2-AMINOPYRIMIDINE MODULATORS OF THE HISTAMINE H4 RECEPTOR

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2-Aminopyrimidine compounds are described, which are useful as H4 receptor modulators. Such compounds may be used in pharmaceutical compositions and methods for the treatment of disease states, disorders, and conditions mediated by H4 receptor activity, such as allergy, asthma, autoimmune diseases, and pruritus.
2-AMINOPYRIMIDINE MODULATORS OF THE HISTAMINE H4 RECEPTOR

[0001] This application is a divisional application of U.S. application Ser. No. 12/070,051, filed on Feb. 14, 2008, which claims the benefit of U.S. provisional patent application Ser. No. 60/889,798, filed on Feb. 14, 2007, all of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to certain 2-aminopyrimidine compounds, pharmaceutical compositions containing them, methods of making them, and methods of using them for the modulation of the histamine H4 receptor and for the treatment of disease states, disorders, and conditions mediated by histamine H4 receptor activity.

BACKGROUND OF THE INVENTION


[0004] A biological activity of histamine in the context of immunology and autoimmune diseases is closely related with the allergic response and its deleterious effects, such as inflammation. Events that elicit the inflammatory response include physical stimulation (including trauma), chemical stimulation, infection, and invasion by a foreign body. The inflammatory response is characterized by pain, increased temperature, redness, swelling, reduced function, or a combination of these.

[0005] Mast cell degranulation (exocytosis) releases histamine and leads to an inflammatory response that may be initially characterized by a histamine-modulated wheal and flare reaction. A wide variety of immunological stimuli (e.g., allergens or antibodies) and non-immunological (e.g., chemical) stimuli may cause the activation, recruitment, and degranulation of mast cells. Mast cell activation initiates allergic inflammatory responses, which in turn cause the recruitment of other effector cells that further contribute to the inflammatory response. It has been shown that histamine induces chemotaxis of mouse mast cells (Hofstra, et al., 2003). Chemotaxis does not occur using mast cells derived from H4 receptor knockout mice. Furthermore, the response is blocked by an H4-specific antagonist, but not by H1, H2 or H3 receptor antagonists (Hofstra, et al., 2003; Thurmord, R. L., et al., J. Pharmacol. Exp. Ther. 2004, 309(1), 404-413). The in vivo migration of mast cells to histamine has also been investigated and shown to be H4 receptor dependent (Thurmord, et al., 2004). The migration of mast cells may play a role in allergic rhinitis and allergy where increases in mast cell number are found (Kirby, J. G., et al., Am. Rev. Respir. Dis. 1987, 136(2), 379-383; Crimi, E., et al., Am. Rev. Respir. Dis. 1991, 144(6), 1282-1286; Amin, K., et al., Am. J. Resp. Crit. Care Med. 2000, 162(6), 2295-2301; Gauvreau, G. M., et al., Am. J. Resp. Crit. Care Med. 2000, 161(5), 1473-1478; Kassel, O., et al., Clin. Exp. Allergy 2001, 31(9), 1432-1440). In addition, it is known that in response to allergens there is a redistribution of mast cells to the epithelial lining of the nasal mucosa (Fokkens, W. J., et al., Clin. Exp. Allergy 1992, 22(7), 701-710; Slater, A., et al., J. Laryngol. Otol. 1996, 110, 929-933). These results show that the chemotactic response of mast cells to histamine is mediated by histamine H4 receptors.

[0006] It has been shown that eosinophils can chemotax towards histamine (O’Reilly, M. E., et al., J. Recept. Signal Transduction 2002, 22(1-4), 431-448; Buckley, K. F., et al., Br. J. Pharmacol. 2003, 140(6), 1117-1127; Ling, et al., 2004). Using H4 selective ligands, it has been shown that histamine-induced chemotaxis of eosinophils is mediated through the H4 receptor (Buckland, et al., 2003; Ling, et al., 2004). Cell surface expression of adhesion molecules CD11b/CD18 (LFA-1) and CD54 (ICAM-1) on eosinophils increases after histamine treatment (Ling, et al., 2004). This increase is blocked by H4 receptor antagonists but not by H1, H2, or H3 receptor antagonists.

[0007] The H4R also plays a role in dendritic cells and T cells. In human monocyte-derived dendritic cells, H4R stimulation suppresses IL-12 p70 production and drives histamine-mediated chemotaxis (Gutzmer, R., et al., J. Immunol. 2005, 174(9), 5224-5232). A role for the H4 receptor in CD8* T cells has also been reported. Gartner, et al., (2002) showed that both H4 and H3 receptors control histamine-induced IL-16 release from human CD8* T cells. IL-16 is found in the bronchoalveolar fluid of allergen- or histamine-challenged asthmatics (Mashikian, V. M., et al., J. Allergy Clin. Immunol. 1998, 101 (6, Part 1), 786-792; Krug, N., et al., Am. J. Resp. Crit. Care Med. 2000, 162(1), 105-111) and is considered important in CD4* cell migration. The activity of the receptor in these cell types indicates an important role in adaptive immune responses such as those active in autoimmune diseases.

