

Biology

H_4 Binding

[0230] Cell pellets from CHO cells expressing the histamine H_4 receptor were homogenised in ice-cold 50mM Tris-HCl/0.5mM $CaCl_2$ buffer containing a protease inhibitor cocktail (Roche®, United Kingdom) using a ground glass homogeniser. Homogenates were centrifuged at 48000g for 30min at 4°C. The membrane pellet was resuspended in fresh buffer and the centrifugation step was repeated as described above. The membrane pellet was resuspended in 50mM Tris-HCl in the same volume as the original cell pellet. Aliquots of membrane preparations were stored at -80°C and were used for [^{3}H]-Histamine binding experiments.

Method 1

[0231] Cell membranes (20-35μg/well) were incubated for 90 minutes shaking at room temperature with 3nM [2,5-^{3}H]Histamine dihydrochloride (30-60Ci/mmol) in 50mM Tris-HCl (pH 7.4), with or without competing H_4 ligands. The reaction was terminated by rapid filtration through 0.5% polyethylenimine-soaked Unifilter GF/B plates (Packard) followed by three washes with 1ml ice-cold 50mM Tris-HCl. Filters were dried for 45min at 45°C and bound radiolabel was determined using scintillation counting techniques. Non-specific binding was defined with 10μM JNJ7777120. For competition binding studies, Ki values were calculated from the IC_{50} value based on an experimentally determined ligand K_d of 5.2nM and a ligand concentration of 5nM according to the Cheng-Prussoff equation where; $K_i = (IC_{50})/(1+([L]/K_d))$.

Method 2

[0232] Cell membranes (15μg/well) were pre-incubated for 120min shaking at 4°C with Ysi WGA beads (250μg/well) in 50mM Tris-HCl (pH 7.4) followed by centrifugation at 1500rpm for 5minutes and resuspension in 50mM Tris-HCl (pH 7.4). The membrane/bead mixture (15μg membrane / 250μg beads well) was incubated for 90minutes shaking at room temperature with 6.5nM [2,5-^{3}H] Histamine dihydrochloride (30-60Ci/mmol) in 50mM Tris-HCl (pH 7.4), with or without competing H_4 ligands. Non-specific binding was defined with 10μM JNJ7777120. Bound radiolabel was determined using scintillation counting techniques after 90 minutes. For competition binding studies, Ki values were calculated from the IC_{50} value based on an experimentally determined ligand K_d of 5.2nM and a ligand concentration of 5nM according to the Cheng-Prussoff equation where; $K_i = (IC_{50})/(1+([L]/K_d))$.

[0233] The compounds of the Examples have been tested in the H_4 binding assay described above using either method 1 or method 2. Preferred examples have a K_i value of less than 1 μM in the H_4 binding assay. Most preferred examples have a K_i value of less than 500 nM in the H_4 binding assay (method 2). The specific K_i values for the Example compounds that have been tested in method 1 and method 2 are given in the table below:

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
1	335	82,3

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
2	NT	485
3	NT	220
4	NT	374
5	NT	263
6	NT	502
7	NT	939
8	NT	593
9	19,3	2,7
10	4,11	2,85
11	31,6	10,6
12	52,4	NT
13	51,8	NT
14	23,3	13,6
15	19,2	NT
16	1740	NT
17	483	NT
18	387	NT
19	132	NT
20	58,1	30,5
21	722	NT
22	59,3	58,9
23	824	NT
24	30,8	NT
25	154	NT
26	30	NT
27	22,4	NT
28	21,3	NT
29	82,9	NT
30	19,3	3,06
31	21,1	NT
32	20,9	NT
33	84,1	NT
34	452	NT
35	662	NT
36	1620	NT
37	181	NT
38	128	NT
39	88,9	NT
41	202	NT
40	192	NT
42	433	NT
43	236	NT
44	20,5	NT
45	420	NT
46	40,1	NT
47	256	NT
48	49,7	NT
49	29,9	10,7
50	279	NT
51	161	NT
52	99,7	NT

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
53	1940	NT
54	414	NT
55	28,9	NT
56	1590	NT
57	20,3	NT
58	301	NT
59	59,2	37,7
60	28,8	3,57
61	1,33	1,66
62	14,1	8,94
63	12,2	1,95
64	4,43	4,63
65	19,8	17,5
66	61,1	NT
67	1,6	0,278
68	6,26	0,979
69	9,38	NT
70	2,14	3,79
71	14	1,29
72	11,9	NT
73	NT	0,88
74	16,8	0,58
75	NT	1,07
76	125	NT
77	255	NT
78	3,66	NT
79	11,2	NT
80	103	NT
81	12,1	NT
82	9,68	NT
83	62,3	NT
84	21,7	NT
85	156	NT
86	142	NT
87	17,4	NT
88	35,8	NT
89	1,93	NT
90	6,42	NT
91	386	NT
92	1350	NT
93	256	NT
94	61,1	NT
95	9,11	NT
96	3,77	NT
97	43,7	NT
98	56,2	NT
99	38,1	23,6
100	NT	40,2
101	NT	463
102	NT	57,3
103	NT	87,9

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
104	NT	118
105	NT	68,8
106	NT	66,1
107	NT	271
108	8,42	NT
109	42,7	NT
110	829	NT
111	1800	201
112	635	NT
113	1480	NT
114	1030	NT
115	494	NT
116	426	NT
117	1620	NT
118	1090	NT
119	7,8	3,44
120	11,2	4,89
121	6,64	2,18
122	8,65	3,65
123	103	NT
124	537	NT
125	223	NT
126	611	NT
127	65,8	NT
128	NT	0,805
129	NT	3,78
130	NT	9,69
131	NT	17,8
132	NT	0,791
133	NT	0,653
134	NT	4,15
135	NT	1,13
136	NT	7,21
137	NT	8,25
138	NT	5,8
139	NT	12,1
140	NT	12,1
141	4,97	
142	NT	3,04
143	NT	72,4
144	NT	16,8
145	NT	14,3
146	NT	13,7
147	NT	17,3
148	NT	4,89
149	NT	5,2
150	NT	11,8
151	NT	12,4
152	NT	16,9
153	NT	11,5
154	NT	1,71

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
155	NT	1,78
156	NT	2,44
157	NT	2,49
158	NT	2,59
159	NT	2,62
160	NT	2,65
161	NT	2,75
162	NT	2,91
163	NT	3,78
164	24,5	3,82
165	NT	3,83
166	NT	3,99
167	NT	6,3
168	NT	6,5
169	NT	6,77
170	NT	8,55
171	NT	9,21
172	NT	9,3
173	NT	10,1
174	NT	10,6
175	NT	12,3
176	NT	15,1
177	NT	16
178	NT	16,1
179	NT	16,5
180	NT	17,4
181	NT	17,6
182	NT	19,8
183	NT	20
184	NT	20,4
185	NT	20,5
186	NT	22,2
187	NT	22,4
188	NT	25,5
189	NT	25,8
190	NT	27,7
191	NT	28,2
192	NT	28,7
193	NT	31
194	NT	32,4
195	NT	32,6
196	NT	33,1
197	NT	33,2
198	NT	33,6
199	NT	33,9
200	NT	34
201	NT	35
202	NT	36,5
203	NT	37,9
204	NT	39
205	NT	39,3

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
206	NT	39,9
207	NT	43,3
208	NT	45,1
209	NT	46,4
210	NT	48,9
211	NT	49,3
212	NT	50
213	NT	52,9
214	NT	54,4
215	NT	57,3
216	NT	70,6
217	NT	80,6
218	NT	80,7
219	NT	82,3
220	NT	88
221	NT	90,3
222	NT	95,2
223	NT	13% at 10μM
224	NT	101
225	NT	102
226	NT	113
227	NT	115
228	NT	117
229	NT	127
230	NT	127
231	NT	131
232	NT	13.88
233	NT	30.4
234	NT	177
235	NT	198
236	NT	205
237	NT	211
238	NT	222
239	NT	235
240	NT	238
241	NT	45% at 1μM
242	NT	258
243	NT	266
244	NT	297
245	NT	298
246	NT	301
247	NT	312
248	NT	329
249	NT	343
250	NT	353
251	NT	355
252	NT	370
253	NT	380
254	NT	380
255	NT	452
256	NT	501

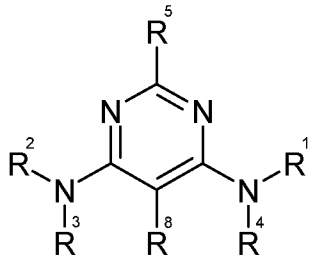
Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
257	NT	100% at 10μM
258	NT	509
259	NT	577
260	NT	100% at 10μM
261	NT	617
262	NT	623
263	NT	626
264	NT	704
265	NT	705
266	NT	708
267	NT	715
268	NT	16% at 10μM
269	NT	839
270	>16200	839
271	NT	870
272	NT	901
273	NT	950
274	NT	1070
275	NT	1160
276	NT	14% at 3.16μM
277	NT	1230
278	NT	1260
279	>9130	1370
280	NT	1430
281	NT	1550
282	NT	1660
283	NT	1700
284	NT	1720
285	NT	1800
286	NT	1940
287	NT	2000
288	NT	2400
289	NT	44% at 10μM
290	NT	24% at 10μM
291	NT	No activity at top dose (6.3μM)
292	NT	2590
293	NT	3040
294	NT	91% at 20μM
295	NT	3180
296	NT	3300
297	NT	30% at 10μM
298	NT	No activity at top dose (10μM)
299	NT	No activity at top dose (10μM)
300	NT	35% at 10μM
301	NT	No activity at top dose (10μM)
302	NT	20% at 10μM
303	NT	38% at 10μM
304	NT	19% at 10μM

Example	Method 2 (Ki (nM))	Method 1 (Ki (nM))
305	NT	No activity at top dose (10μM)
306	NT	18% at 10μM
307	NT	24% at 10μM
308	NT	No activity at top dose (10μM)
309	NT	26% at 10μM
310	NT	No activity at top dose (10μM)
311	NT	80% at 20μM
312	NT	21% at 20μM
313	NT	70% at 20μM
314	NT	No activity at top dose (10μM)
315	NT	5190
316	NT	No activity at top dose (10μM)
317	NT	No activity at top dose (10μM)
318	NT	No activity at top dose (10μM)
319	NT	6010
320	NT	46% at 6.3μM
321	NT	15% at 20μM
322	NT	57% at 20μM
323	NT	85% at 20μM
324	NT	55% at 20μM
325	NT	43% at 20μM
326	NT	48% at 20μM
327	376	NT
328	554	NT
329	1420	NT
330	1440	NT
331	2670	NT
332	2690	NT
333	3120	NT
334	5070	NT
335	5350	NT
336	6330	NT
337	7220	NT
338	7930	NT
339	9070	NT
340	50% at 40μM	NT
341	16300	NT
342	13% at 40μM	NT
343	53% at 40μM	NT
344	40% at 40μM	NT
345	49% at 40μM	NT
346	38400	NT
347	NT	NT
348	NT	NT
349	NT	NT
350	NT	NT
351	NT	NT
352	NT	NT
353	NT	NT
354	NT	NT
355	NT	NT
356	NT	NT
357	NT	NT
358	NT	NT
359	NT	NT
360	NT	NT
361	NT	NT
362	NT	NT
363	NT	NT
364	NT	NT
365	NT	NT
366	NT	NT
367	NT	NT
368	NT	NT
369	NT	NT
370	NT	NT
371	NT	NT
372	NT	NT
373	NT	NT
374	NT	NT
375	NT	NT
376	NT	NT