[0008] In vivo H4 receptor antagonists were able to block neutrophilia in zymosan-induced peritonitis or pleurisy models (Takeshita, K., et al., J. Pharmacol. Exp. Ther. 2003, 307(3), 1072-1078; Thurmord, et al., 2004). In addition, H4 receptor antagonists have activity in a widely used and well-characterized model of colitis (Varga, C., et al., Eur. J. Pharmacol. 2005, 522(1-3), 130-138). These results support the conclusion that H4 receptor antagonists have the capacity to be anti-inflammatory in vivo.

[0009] Another physiological role of histamine is as a mediator of itch and H1 receptor antagonists are not com-
pletely effective in the clinic. Recently, the H₄ receptor has also been implicated in histamine-induced scratching in mice (Bell, J. K., et al., Br. J. Pharmacol. 2004, 142(2), 374-380). The effects of histamine could be blocked by H₄ antagonists. These results support the hypothesis that the H₄ receptor is involved in histamine-induced itch and that H₄ receptor antagonists will therefore have positive effects in treating pruritus. Histamine H₄ receptor antagonists have been shown to attenuate experimental pruritus (Dunford, P. J. et al. J. Allergy Clin. Immunol. 2007, 119(1), 176-183).

[0010] Modulation of H₄ receptors controls the release of inflammatory mediators and inhibits leukocyte recruitment, thus providing the ability to prevent and/or treat H₄-mediated diseases and conditions, including the deleterious effects of allergic responses such as inflammation. Compounds according to the present invention have H₄ receptor modulating properties. Compounds according to the present invention have leukocyte recruitment inhibiting properties. Compounds according to the present invention have anti-inflammatory properties.


[0013] Thus, small-molecule histamine H₄ receptor modulators according to this invention control the release of inflammatory mediators and inhibit leukocyte recruitment, and may be useful in treating inflammation of various etiologies, including the following conditions and diseases: inflammatory disorders, allergic disorders, dermatological disorders, autoimmune disease, lymphatic disorders, pruritus, and immunodeficiency disorders. Diseases, disorders and medical conditions that are mediated by histamine H₄ receptor activity include those referred to herein.


[0016] However, there remains a need for potent histamine H₄ receptor modulators with desirable pharmaceutical properties. Certain 2-aminopyrimidine derivatives have been found in the context of this invention to have histamine H₄ receptor-modulating activity.

**SUMMARY OF THE INVENTION**

[0017] In one aspect the invention relates to chemical entity selected from compounds of the following Formula (I):

![Chemical Structure](image)

[0018] wherein

[0019] R¹ is:

[0020] a) a C₄₋₆ alkyl group, optionally substituted with —OH, —OC₃₋₄ alkyl, —CF₃, or —O— (monocyclic cycloalkyl);

[0021] b) a benzyl, —CH₂— (monocyclic heteroaryly), or phenethyl group, each optionally substituted with halo;

[0022] c) a monocyclic cycloalkyl, —(CH₂)₃—, tetrahydrofuranyl, or —(CH₂)₃—, tetrahydropyranyl group, each optionally fused to a phenyl ring, and each optionally substituted with C₆₋₁₄ alkyl or phenyl or

[0023] d) an adamantyl group;

[0024] R² is H, F, methyl, or methoxy;

[0025] or R¹ and R² taken together form —(CH₂)₃— or —(CH₂)₃OCH₂— and

[0026] —N(R³)R⁴ is one of the following acyclic, monocyclic, spirocyclic, bridged, or fused ring systems:
metabolites of Formula (I). Pharmaceutical compositions according to the invention may further comprise a pharmaceutically acceptable excipient.

[0034] In another aspect, the invention is directed to a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by histamine H₄ receptor activity, comprising administering to the subject in need of such treatment an effective amount of at least one chemical entity selected from compounds of Formula (I), pharmaceutically acceptable salts of compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of compounds of Formula (I).

[0035] In certain preferred embodiments of the inventive method, the disease, disorder, or medical condition is inflammation. Inflammation herein refers to the response that develops as a consequence of histamine release, which in turn is caused by at least one stimulus. Examples of such stimuli are immunological stimuli and non-immunological stimuli.

[0036] In another aspect, the chemical entities of the present invention are useful as histamine H₄ receptor modulators. Thus, the invention is directed to a method for modulating histamine H₄ receptor activity, including when such receptor is in a subject, comprising exposing histamine H₄ receptor to an effective amount of at least one chemical entity selected from compounds of Formula (I), pharmaceutically acceptable salts of compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of compounds of Formula (I).

[0037] In another aspect, the present invention is directed to methods of making compounds of Formula (I) and pharmaceutically acceptable salts thereof.

[0038] An object of the present invention is to overcome or ameliorate at least one of the disadvantages of the conventional methodologies and/or prior art, or to provide a useful alternative thereto.

[0039] Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

DETAILED DESCRIPTION OF INVENTION AND ITS PREFERRED EMBODIMENTS

[0040] For the sake of brevity, the disclosures of the publications, including patents, cited in this specification are herein incorporated by reference.