NT: not tested

Claims

1. A compound of Formula (I):



or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, wherein:

R^1 is C_{1-8}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl- optionally substituted with methyl, alkoxyalkyl containing 3 to 8 carbon atoms, het-C_{0-6}alkyl-, CF_3-C_{1-6}alkyl-, CF_3OC_{2-3}alkyl- or C_{1-6}hydroxyalkyl;

R^3 and R^2 together with the nitrogen atom to which they are bound form a 4 to 8 membered non-aromatic heterocyclic group which optionally contains one or more further heteroatoms or groups independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group, a spiro bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl, provided that the ring system as a whole contains at least two nitrogen atoms or contains one nitrogen atom and is substituted by a group which contains at least one nitrogen atom;

R^4 is H;

R^5 is H or NH_2;

R^6 and R^7 are each independently selected from H, C_{1-6}alkyl and $(CH_2)_jC_{3-7}$cycloalkyl; or R^6 and R^7, together with the nitrogen atom to which they are bound, form a 4, 5 or 6 membered heterocyclic group;

R^8 is H;

aryl is phenyl optionally substituted by one or more groups independently selected from C_{1-8}alkyl, C_{1-8}alkoxy, OH, halo, CF_3, CHF_2, OCF_3, $OCHF_2$, SCF_3, hydroxy-C_{1-6}alkyl, C_{1-4}alkoxy-C_{1-6}alkyl, C_{1-4}alkyl-S-C_{1-4}alkyl, CF_2CF_3, CH_2CF_3, CF_2CH_3, $C(O)NR^{13}R^{14}$, C_{3-8}cycloalkyl, C_{3-7}cycloalkyl-C_{1-4}alkyl, C_{3-7}cycloalkyl-C_{1-4}alkoxy, R^{13} and R^{14} are each independently selected from H, C_{1-6}alkyl and $(CH_2)_mC_{3-7}$cycloalkyl; or R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 4, 5 or 6 membered heterocyclic group;

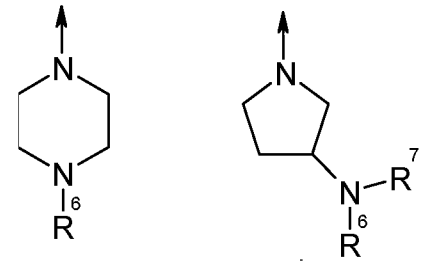
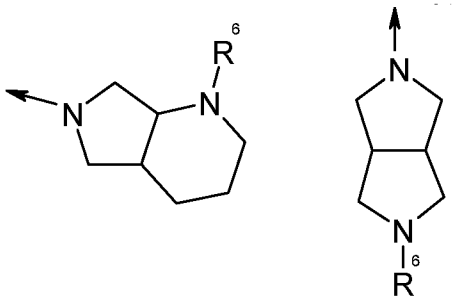
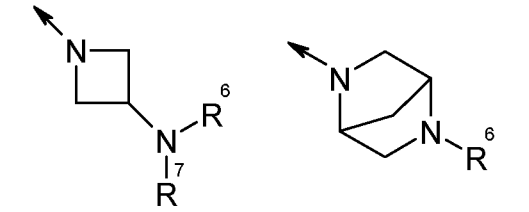
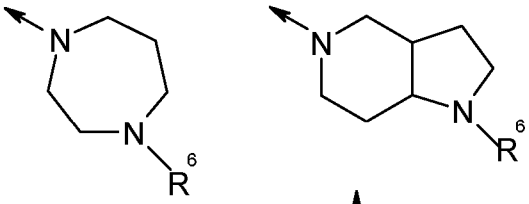
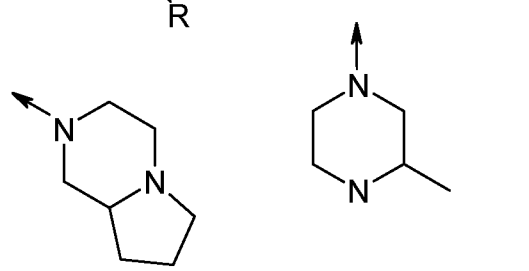
a, b, c, d, j and m are each independently selected from 0, 1, 2 and 3; y is independently selected from 1, 2 and 3;

het is 4 to 8 membered non-aromatic heterocyclic group which contains at least one heteroatom or group independently selected from N, O, S, S(O) and $S(O)_2$, wherein the heterocyclic group is optionally a bridged bicyclic group or is optionally fused to a 3-, 4-, 5- or 6- membered carbocyclic group or a 4-, 5- or 6-membered heterocyclic group which contains at least one ring member independently selected from N, O, S, S(O) and $S(O)_2$, and wherein the ring system as a whole is optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$cycloalkyl, alkoxyalkyl containing 2 to 8 carbon atoms, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryl and C_{1-6}hydroxyalkyl; and

het^1 is an aromatic or non-aromatic 4-, 5- or 6- membered heterocycle which contains at least one N, O or S heteroatom, optionally fused to a 4-, 5- or 6-membered carbocyclic group or a second 4-, 5- or 6-membered heterocycle which contains at least one N, O or S heteroatom.

2. The compound according to claim 1, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, wherein R^1 is C_{3-7}cycloalkyl-C_{0-6}alkyl- optionally substituted with methyl.

3. The compound according to claim 1 or claim 2, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, wherein R^2 and R^3, together with the nitrogen atom to which they are bound, form a group selected from the following ring systems:

wherein the ring system as a whole may be substituted by one or more C_{1-6}alkyl or $(CH_2)_aC_{3-7}$cycloalkyl groups.

4. The compound according to claim 3, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, wherein R^6 and R^7 are independently selected from H or CH_3.

5. The compound according to claim 1, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, said compound being selected from

N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine tartrate,
N^4-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
N-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amine,

N^4-(2,2-Dimethylpropyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclopropyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-(3-Methylamino-azetidin-1-yl)-N^4-(3,3,3-trifluoro-propyl)-pyrimidine-2,4-diamine,
N^4-Cyclopropylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-(3,3-Dimethyl-butyl)-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Cyclopentylmethyl-6-(3-methylamino-azetidin-1-yl)-pyrimidine-2,4-diamine,
N^4-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine,
N^4-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbutyl)pyrimidine-2,4-diamine,
N^4-Butyl-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(2-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-Isobutyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-Bicyclo[1.1.1]pent-1-yl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-[3-Methyl-3-(methylamino)azetidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidine-2,4-diamine,
N^4-(*tert*-Butyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(1-methylcyclopropyl)pyrimidine-2,4-diamine,
N^4-(*tert*-Butyl)-6-[(4aS*,7aS*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-piperazin-1-ylpyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidine-2,4-diamine hydrochloride,
N^4-(2,2-Dimethylpropyl)-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine,
6-Piperazin-1-yl-N^4-propylpyrimidine-2,4-diamine,
N^4-(Cyclopropylmethyl)-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-(2,2-Dimethylpropyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
N^4-Isopropyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
4-[3-(Methylam ino)azetidin-1-yl]-6-(4-methylpiperidin-1-yl)pyrim idin-2-am ine,
N^4-(Cyclopentylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
N^4-Cyclobutyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-propylpyrimidine-2,4-diamine, and
N^4-Ethyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidine-2,4-diamine.

6. A compound according to claim 1, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, said compound being N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.

7. A salt according to claim 6, said salt being N^4-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine L-tartrate.

8. A pharmaceutical composition including a compound according to any of claims 1 to 6, or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, or the salt according to claim 7, together with a pharmaceutically acceptable excipient.

9. A compound according to any of claims 1 to 6 or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, or the salt according to claim 7, for use as a medicament.

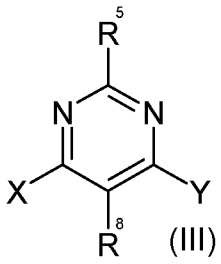
10. The use of a compound according to any of claims 1 to 6 or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, or the salt according to claim 7, for the manufacture of a medicament to treat a disease selected from inflammatory diseases, respiratory diseases (e.g. adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis), allergy; allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion, female and male sexual dysfunction,

skin diseases such as dermatitis and psoriasis, cardiac dysfunctions such as myocardial ischaemia and arrythmia, diseases of the gastrointestinal tract such as inflammatory bowel disease, Crohn's disease and colitis ulcerosa, cancer, rheumatoid arthritis, hypotension, pain and overactive bladder conditions.

11. A compound according to any of claims 1 to 6 or a pharmaceutically and/or veterinarily acceptable salt or solvate thereof, or the salt according to claim 7, for use in treating a disease selected from inflammatory diseases, respiratory diseases (e.g. adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis), allergy; allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion, female and male sexual dysfunction, skin diseases such as dermatitis and psoriasis, cardiac dysfunctions such as myocardial ischaemia and arrythmia, diseases of the gastrointestinal tract such as inflammatory bowel disease, Crohn's disease and colitis ulcerosa, cancer, rheumatoid arthritis, hypotension, pain and overactive bladder conditions.

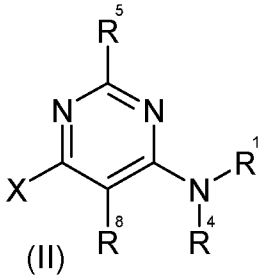
12. A process for preparing a compound according to any of claims 1 to 6, comprising the steps of:

(a) reacting a compound of Formula (III)



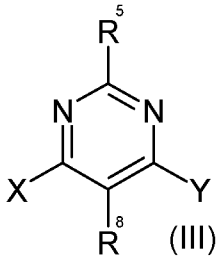
(III)

with an amine $HN(R^1)(R^4)$ to provide a compound of formula (II)



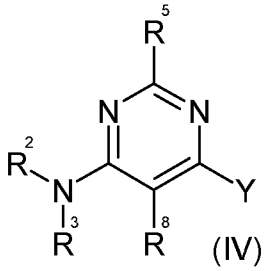
(II)

followed by reaction with an amine $HN(R^2)(R^3)$ to provide a compound of formula (I); or
(b) reacting a compound of formula (III)



(III)

with an amine $HN(R^2)(R^3)$ to provide a compound of formula (IV)



(IV)

followed by reaction with an amine $HN(R^1)(R^4)$ to provide a compound of formula (I);
where X and Y are leaving groups and R^1, R^2, R^3, R^4, R^5 and R^8 are as defined in claim 1.

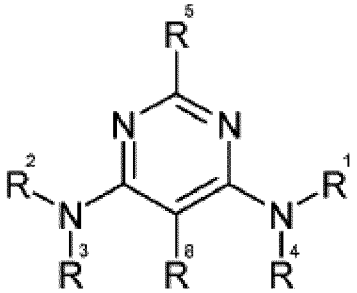
13. Combination of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, or the salt according to claim 7, with other therapeutic agent(s) selected from:

- Histamine H_1 receptor antagonists, in particular loratidine, desloratidine, fexofenadine and cetirizine
- Histamine H_3 receptor antagonists
- Histamine H_2 receptor antagonists
- Leukotriene antagonists, including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4; for example Montelukast
- Phosphodiesterase inhibitors, including PDE3 inhibitors, PDE4 inhibitors, PDE5 inhibitors, PDE7 inhibitors and inhibitors of two or more phosphodiesterases, such as dual PDE3/PDE4 inhibitors
- neurotransmitter re-uptake inhibitors, in particular fluoxetine, setraline, paroxetine, ziprasidone
- 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists
- α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use
- Muscarinic M3 receptor antagonists or anticholinergic agents
- β_2-adrenoceptor agonists
- Dual acting β_2/M3 agents
- Xanthines, such as theophylline and aminophylline
- Non-steroidal anti-inflammatories, such as sodium cromoglycate and nedocromil sodium
- Ketotifen
- COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors
- Oral or inhaled Glucocorticosteroids
- Monoclonal antibodies active against endogenous inflammatory entities
- Anti-tumor necrosis factor (anti-TNF-α) agents
- Adhesion molecule inhibitors including VLA-4 antagonists
- Kinin-B_1- and B_2 -receptor antagonists
- Immunosuppressive agents
- Inhibitors of matrix metalloproteases (MMPs)
- Tachykinin NK_1, NK_2 and NK_3 receptor antagonists
- Elastase inhibitors
- Adenosine A2a receptor agonists
- Inhibitors of urokinase
- Compounds that act on dopamine receptors, e.g. D2 agonists
- Modulators of the NFκb pathway, e.g. IKK inhibitors
- Agents that can be classed as mucolytics or anti-tussive
- Antibiotics
- Modulators of cytokine signaling pathways, such as p38 MAP kinase inhibitors, syk tyrosine kinase inhibitors or JAK kinase inhibitors
- Modulators of the prostaglandin pathways, including inhibitors of H-PDGS and antagonists of DP-1 and CRTH2
- Antagonists of chemokine receptors CXCR1 and CXCR2
- Antagonists of chemokine receptors CCR3, CCR4 and CCR5
- Inhibitors of cytosolic and soluble phospholipase A_2 ($cPLA_2$ and $sPLA_2$)
- Prostaglandin D2 receptor antagonists (DP1 and CRTH2)
- Inhibitors of Prostaglandin D synthase (PGDS)
- Inhibitors of phosphoinositide-3-kinase,
- HDAC inhibitors,
- p38 inhibitors and/or

• CXCR2 antagonists.

Patentansprüche

1. Verbindung der Formel (I):



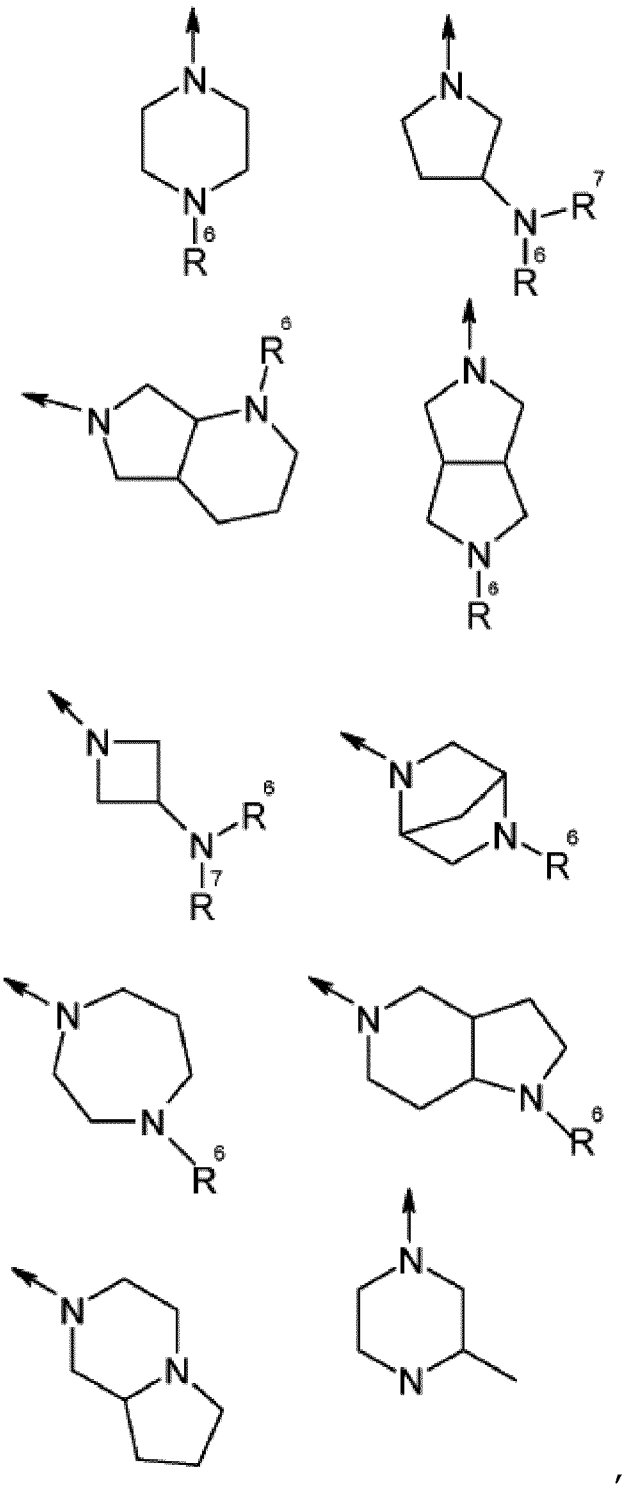
oder ein pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei:

R^1 C_{1-8}-Alkyl, C_{3-7}-Cycloalkyl-C_{0-6}-alkyl-, das gegebenenfalls mit Methyl substituiert ist, Alkoxyalkyl, das 3 bis 8 Kohlenstoffatome enthält, Het-C_{0-6}-alkyl-, CF_3-C_{1-6}-Alkyl-, CF_3OC_{2-3}-Alkyl- oder C_{1-6}-Hydroxyalkyl ist;
R^3 und R^2 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4- bis 8-gliedrige nichtaromatische heterocyclische Gruppe bilden, die gegebenenfalls ein bzw. eine oder mehrere weitere Heteroatome oder Gruppen enthält, die unabhängig aus N, 0, S, S(O) und $S(O)_2$ ausgewählt sind, wobei die heterocyclische Gruppe gegebenenfalls eine verbrückte bicyclische Gruppe oder eine bicyclische Spiro-Gruppe ist oder gegebenenfalls an eine 3-, 4-, 5- oder 6-gliedrige carbocyclische Gruppe oder eine 4-, 5- oder 6-gliedrige heterocyclische Gruppe anelliert ist, die mindestens ein Ringelement enthält, das unabhängig aus N, 0, S, S(O) und $S(O)_2$ ausgewählt ist, und wobei das Ringsystem als Ganzes gegebenenfalls durch einen oder mehrere Substituenten substituiert ist, die unabhängig aus C_{1-6}-Alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$-Cycloalkyl, Alkoxyalkyl, das 2 bis 8 Kohlenstoffatome enthält, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$-Aryl und C_{1-6}-Hydroxyalkyl ausgewählt sind, vorausgesetzt, dass das Ringsystem als Ganzes mindestens zwei Stickstoffatome enthält oder ein Stickstoffatom enthält und durch eine Gruppe substituiert ist, die mindestens ein Stickstoffatom enthält;
R^4 H ist;
R^5 H oder NH_2 ist;
R^6 und R^7 jeweils unabhängig aus H, C_{1-6}-Alkyl und $(CH_2)_jC_{3-7}$-Cycloalkyl ausgewählt sind oder R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-, 5- oder 6-gliedrige heterocyclische Gruppe bilden;
R^8 H ist;
Aryl Phenyl ist, das gegebenenfalls durch eine oder mehrere Gruppen substituiert ist, die unabhängig aus C_{1-8}-Alkyl, C_{1-8}-Alkoxy, OH, Halo, CF_3, CHF_2, OCF_3, $OCHF_2$, SCF_3, Hydroxy-C_{1-6}-alkyl, C_{1-4}-Alkoxy-C_{1-6}-alkyl, C_{1-4}-Alkyl-S-C_{1-4}-alkyl, CF_2CF_3, CH_2CF_3, CF_2CH_3, $C(O)NR^{13}R^{14}$, C_{3-8}-Cycloalkyl, C_{3-7}-Cycloalkyl-C_{1-4}-alkyl, C_{3-7}-Cycloalkyl-C_{1-4}-alkoxy ausgewählt sind,
R^{13} und R^{14} jeweils unabhängig aus H, C_{1-6}-Alkyl und $(CH_2)_mC_{3-7}$-Cycloalkyl ausgewählt sind oder R^{13} und R^{14} zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine 4-, 5- oder 6-gliedrige heterocyclische Gruppe bilden;
a, b, c, d, j und m jeweils unabhängig aus 0, 1, 2 und 3 ausgewählt sind;
y unabhängig aus 1, 2 und 3 ausgewählt ist;
het eine 4- bis 8-gliedrige nichtaromatische heterocyclische Gruppe ist, die mindestens ein Heteroatom oder eine Gruppe enthält, das bzw. die unabhängig aus N, 0, S, S(O) und $S(O)_2$ ausgewählt ist, wobei die heterocyclische Gruppe gegebenenfalls eine verbrückte bicyclische Gruppe ist oder gegebenenfalls an eine 3-, 4-, 5- oder 6-gliedrige carbocyclische Gruppe oder eine 4-, 5- oder 6-gliedrige heterocyclische Gruppe anelliert ist, die mindestens ein Ringelement enthält, das unabhängig aus N, 0, S, S(O) und $S(O)_2$ ausgewählt ist, und wobei das Ringsystem als Ganzes gegebenenfalls durch einen oder mehrere Substituenten substituiert ist, die unabhängig aus C_{1-6}-Alkyl, NR^6R^7, $(CH_2)_aC_{3-7}$-Cycloalkyl, Alkoxyalkyl, das 2 bis 8 Kohlenstoffatome enthält, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$-Aryl und C_{1-6}-Hydroxyalkyl ausgewählt sind; und
het^1 ein aromatischer oder nichtaromatischer 4-, 5- oder 6-gliedriger Heterocyclus ist, der mindestens ein N-, 0- oder S-Heteroatom enthält, das gegebenenfalls an eine 4-, 5-, oder 6-gliedrige carbocyclische Gruppe oder

einen zweiten 4-, 5- oder 6-gliedrigen Heterocyclus anelliert ist, der mindestens ein N-, 0- oder S-Heteroatom enthält.

2. Verbindung nach Anspruch 1 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei R^1 C_{3-7}-Cycloalkyl-C_{0-6}-alkyl- ist, das gegebenenfalls mit Methyl substituiert ist.

3. Verbindung nach Anspruch 1 oder 2 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei R^2 und R^3 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Gruppe bilden, die aus den folgenden Ringsystemen ausgewählt ist:



wobei das Ringsystem als Ganzes durch eine oder mehrere C_{1-6}-Alkyl- oder $(CH_2)_aC_{3-7}$-Cycloalkylgruppen substituiert sein kann.

4. Verbindung nach Anspruch 3 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei R^6 und R^7 unabhängig aus H oder CH_3 ausgewählt sind.

5. Verbindung nach Anspruch 1 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei die Verbindung aus folgenden ausgewählt ist:

N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
N^4-(Cyclopropylmethyl)-6-[(3*R*)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamintartrat,
N^4-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
N-Isobutyl-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amin,
N-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-4-amin,
N^4-(2,2-Dimethylpropyl)-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-Cyclopropyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-Cyclobutyl-6-[(4aR*,7aR*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-2,4-diamin,
6-(3-Methylaminoazetidin-1-yl)-N^4-(3,3,3-trifluorpropyl)pyrimidin-2,4-diamin,
N^4-Cyclopropylmethyl-6-(3-methylaminoazetidin-1-yl)pyrimidin-2,4-diamin,
N^4-(3,3-Dimethylbutyl)-6-(3-methylaminoazetidin-1-yl)pyrimidin-2,4-diamin,
N^4-Cyclopentylmethyl-6-(3-methylaminoazetidin-1-yl)pyrimidin-2,4-diamin,
N^4-Isobutyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-2,4-diamin,
6-[3-(Methylamino)azetidin-1-yl]-N^4-propylpyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[(3R)-3-methylpiperazin-1-yl]pyrimidin-2,4-diamin,
N^4-Ethyl-6-(4-methylpiperazin-1-yl)pyrimidin-2,4-diamin,
N^4-(Cyclopropylmethyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2,4-diamin,
6-[3-(Methylamino)azetidin-1-yl]-N^4-(2-methylbutyl)pyrimidin-2,4-diamin,
N^4-Butyl-6-[3-(methylamino)azetidin-1-yl]pyrimidin-2,4-diamin,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(2-methylcyclopropyl)pyrimidin-2,4-diamin,
N^4-Isobutyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-2,4-diamin,
N^4-(Cyclopropylmethyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidin-2,4-diamin,
N^4-Bicyclo[1.1.1]pent-1-yl-6-[(3R)-3-(methylamino)pyrrolidin-1-yllpyrimidin-2,4-diamin,
6-[3-Methyl-3-(methylamino)azetidin-1-yl]-N^4-propylpyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-(3-pyrrolidin-1-ylazetidin-1-yl)pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[3-(isopropylamino)azetidin-1-yl]pyrimidin-2,4-diamin,
N^4-(*tert.*-Butyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-(1-methylcyclopropyl)pyrimidin-2,4-diamin,
N^4-(*tert.*-Butyl)-6-[(4aS*,7aS*)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-piperazin-1-ylpyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[3-(methylamino)azetidin-1-yl]pyrimidin-2,4-diamin-Hydrochlorid,
N^4-(2,2-Dimethylpropyl)-6-[(3aR*,7aS*)-octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl]pyrimidin-2,4-diamin,
6-Piperazin-1-yl-N^4-propylpyrimidin-2,4-diamin,
N^4-(Cyclopropylmethyl)-6-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-(2,2-Dimethylpropyl)-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
N^4-Isopropyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
4-[3-(Methylamino)azetidin-1-yl]-6-(4-methylpiperidin-1-yl)pyrimidin-2-amin,
N^4-(Cyclopentylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin,
N^4-Cyclobutyl-6-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]pyrimidin-2,4-diamin,
6-[(3R)-3-(Methylamino)pyrrolidin-1-yl]-N^4-propylpyrimidin-2,4-diamin und
N^4-Ethyl-6-(4-methyl-1,4-diazepan-1-yl)pyrimidin-2,4-diamin.

6. Verbindung nach Anspruch 1 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon, wobei die Verbindung N^4-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin ist.

7. Salz nach Anspruch 6, wobei das Salz N^4-(Cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidin-2,4-diamin-L-tartrat ist.

8. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 6 oder ein pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon oder das Salz nach Anspruch 7 zusammen mit einem pharmazeutisch akzeptablen Hilfsstoff enthält.

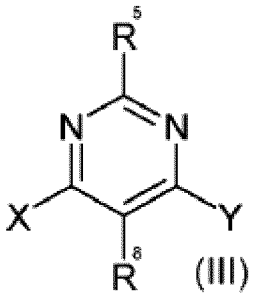
9. Verbindung nach einem der Ansprüche 1 bis 6 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon oder Salz nach Anspruch 7 zur Verwendung als ein Arzneimittel.

10. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 6 oder eines pharmazeutisch und/oder veterinärmedizinisch akzeptablen Salzes oder Solvats davon oder des Salzes nach Anspruch 7 zur Herstellung eines Arzneimittels, um eine Erkrankung zu behandeln, die aus Entzündungserkrankungen, Atemwegserkrankungen (z. B. Atemnotsyndrom des Erwachsenen, Schocklunge, Bronchitis, chronische Bronchitis, chronisch-obstruktive Lungenerkrankung, Mukoviszidose, Asthma, Emphysem, Rhinitis, chronische Sinusitis), Allergie; allergieinduzierten Atemwegsreaktionen, allergischer Rhinitis, viraler Rhinitis, nicht-allergischer Rhinitis, perennialer und saisonaler Rhinitis, Nasenverstopfung, allergischer Nasenverstopfung, funktioneller Sexualstörung der Frau und des Mannes, Hauterkrankungen, wie Dermatitis und Psoriasis, kardialen Dysfunktionen, wie Myokardischämie und Arrhythmie, Erkrankungen des Magen-Darm-Trakts, wie entzündliche Darmerkrankung, Morbus Crohn und Colitis ulcerosa, Krebs, rheumatoider Arthritis, Hypotonie, Schmerzen und überaktiven Blasenzuständen ausgewählt ist.

11. Verbindung nach einem der Ansprüche 1 bis 6 oder pharmazeutisch und/oder veterinärmedizinisch akzeptables Salz oder Solvat davon oder Salz nach Anspruch 7 zur Verwendung beim Behandeln einer Erkrankung, die aus Entzündungserkrankungen, Atemwegserkrankungen (z. B. Atemnotsyndrom des Erwachsenen, Schocklunge, Bronchitis, chronische Bronchitis, chronisch-obstruktive Lungenerkrankung, Mukoviszidose, Asthma, Emphysem, Rhinitis, chronische Sinusitis), Allergie; allergieinduzierten Atemwegsreaktionen, allergischer Rhinitis, viraler Rhinitis, nicht-allergischer Rhinitis, perennialer und saisonaler Rhinitis, Nasenverstopfung, allergischer Nasenverstopfung, funktioneller Sexualstörung der Frau und des Mannes, Hauterkrankungen, wie Dermatitis und Psoriasis, kardialen Dysfunktionen, wie Myokardischämie und Arrhythmie, Erkrankungen des Magen-Darm-Trakts, wie entzündliche Darmerkrankung, Morbus Crohn und Colitis ulcerosa, Krebs, rheumatoider Arthritis, Hypotonie, Schmerzen und überaktiven Blasenzuständen ausgewählt ist.

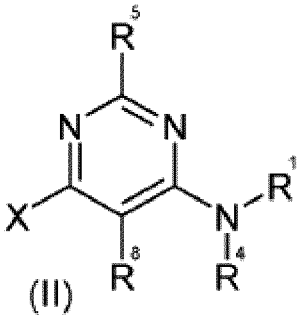
12. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 6, das die folgenden Schritte umfasst:

(a) Umsetzen einer Verbindung der Formel (III):



(III)

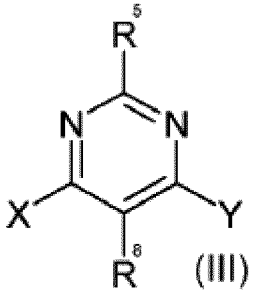
mit einem Amin $HN(R^1)(R^4)$, um eine Verbindung der Formel (II) bereitzustellen:



(II)

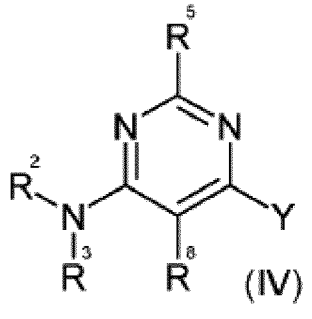
,

gefolgt von einer Reaktion mit einem Amin $HN(R^2)(R^3)$, um eine Verbindung der Formel (I) bereitzustellen; oder (b) Umsetzen einer Verbindung der Formel (III):



(III)

mit einem Amin $HN(R^2)(R^3)$, um eine Verbindung der Formel (IV) bereitzustellen:



(IV)

,

gefolgt von einer Reaktion mit einem Amin $HN(R^1)(R^4)$, um eine Verbindung der Formel (I) bereitzustellen; wobei X und Y Abgangsgruppen sind und R^1, R^2, R^3, R^4, R^5 und R^8 wie in Anspruch 1 definiert sind.

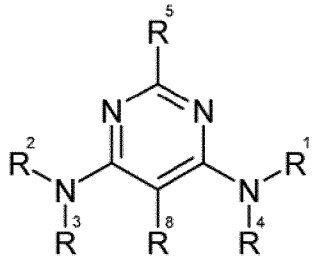
13. Kombination einer Verbindung nach einem der Ansprüche 1 bis 6 oder eines pharmazeutisch akzeptablen Salzes oder Solvats davon oder des Salzes nach Anspruch 7 mit einem oder mehreren anderen Therapeutika, die aus folgenden ausgewählt sind:

- Histamin-H_1-Rezeptor-Antagonisten, insbesondere Loratadin, Desloratadin, Fexofenadin und Cetirizin
- Histamin-H_3-Rezeptor-Antagonisten
- Histamin-H_2-Rezeptor-Antagonisten
- Leukotrien-Antagonisten, einschließlich Antagonisten von LTB_4, LTC_4, LTD_4 und LTE_4; beispielsweise Montelukast
- Phosphodiesterase-Hemmer, einschließlich PDE3-Hemmer, PDE4-Hemmer, PDE5-Hemmer, PDE7-Hemmer und Hemmer von zwei oder mehr Phosphodiesterasen, wie Dual-PDE3/PDE4-Hemmer
- Neurotransmitter-Wiederaufnahmehemmer, insbesondere Fluoxetin, Sertralin, Paroxetin, Ziprasidon
- 5-Lipoxygenase-Hemmer (5-LO-Hemmer) oder Antagonisten von 5-Lipoxygenase-aktivierendem Protein (FLAP)
- α_1- und α_2-Adrenozeptor-Agonist-Vasokonstriktor-Sympathomimetika zur Dekongestionsmittelverwendung

- muskarinische M3-Rezeptor-Antagonisten oder Anticholinergika
- β_2-Adrenozeptor-Agonisten
- dual wirkende β_2/M3-Mittel
- Xanthine, wie Theophyllin und Aminophyllin
- nicht-steroidale Antirheumatika, wie Natrium-Cromoglycat und Nedocromil-Natrium
- Ketotifen
- COX-1-Hemmer (NSAID) und COX-2-selektive Hemmer
- orale oder inhalierte Glukokortikosteroide
- monoklonale Antikörper, die gegen endogene entzündliche Einheiten wirksam sind
- Anti-Tumor-Nekrose-Faktor-Mittel (Anti-TNF-α-Mittel)
- Adhäsionsmolekülhemmer, einschließlich VLA-4-Antagonisten
- Kinin-B_1- und -B_2-Rezeptor-Antagonisten
- Immunsuppressiva
- Hemmer von Matrix-Metalloproteasen (MMP)
- Tachykinin-NK_1-, -NK_2- und -NK_3-Rezeptor-Antagonisten
- Elastase-Hemmer
- Adenosin-A2a-Rezeptor-Agonisten
- Hemmer von Urokinase
- Verbindungen, die auf Dopamin-Rezeptoren einwirken, z. B. D2-Agonisten
- Modulatoren des NFκb-Wegs, z. B. IKK-Hemmer
- Mittel, die als Mukolytika oder Antitussiva klassifiziert werden können
- Antibiotika
- Modulatoren von Zytokinsignalwegen, wie p38-MAP-Kinase-Hemmer, Syk-Tyrosinkinase-Hemmer oder JAK-Kinase-Hemmer
- Modulatoren der Prostaglandinwege, einschließlich Hemmer von H-PDGS und Antagonisten von DP-1 und CRTH2
- Antagonisten der Chemokin-Rezeptoren CXCR1 und CXCR2
- Antagonisten der Chemokin-Rezeptoren CCR3, CCR4 und CCR5
- Hemmer der zytosolischen und der löslichen Phospholipase A_2 ($cPLA_2$ und $sPLA_2$)
- Prostaglandin-D2-Rezeptor-Antagonisten (DPR1 und CRTH2)
- Hemmer von Prostaglandin-D-Synthase (PGDS)
- Hemmer von Phosphoinositid-3-Kinase,
- HDAC-Hemmer,
- p38-Hemmer und/oder
- CXCR2-Antagonisten.

Revendications

1. Composé de formule (I) :



ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, dans lequel :

R^1 est un groupe alkyle en C_{1-8}, (cycloalkyl en C_{3-7}) (alkyl en C_{0-6})- éventuellement substitué par méthyle, alcoxyalkyle contenant 3 à 8 atomes de carbone, hét-(alkyl en C_{0-6})-, CF_3-(alkyl en C_{1-6})-, CF_3O(alkyl en C_{2-3})- ou hydroxyalkyle en C_1-6 ;
R^3 et R^2 conjointement avec l'atome d'azote auquel ils sont liés forment un groupe hétérocyclique non aromatique à 4 à 8 chaînons qui contient éventuellement un ou plusieurs autres hétéroatomes ou groupes indépendamment

choisis parmi N, 0, S, S(O) et $S(O)_2$, le groupe hétérocyclique étant éventuellement un groupe bicyclique ponté, un groupe spirobicyclique ou étant éventuellement condensé avec un groupe carbocyclique à 3, 4, 5 ou 6 chaînons ou avec un groupe hétérocyclique à 4, 5 ou 6 chaînons qui contient au moins un chaînon de cycle indépendamment choisi parmi N, 0, S, S(O) et $S(O)_2$ et le système cyclique dans son ensemble étant éventuellement substitué par un ou plusieurs substituants indépendamment choisis parmi les substituants alkyle en C_{1-6}, NR^6R^7, $(CH_2)_a$(cycloalkyle en C_{3-7}), alcoxyalkyle contenant 2 à 8 atomes de carbone, $(CH_2)_b$hét^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryle et hydroxyalkyle en C_{1-6}, à condition que le système cyclique dans son ensemble contienne au moins deux atomes d'azote ou contienne un atome d'azote et soit substitué par un groupe qui contient au moins un atome d'azote ;

R^4 est H;

R^5 est H ou NH_2;

R^6 et R^7 sont chacun indépendamment choisis parmi H, un groupe alkyle en C_{1-6} et un groupe $(CH_2)_j$(cycloalkyle en C_{3-7}); ou R^6 et R^7, conjointement avec l'atome d'azote auquel ils sont liés, forment un groupe hétérocyclique à 4, 5 ou 6 chaînons;

R^8 est H ;

aryle est un groupe phényle éventuellement substitué par un ou plusieurs groupes indépendamment choisis parmi les groupes alkyle en C_{1-8}, alcoxy en C_{1-8}, OH, halogéno, CF_3, CHF_2, OCF_3, $OCHF_2$, SCF_3, hydroxy (alkyle en C_{1-6}), (alcoxy en C_{1-4}) (alkyle en C_{1-6}), (alkyl en C_{1-4})-S-(alkyle en C_{1-4}), CF_2CF_3, CH_2CF_3, CF_2CH_3, C (0) $NR^{13}R^{14}$, cycloalkyle en C_{3-8}, (cycloalkyl en C_{3-7}) (alkyle en C_{1-4}), (cycloalkyl en C_{3-7}) (alcoxy en C_{1-4}),

R^{13} et R^{14} sont chacun indépendamment choisis parmi H, un groupe alkyle en C_{1-6} et un groupe $(CH_2)_m$(cycloalkyle en C_{3-7}); ou R^{13} et R^{14}, conjointement avec l'atome d'azote auquel ils sont liés, forment un groupe hétérocyclique à 4, 5 ou 6 chaînons ;

a, b, c, d, j et m sont chacun indépendamment choisis parmi 0, 1, 2 et 3 ;

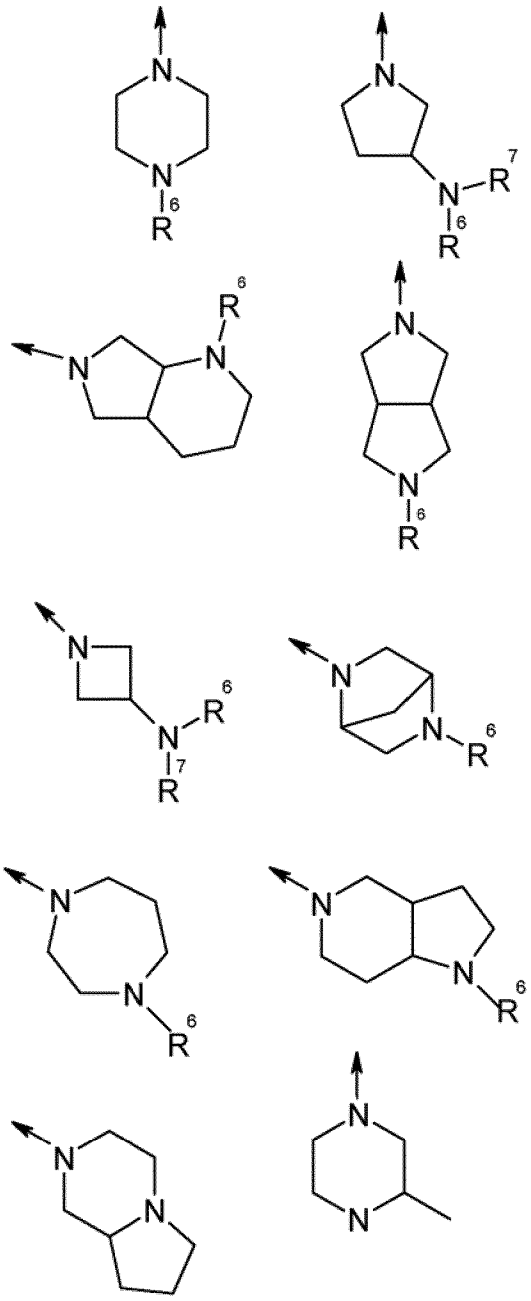
y est indépendamment choisi parmi 1, 2 et 3 ;

hét est un groupe hétérocyclique non aromatique à 4 à 8 chaînons qui contient au moins un hétéroatome ou groupe indépendamment choisi parmi N, 0, S, S(O) et $S(O)_2$, le groupe hétérocyclique étant éventuellement un groupe bicyclique ponté ou étant éventuellement condensé avec un groupe carbocyclique à 3, 4, 5 ou 6 chaînons ou avec un groupe hétérocyclique à 4, 5 ou 6 chaînons qui contient au moins un chaînon de cycle indépendamment choisi parmi N, 0, S, S(O) et $S(O)_2$ et le système cyclique dans son ensemble étant éventuellement substitué par un ou plusieurs substituants indépendamment choisis parmi les substituants alkyle en C_{1-6}, NR^6R^7, $(CH_2)_a$(cycloalkyle en C_{3-7}), alcoxyalkyle contenant 2 à 8 atomes de carbone, $(CH_2)_b$hét^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aryle et hydroxyalkyle en C_{1-6}; et

hét^1 est un hétérocycle aromatique ou non aromatique à 4, 5 ou 6 chaînons qui contient au moins un hétéroatome N, 0 ou S, éventuellement condensé avec un groupe carbocyclique à 4, 5 ou 6 chaînons ou avec un second hétérocycle à 4, 5 ou 6 chaînons qui contient au moins un hétéroatome N, 0 ou S.

2. Composé selon la revendication 1, ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, dans lequel R^1 est un groupe (cycloalkyl en C_{3-7})(alkyl en C_{0-6})- éventuellement substitué par méthyle.

3. Composé selon la revendication 1 ou la revendication 2, ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, dans lequel R^2 et R^3, conjointement avec l'atome d'azote auquel ils sont liés, forment un groupe choisi parmi les systèmes cycliques suivantes :



le système cyclique dans son ensemble pouvant être substitué par un ou plusieurs groupes alkyle en C_{1-6} ou $(CH_2)_a$(cycloalkyle en C_{3-7}).

4. Composé selon la revendication 3, ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, dans lequel R^6 et R^7 sont indépendamment choisis entre H et CH_3.

5. Composé selon la revendication 1, ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ledit composé étant choisi parmi

la N^4-(cyclopropylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
le tartrate de N^4-(cyclopropylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la N^4-isobutyl-6-[(3R)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la *N*-isobutyl-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidin-4-amine,
la *N*-(cyclopropylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidin-4-amine,

la N^4-(2,2-diméthylpropyl)-6-[(4a*R**,7a*R**)-octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-cyclopropyl-6-[(4a*R**,7a*R**)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-cyclobutyl-6-[(4a*R**,7a*R**)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[3-(méthylamino)azétidin-1-yl]pyrimidine-2,4-diamine,
la 6-(3-méthylaminoazétidin-1-yl)-N^4-(3,3,3-trifluoropropyl)pyrimidine-2,4-diamine,
la N^4-cyclopropylméthyl-6-(3-méthylaminoazétidin-1-yl)pyrimidine-2,4-diamine,
la N^4-(3,3-diméthylbutyl)-6-(3-méthylaminoazétidin-1-yl)pyrimidine-2,4-diamine,
la N^4-cyclopentylméthyl-6-(3-méthylaminoazétidin-1-yl)pyrimidine-2,4-diamine,
la N^4-isobutyl-6-[3-(méthylamino)azétidin-1-yl]pyrimidine-2,4-diamine,
la 6-[3-(méthylamino)azétidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[(3*R*)-3-méthylpipérazin-1-yl]pyrimidine-2,4-diamine,
la N^4-éthyl-6-(4-méthylpipérazin-1-yl)pyrimidine-2,4-diamine,
la N^4-(cyclopropylméthyl)-6-(4-méthylpipérazin-1-yl)pyrimidine-2,4-diamine,
la 6-[3-(méthylamino)azétidin-1-yl]-N^4-(2-méthylbutyl)pyrimidine-2,4-diamine,
la N^4-butyl-6-[3-(méthylamino)azétidin-1-yl]pyrimidine-2,4-diamine,
la 6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]-N^4-(2-méthylcyclopropyl)pyrimidine-2,4-diamine,
la N^4-isobutyl-6-(4-méthyl-1,4-diazépan-1-yl)pyrimidine-2,4-diamine,
la N^4-(cyclopropylméthyl)-6-(3-pyrrolidin-1-ylazétidin-1-yl)pyrimidine-2,4-diamine,
la N^4-bicyclo[1.1.1]pent-1-yl-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la 6-[3-méthyl-3-(méthylamino)azétidin-1-yl]-N^4-propylpyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-(3-pyrrolidin-1-ylazétidin-1-yl)pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[3-(isopropylamino)azétidin-1-yl]pyrimidine-2,4-diamine,
la N^4-(*tert*-butyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la 6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]-N^4-(1-méthylcyclopropyl)pyrimidine-2,4-diamine,
la N^4-(*tert*-butyl)-6-[(4a*S**,7a*S**)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-pipérazin-1-ylpyrimidine-2,4-diamine,
le chlorhydrate de N^4-(2,2-diméthylpropyl)-6-[3-(méthylamino)azétidin-1-yl]pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[(3a*R**,7a*S**)-octahydro-5*H*-pyrrolo[3,2-c]pyridin-5-yl]pyrimidine-2,4-diamine,
la 6-pipérazin-1-yl-N^4-propylpyrimidine-2,4-diamine,
la N^4-(cyclopropylméthyl)-6-[(4a*R*,7a*R*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-(2,2-diméthylpropyl)-6-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la N^4-isopropyl-6-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la 4-[3-(méthylamino)azétidin-1-yl]-6-(4-méthylpipéridin-1-yl)pyrimidin-2-amine,
la N^4-(cyclopentylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine,
la N^4-cyclobutyl-6-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]pyrimidine-2,4-diamine,
la 6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]-N^4-propylpyrimidine-2,4-diamine et
la N^4-éthyl-6-(4-méthyl-1,4-diazépan-1-yl)pyrimidine-2,4-diamine.

6. Composé selon la revendication 1, ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ledit composé étant la N^4-(cyclopropylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.

7. Sel selon la revendication 6, ledit sel étant le L-tartrate de N^4-(cyclopropylméthyl)-6-[(3*R*)-3-(méthylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine.

8. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 6, ou un sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ou le sel selon la revendication 7, conjointement avec un excipient pharmaceutiquement acceptable.

9. Composé selon l'une quelconque des revendications 1 à 6 ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ou sel selon la revendication 7, destiné à être utilisé en tant que médicament.

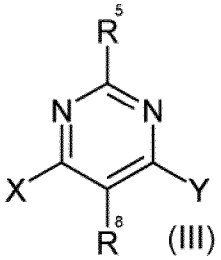
10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 6 ou d'un sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ou du sel selon la revendication 7, pour la fabrication d'un médicament pour traiter une maladie choisie parmi les maladies inflammatoires, les maladies respiratoires (par exemple le syndrome de détresse respiratoire de l'adulte, le syndrome de détresse respiratoire aiguë, la bronchite, la bronchite chronique, la bronchopneumopathie chronique obstructive, la mucoviscidose, l'asthme, l'emphysème, la rhinite, la

sinusite chronique), une allergie ; les réponses des voies respiratoires induites par une allergie, la rhinite allergique, une rhinite virale, une rhinite non allergique, les rhinites apériodique et saisonnière, la congestion nasale, la congestion allergique, les dysfonctions sexuelles féminine et masculine, les maladies de la peau telles que la dermatite et le psoriasis, les dysfonctions cardiaques telles que l'ischémie myocardique et l'arythmie, les maladies du tractus gastrointestinal telles qu'une maladie inflammatoire de l'intestin, la maladie de Crohn et la rectocolite hémorragique, un cancer, la polyarthrite rhumatoïde, l'hypotension, la douleur et les affections liées à une vessie hyperactive.

11. Composé selon l'une quelconque des revendications 1 à 6 ou sel ou solvate pharmaceutiquement et/ou vétérinairement acceptable de celui-ci, ou sel selon la revendication 7, destiné à être utilisé en traitement d'une maladie choisie parmi les maladies inflammatoires, les maladies respiratoires (par exemple le syndrome de détresse respiratoire de l'adulte, le syndrome de détresse respiratoire aiguë, la bronchite, la bronchite chronique, la bronchopneumopathie chronique obstructive, la mucoviscidose, l'asthme, l'emphysème, la rhinite, la sinusite chronique), une allergie ; les réponses des voies respiratoires induites par une allergie, la rhinite allergique, une rhinite virale, une rhinite non allergique, les rhinites apériodique et saisonnière, la congestion nasale, la congestion allergique, les dysfonctions sexuelles féminine et masculine, les maladies de la peau telles que la dermatite et le psoriasis, les dysfonctions cardiaques telles que l'ischémie myocardique et l'arythmie, les maladies du tractus gastrointestinal telles qu'une maladie inflammatoire de l'intestin, la maladie de Crohn et la rectocolite hémorragique, un cancer, la polyarthrite rhumatoïde, l'hypotension, la douleur et les affections liées à une vessie hyperactive.

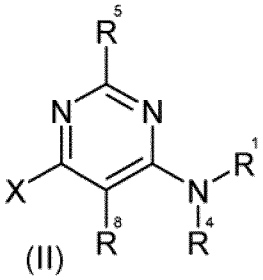
12. Procédé pour la préparation d'un composé selon l'une quelconque des revendications 1 à 6, comprenant les étapes de :

(a) réaction d'un composé de formule (III)



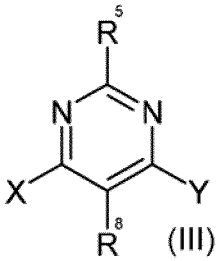
(III)

avec une amine $HN(R^1)(R^4)$ pour fournir un composé de formule (II)



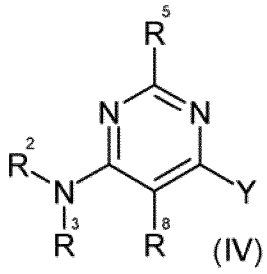
(II)

suivie de la réaction avec une amine $HN(R^2)(R^3)$ pour fournir un composé de formule (I) ; ou
(b) réaction d'un composé de formule (III)



(III)

avec une amine $HN(R^2)(R^3)$ pour fournir un composé de formule (IV)



(IV)

suivie de la réaction avec une amine $HN(R^1)(R^4)$ pour fournir un composé de formule (I) ;

dans lequel X et Y sont des groupes partants et R^1, R^2, R^3, R^4, R^5 et R^8 sont tels que définis dans la revendication 1.

13. Association d'un composé selon l'une quelconque des revendications 1 à 6, ou d'un sel ou solvate pharmaceutiquement acceptable de celui-ci, ou du sel selon la revendication 7, avec un ou plusieurs autres agents thérapeutiques choisis parmi :

- les antagonistes des récepteurs histaminiques H_1, en particulier la loratadine, la desloratadine, la fexofénadine et la cétirizine
- les antagonistes des récepteurs histaminiques H_3
- les antagonistes des récepteurs histaminiques H_2
- les antagonistes des leucotriènes, notamment les antagonistes de LTB_4, LTC_4, LTD_4 et LTE_4 ; par exemple le montélukast
- les inhibiteurs de phosphodiestérases, notamment les inhibiteurs de la PDE3, les inhibiteurs de la PDE4, les inhibiteurs de la PDE5, les inhibiteurs de la PDE7 et les inhibiteurs de deux ou plus de deux phosphodiestérases, tels que les doubles inhibiteurs de PDE3/PDE4
- les inhibiteurs de la recapture de neurotransmetteurs, en particulier la fluoxétine, la sertraline, la paroxétine, la ziprasidone
- les inhibiteurs de la 5-lipoxygénase (5-LO) ou les antagonistes de la protéine d'activation de la 5-lipoxygénase (FLAP)
- les agents sympathomimétiques vasoconstricteurs agonistes des adrénorécepteurs α_1 et α_2 destinés à être utilisés comme décongestionnants
- les antagonistes des récepteurs muscariniques M3 ou les agents anticholinergiques
- les antagonistes des adrénorécepteurs β_2
- les agents β_2/M3 à double action
- les xanthines, telles que la théophylline et l'aminophylline
- les anti-inflammatoires non stéroïdiens, tels que le cromoglycate de sodium et le nédocromil sodique
- le kétotifène
- les inhibiteurs de la COX-1 (les AINS) et les inhibiteurs sélectifs de la COX-2
- les glucocorticostéroïdes oraux ou inhalés
- les anticorps monoclonaux actifs à l'encontre d'entités inflammatoires endogènes
- les agents anti-facteur de nécrose tumorale (anti-TNF-α)
- les inhibiteurs de molécules d'adhésion notamment les antagonistes du VLA-4
- les antagonistes des récepteurs B_1 et B_2 des kinines
- les agents immunosuppresseurs
- les inhibiteurs de métalloprotéases matricielles (MMP)
- les antagonistes des récepteurs NK_1, NK_2 et NK_3 des tachykinines
- les inhibiteurs de l'élastase
- les agonistes des récepteurs A2a de l'adénosine
- les inhibiteurs d'urokinase
- les composés qui agissent sur les récepteurs dopaminergiques, par exemple les agonistes de D2
- les modulateurs de la voie du NFκb, par exemple les inhibiteurs de l'IKK
- les agents qui peuvent être classés comme mucolytiques ou antitussifs
- les antibiotiques
- les modulateurs de voies de signalisation des cytokines, tels que les inhibiteurs de la p38 MAP kinase, les

inhibiteurs de la syk tyrosine kinase ou les inhibiteurs de la JAK kinase

- les modulateurs des voies des prostaglandines, notamment les inhibiteurs de la H-PDGS et les antagonistes du DP-1 et du CRTH2
- les antagonistes des récepteurs des chimiokines CXCR1 et CXCR2
- les antagonistes des récepteurs des chimiokines CCR3, CCR4 et CCR5
- les inhibiteurs de phospholipase A_2 cytosolique et soluble ($cPLA_2$ et $sPLA_2$)
- les antagonistes des récepteurs D2 des prostaglandines (DP1 et CRTH2)
- les inhibiteurs de la prostaglandine D synthase (PGDS)
- les inhibiteurs de la phosphoinositide-3-kinase,
- les inhibiteurs de la HDAC,
- les inhibiteurs de p38 et/ou
- les antagonistes du CXCR2.

REFERENCES CITED IN THE DESCRIPTION

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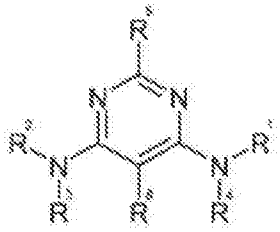
SZTNH-100054162

Pirimidin-származékok

Szabadalmi igénypontok

1. (I):

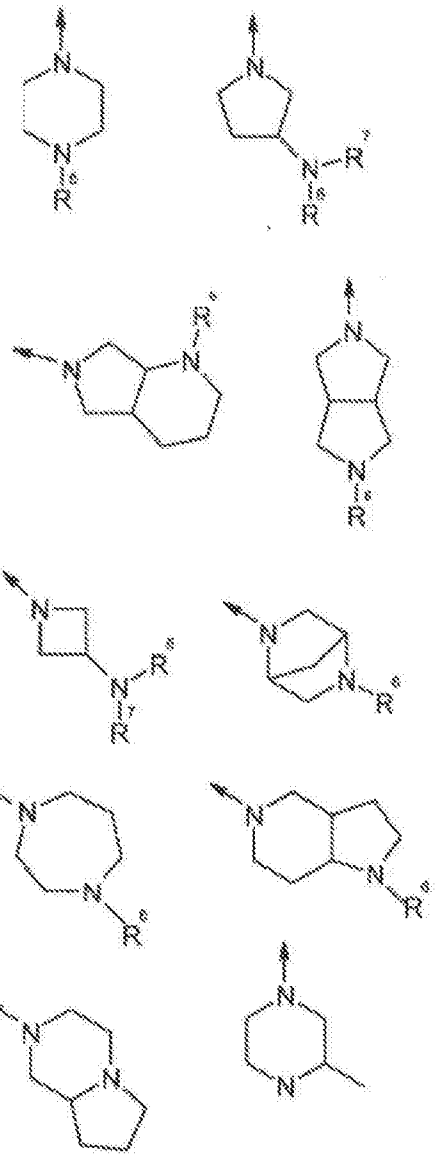


képletű vegyület vagy egy gyógyászatilag és/vagy elfogadható sója vagy szolvátja, ahol:
R^1 1-8 szénatomos alkil, adott esetben metilcsoporttal szubsztituált 3-7 szénatomos cikloalkil-(0-6 szénatomos)-alkil-, 3-8 szénatomot tartalmazó alkoxialkil, het-(0-6 szénatomos)-alkil-, CF_3-(1-6 szénatomos)-alkil-, CF_3O-(2-3 szénatomos)-alkil- vagy 1-6 szénatomos hidroxialkilcsoport;
R^3 és R^2 a hozzájuk kapcsolódó nitrogénatommal együtt egy 4-8-tagú nem-aromás heterociklusos csoportot alkot, mely adott esetben egy vagy több további, egymástól függetlenül N, O, S, S(O) és $S(O)_2$ közül választott heteroatomot vagy csoportot tartalmaz, ahol a heterociklusos csoport adott esetben egy áthidalt biciklusos csoport, egy spiro-biciklusos csoport vagy adott esetben egy 3-, 4-, 5- vagy 6-tagú karbociklusos csoporthoz vagy egy 4-, 5- vagy 6-tagú heterociklusos csoporthoz kondenzált, mely legalább egy, egymástól függetlenül N, O, S, S(O) és $S(O)_2$ közül választott gyűrűtagot tartalmaz, és ahol a teljes gyűrűrendszer adott esetben egy vagy több, egymástól függetlenül 1-6 szénatomos alkil, NR^6R^7, $(CH_2)_a$-(3-7 szénatomos)-cikloalkil, 2-8 szénatomos alkoxialkil, $(CH_2)_bhet^1$, $(CH_2)_cCF_3$, $(CH_2)_dOCF_3$, $(CH_2)_earil$ és 1-6 szénatomos hidroxialkilcsoport közül választott szubsztituenst tartalmaz, azzal a feltétellel, hogy a teljes gyűrűrendszer legalább két nitrogénatomot tartalmaz, vagy egy nitrogénatomot tartalmaz és egy legalább egy nitrogénatomot tartalmazó csoporttal szubsztituált;
R^4 H;
R^5 H vagy NH_2;

R^6 és R^7 egymástól függetlenül H, 1-6 szénatomos alkil és $(CH_2)_j$(3-7 szénatomos)-cikloalkilcsoport közül választott; vagy R^6 és R^7, a hozzájuk kapcsolódó nitrogénatommal együtt, egy 4, 5 vagy 6-tagú heterociklusos csoportot alkot;
R^8 H;
aril egy adott esetben egy vagy több, egymástól függetlenül 1-8 szénatomos alkil, 1-8 szénatomos alkoxi, OH, halogénatom, CF_3, CHF_2, OCF_3, $OCHF_2$, SCF_3, hidroxi-(1-6 szénatomos)-alkil, 1-4 szénatomos alkoxi-(1-6 szénatomos)-alkil, 1-4 szénatomos alkil-S-1-4 szénatomos alkil, CF_2CF_3, CH_2CF_3, CF_2CH_3, $C(O)NR^{13}R^{14}$, 3-8 szénatomos cikloalkil, 3-7 szénatomos cikloalkil-(1-4 szénatomos)-alkil, 3-7 szénatomos cikloalkil-(1-4 szénatomos)-alkoxicsoport közül választott csoporttal szubsztituált fenilcsoport,
R^{13} és R^{14} egymástól függetlenül H, 1-6 szénatomos alkil és $(CH_2)_m$(3-7 szénatomos)-cikloalkilcsoport közül választott; vagy R^{13} és R^{14}, a hozzájuk kapcsolódó nitrogénatommal együtt, egy 4, 5 vagy 6-tagú heterociklusos csoportot alkot;
a, b, c, d, j és m egymástól függetlenül 0, 1, 2 és 3 közül választott;
y egymástól függetlenül 1, 2 és 3 közül választott;
het egy 4-8-tagú nem-aromás heterociklusos csoport mely legalább egy, egymástól függetlenül N, O, S, S(O) és $S(O)_2$ közül választott heteroatomot vagy csoportot tartalmaz, ahol a heterociklusos csoport adott esetben egy áthidalt biciklusos csoport vagy egy adott esetben egy 3-, 4-, 5- vagy 6-tagú karbociklusos csoporttal vagy egy 4-, 5- vagy 6-tagú heterociklusos csoporttal kondenzált, mely legalább egy, egymástól függetlenül N, O, S, S(O) és $S(O)_2$ közül választott gyűrűtagot tartalmaz, és ahol a teljes gyűrűrendszer adott esetben egy vagy több, egymástól függetlenül 1-6 szénatomos alkil, NR^6R^7, $(CH_2)_n$3-7 szénatomos cikloalkil, 2-8 szénatomos alkoxialkil, $(CH_2)_b$het^1, $(CH_2)_cCF_3$, $(CH_2)_yOCF_3$, $(CH_2)_d$aril és 1-6 szénatomos hidroxialkilcsoport közül választott szubsztituenst tartalmaz; és
het^1 egy aromás vagy nem-aromás 4-, 5- vagy 6-tagú heterociklusos csoport, mely legalább egy N, O vagy S heteroatomot tartalmaz, adott esetben egy 4-, 5- vagy 6-tagú karbociklusos csoporttal vagy egy második 4-, 5- vagy 6-tagú heterociklusos csoporttal kondenzált, mely legalább egy N, O vagy S heteroatomot tartalmaz.

2. Az 1. igénypont szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, ahol R^1 adott esetben metilcsoporttal szubsztituált 3-7 szénatomos cikloalkil-(0-6 szénatomos)-alkilcsoport.

3. Az 1. vagy 2. igénypont szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, ahol R^2 és R^3, a hozzájuk kapcsolódó nitrogénatommal együtt, egy, az alábbi gyűrűrendszerek közül választott csoportot alkot:



ahol a teljes gyűrűrendszer egy vagy több 1-6 szénatomos alkil vagy $(CH_2)_n$-(3-7 szénatomos cikloalkil)-csoporttal lehet szubsztituálva.

4. A 3. igénypont szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, ahol R^6 és R^7 egyre egymástól függetlenül H vagy CH_3 közül választott.

5. Az 1. igénypont szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, mely vegyület:

N^4-(ciklopropilmetil)-6-[(3*R*)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,

N^4-(ciklopropilmetil)-6-[(3*R*)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin tartarát,

N^4-izobutil-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,

N-izobutil-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-4-amin,

N-(ciklopropilmetil)-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-4-amin,

N^4-(2,2-dimetilpropil)-6-[(4aR*,7aR*)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,

N^4-ciklopropil-6-[(4aR*,7aR*)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,

N^4-ciklobutil-6-[(4aR*,7aR*)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-[3-(metilamino)azetidin-1-il]pirimidin-2,4-diamin,

6-(3-metilamino-azetidin-1-il)-N^4-(3,3,3-trifluor-propil)-pirimidin-2,4-diamin,

N^4-ciklopropilmetil-6-(3-metilamino-azetidin-1-il)-pirimidin-2,4-diamin,

N^4-(3,3-dimetil-butil)-6-(3-metilamino-azetidin-1-il)-pirimidin-2,4-diamin,

N^4-ciklopentilmetil-6-(3-metilamino-azetidin-1-il)-pirimidin-2,4-diamin,

N^4-izobutil-6-[3-(metilamino)azetidin-1-il]pirimidin-2,4-diamin,

6-[3-(metilamino)azetidin-1-il]-N^4-propilpirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-[(3R)-3-metilpiperazin-1-il]pirimidin-2,4-diamin,

N^4-etil-6-(4-metilpiperazin-1-il)pirimidin-2,4-diamin,

N^4-(ciklopropilmetil)-6-(4-metilpiperazin-1-il)pirimidin-2,4-diamin,

6-[3-(metilamino)azetidin-1-il]-N^4-(2-metilbutil)pirimidin-2,4-diamin,

N^4-butil-6-[3-(metilamino)azetidin-1-il]pirimidin-2,4-diamin,

6-[(3R)-3-(metilamino)pirrolidin-1-il]-N^4-(2-metilciklopropil)pirimidin-2,4-diamin,

N^4-izobutil-6-(4-metil-1,4-diazepan-1-il)pirimidin-2,4-diamin,

N^4-(ciklopropilmetil)-6-(3-pirrolidin-1-ilazetidin-1-il)pirimidin-2,4-diamin,

N^4-biciklo[1.1.1]pent-1-il-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,

6-[3-metil-3-(metilamino)azetidin-1-il]-N^4-propilpirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-(hexahidropirrolo[1,2-a]pirazin-2(1H)-il)pirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-(3-pirrolidin-1-ilazetidin-1-il)pirimidin-2,4-diamin,

N^4-(2,2-dimetilpropil)-6-[3-(izopropilamino)azetidin-1-il]pirimidin-2,4-diamin,

N^4-(*terc*-butil)-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,

6-[(3R)-3-(metilamino)pirrolidin-1-il]-N^4-(1-metilciklopropil)pirimidin-2,4-diamin,

N^4-(*terc*-butil)-6-[(4aS*,7aS*)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,
N^4-(2,2-dimetilpropil)-6-piperazin-1-ilpirimidin-2,4-diamin,
N^4-(2,2-dimetilpropil)-6-[3-(metilamino)azetidin-1-il]pirimidin-2,4-diamin hidroklorid,
N^4-(2,2-dimetilpropil)-6-[(3aR*,7aS*)-oktahidro-5H-pirrolo[3,2-c]piridin-5-il]pirimidin-2,4-diamin,
6-piperazin-1-il-N^4-propilpirimidin-2,4-diamin,
N^4-(ciklopropilmetil)-6-[(4aR,7aR)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,
N^4-(2,2-dimetilpropil)-6-[(4aS,7aS)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,
N^4-izopropil-6-[(4aS,7aS)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,
4-[3-(metilamino)azetidin-1-il]-6-(4-metilpiperidin-1-il)pirimidin-2-amin,
N^4-(ciklopentilmetil)-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin,
N^4-ciklobutil-6-[(4aS,7aS)-oktahidro-6H-pirrolo[3,4-b]piridin-6-il]pirimidin-2,4-diamin,
6-[(3R)-3-(metilamino)pirrolidin-1-il]-N^4-propilpirimidin-2,4-diamin, és
N^4-etil-6-(4-metil-1,4-diazepan-1-il)pirimidin-2,4-diamin
közül választott.

6. Egy 1. igénypont szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, mely vegyület a N^4-(ciklopropilmetil)-6-[(3*R*)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin.

7. Egy 6. igénypont szerinti só, mely só a N^4-(ciklopropilmetil)-6-[(3R)-3-(metilamino)pirrolidin-1-il]pirimidin-2,4-diamin L-tartarát.

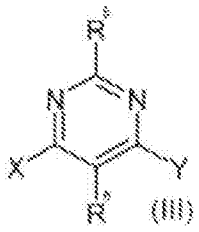
8. Gyógyászati készítmény, mely egy 1-6. igénypontok bármelyike szerinti vegyületet vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sóját vagy szolvátját, vagy egy 7. igénypont szerinti sót tartalmaz, egy gyógyászatilag elfogadható kötőanyaggal együtt.

9. Egy 1-6. igénypontok bármelyike szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja, vagy a 7. igénypont szerinti só gyógyszerként történő alkalmazásra.

10. Egy 1-6. igénypontok bármelyike szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja alkalmazása gyulladásos betegségek, légúti betegségek (például felnőttkori légzési distress szindróma, akut légzési distress szindróma, bronchitis, krónikus bronchitis, krónikus elzáródásos tüdőbetegség, cystás fibrosis, asztma, emphysema, rhinitis, krónikus sinusitis), allergia; allergia által indukált légúti válaszok, allergiás rhinitis, vírusos rhinitis, nem-allergiás rhinitis, állandó és szezonális rhinitis, orrdugulás, allergiás congestio, női és férfi szexuális diszfunkciók, bőrbetegségek, például dermatitis és psoriasis, szívzavarok, például myocardialis ischaemia és arritmia, a gyomor és bélrendszer betegsége, például gyulladásos bélbetegség, Crohn-betegség és colitis ulcerosa, rák, rheumatoid arthritis, magas vérnyomás, fájdalom és hólyag-túlaktivitási állapotok közül kikerülő betegség kezelésére szolgáló gyógyszer előállítására.

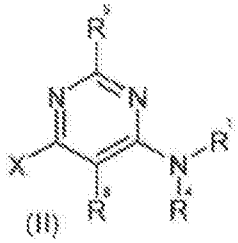
11. Egy 1-6. igénypontok bármelyike szerinti vegyület vagy egy gyógyászatilag és/vagy állatgyógyászatilag elfogadható sója vagy szolvátja gyulladásos betegségek, légúti betegségek (például felnőttkori légzési distress szindróma, akut légzési distress szindróma, bronchitis, krónikus bronchitis, krónikus elzáródásos tüdőbetegség, cystás fibrosis, asztma, emphysema, rhinitis, krónikus sinusitis), allergia; allergia által indukált légúti válaszok, allergiás rhinitis, vírusos rhinitis, nem-allergiás rhinitis, állandó és szezonális rhinitis, orrdugulás, allergiás congestio, női és férfi szexuális diszfunkciók, bőrbetegségek, például dermatitis és psoriasis, szívzavarok, például myocardialis ischaemia és arritmia, a gyomor és bélrendszer betegsége, például gyulladásos bélbetegség, Crohn-betegség és colitis ulcerosa, rák, rheumatoid arthritis, magas vérnyomás, fájdalom és hólyag-túlaktivitási állapotok közül kikerülő betegség kezelésében történő alkalmazásra.

12. Eljárás egy 1-6. igénypontok bármelyike szerinti vegyület előállítására, melynek során:
(a) egy (III):



(III)

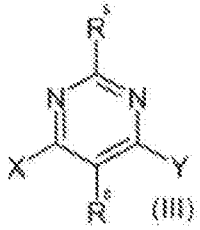
képletű vegyületet egy $HN(R^1)(R^4)$ képletű aminnal reagáltatunk a (II):



(II)

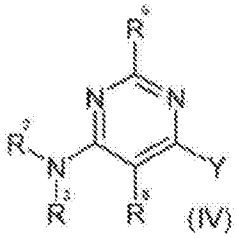
képletű vegyület előállítására, majd ezt egy $HN(R^2)(R^3)$ képletű aminnal reagáltatjuk az (I) képletű vegyület előállítására; vagy

(b) egy (III):



(III)

képletű vegyületet egy $HN(R^2)(R^3)$ képletű aminnal reagáltatunk egy (IV):



(IV)

képletű vegyület előállítására, majd ezt egy $HN(R^1)(R^8)$ képletű aminnal reagáltatjuk az (I) képletű vegyület előállítására;

ahol X és Y kilépő csoportok és R^1, R^2, R^3, R^4, R^5 és R^8 az 1. igénypontban megadott.

13. Egy 1-6. igénypontok bármelyike szerinti vegyület, vagy egy gyógyászatilag elfogadható sója vagy szolvátja, vagy a 7. igénypont szerinti só más terápiás szerrel vagy szerekkel alkotott kombinációja, ahol a más terápiás szer:

• hisztamin H_1 receptor antagonisták, különösen loratidin, desloratidin, fexofenadin és cetirizin

• hisztamin H_3 receptor antagonisták

• hisztamin H_2 receptor antagonisták

• leukotrién antagonisták, ideértve az of LTB_4, LTC_4, LTD_4, és LTE_4 antagonistákat; például Montelukast

• foszfodiészteráz inhibitorok, ideértve a PDE3 inhibitorokat, PDE4 inhibitorokat, PDE5 inhibitorokat, PDE7 inhibitorokat és két vagy több foszfodiészteráz inhibitorait, például duális PDE3/PDE4 inhibitorokat

• neurotranszmitter re-uptake inhibitorok, különösen fluoxetin, setralin, paroxetin, ziprasidon

• 5-lipoxigenáz (5-LO) inhibitorok vagy 5-lipoxigenáz aktiváló protein (FLAP) antagonisták

• pangást csökkentő alkalmazásra szolgáló α1- és α2-adrenoceptor agonista vasoconstrictor sympathomimetikum szerek

• muszkarin M3 receptor antagonisták vagy antikolinerg szerek

• β2-adrenoceptor agonisták

• Duálisan ható β2/M3 szerek

• xantinok, például teofillin és aminofillin

• nem-szteroid gyulladásgátlók, például nátrium kromoglikolát és nedocromil nátrium

• ketotifen

• COX-1 inhibitorok (NSAIDs) és COX-2 szelektív inhibitorok

• orális vagy inhalált glükokortikoszteroidok

• endogén gyulladásos helyek elleni monoklonális antitestek

• anti-tumor nekrózis faktor (anti-TNF-α) szerek

• adhéziós molekula inhibitorok, ideértve a VLA-4 antagonistákat

• kinin-B_1- és B_2 -receptor antagonisták

• immunszupresszív szerek

• of mátrix metalloproteázok (MMPs) inhibitorai

• tachykinin NK_1, NK_2 és NK_3 receptor antagonisták

• elasztáz inhibitorok

• adenozin A2a receptor agonisták

• urokináz inhibitorok

• dopamin receptorokra ható vegyületek, például D2 agonisták

• a NFκb reakcióút modulátorai, például IKK inhibitorok

• a mukolitikumokhoz vagy antitusszív csoportba sorolható szerek

• antibiotikumok

• citokin jelző reakcióút modulátorok, például p38 MAP kináz inhibitorok, syk tirozinkináz inhibitorok vagy JAK kináz inhibitorok

• a prosztaglandin reakcióutak modulátorai, ideértve a H-PDGS inhibitorokat és DP-1 és CRTH2 antagonistákat

• CXCR1 és CXCR2 kemokin receptor antagonisták

- CCR3, CCR4 és CCR5 kemokin receptor antagonisták
- of cytosolicus és vízoldható foszfolipáz A2 ($cPLA_2$ és $sPLA_2$) inhibitorok
- prosztaglandin D2 receptor antagonisták (DP1 és CRTH2)
- prosztaglandin D szintáz (PGDS) inhibitorok
- foszfoinozitid-3-kináz inhibitorok,
- HDAC inhibitorok,
- p38 inhibitorok és/vagy
- CXCR2 antagonisták

közül választott(ak).