[0041] As used herein, the terms “including”, “containing” and “comprising” are used herein in their open, non-limiting sense.

[0042] The term “alkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkyl groups include methyl (Me, which also may be structurally depicted by a bond, “-”), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0043] The term “cycloalkyl” refers to a saturated or partially saturated, monocyclic, fused polycyclic, or spiro polycyclic carbocycle having from 3 to 12 ring atoms per carbocycle. Illustrative examples of cycloalkyl groups include the following entities, in the form of properly bonded moieties:
A “heterocycloalkyl” refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring structure selected from carbon atoms and up to three heteroatoms selected from nitrogen, oxygen, and sulfur. The ring structure may optionally contain up to two oxo groups on carbon or sulfur ring members. Illustrative entities, in the form of properly bonded moieties, include:

The term “heteroaryl” refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:

Those skilled in the art will recognize that the species of heteroaryl, cycloalkyl, and heterocycloalkyl groups listed or illustrated above are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

The term “halogen” represents chlorine, fluorine, bromine, or iodine. The term “halo” represents chloro, fluoro, bromo, or iodo.

The term “substituted” means that the specified group or moiety bears one or more substituents. The term “unsubstituted” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more
substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system.

Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (i.e., cis and trans isomers), as tautomers, or as atropomers. Additionally, any formula given herein is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof. In certain embodiments of the invention, pharmaceutically acceptable salts of compounds of Formula (I) were obtained in a crystalline form. In a preferred embodiment, bis hydrochloride salts of compounds of Formula (I) were obtained in a crystalline form.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that, whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

Reference to a chemical entity herein stands for a reference to any one of: (a) the actually recited form of such chemical entity, and (b) any of the forms of such chemical entity in the medium in which the compound is being considered when named. For example, reference herein to a compound such as R—COOH encompasses reference to any one of: for example, R—COOH, R—COOHₐq, and R—COO⁻. In this example, R—COOHₐq refers to the solid compound, as it could be for example in a tablet or some other solid pharmaceutical composition or preparation; R—COOH refers to the undissociated form of the compound in a solvent; and R—COO⁻ refers to the dissociated form of the compound in a solvent, such as the dissociated form of the compound in an aqueous environment, whether such dissociated form derives from R—COOH, from a salt thereof, or from any other entity that yields R—COO⁻ upon dissociation in the medium being considered. In another example, an expression such as “exposing an entity to a compound of formula R—COOH” refers to the exposure of such entity to the form, or forms, of the compound R—COOH that exists, or exist, in the medium in which such exposure takes place. In this regard, if such entity is for example in an aqueous environment, it is understood that the compound R—COOH is in such same medium, and therefore the entity is being exposed to species such as R—COOHₐq and/or R—COO⁻ where the subscript “ₐq” stands for “aqueous” according to its conventional meaning in chemistry and biochemistry. A carboxylic acid functional group has been chosen in these nomenclature examples; this choice is not intended, however, as a limitation but it is merely an illustration. It is understood that analogous examples can be provided in terms of other functional groups, including but not limited to hydroxyl, basic nitrogen members, such as those in amines, and any other group that interacts or transforms according to known manners in the medium that contains the compound. Such interactions and transformations include, but are not limited to, dissociation, association, tautomerism, solvolysis, including hydrolysis, solvation, including hydration, protonation, and deprotonation. No further examples in this regard are provided herein because these interactions and transformations in a given medium are known by any one of ordinary skill in the art.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ³⁸S, ³⁹K, ¹⁹F, ³¹P, and ¹₂⁵I, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ¹³C), reaction kinetic studies (with, for example ²H or ³H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radiolabel treatment of patients. In particular, an ¹³C or ¹⁴C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ²H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the same choice of the species for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula, unless stated otherwise.

By way of an example on substituent terminology, if substituent S₁ example is one of S₁ and S₂, and substituent S₂ example is one of S₁ and S₃, then these assignments refer to embodiments of this invention given according to the choices S₁ example is S₁ and S₂ example is S₂; S₁ example is S₁ and S₂ example is S₃; S₁ example is S₂ and S₂ example is S₁; S₁ example is S₂ and S₂ example is S₃; S₁ example is S₃ and S₂ example is S₁; S₁ example is S₃ and S₂ example is S₂; S₁ example is S₃ and S₂ example is S₃; and equivalents of each one of such choices. The shorter terminology “S₁ example is one of S₁ and S₂” and “S₂ example is one of S₁ and S₃” is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing first example on substituent terminology, which is stated in generic terms, is meant to illustrate the various
substituent assignments described herein. The foregoing
convention given herein for substituents extends, when appli-
cable, to members such as \( R^{1-4}, R^{5-6}, \) and \( q, \) and any other
generic substituent symbol used herein.

Furthermore, when more than one assignment is
given for any member or substituent, embodiments of this
invention comprise the various groupings that can be made
from the listed assignments, taken independently, and equiva-
lents thereof. By way of a second example on substituent
terminology, if it is herein described that substituent \( S_{\text{example}} \)
is one of \( S_1, S_2, \) and \( S_3, \) this listing refers to embodiments of
this invention for which \( S_{\text{example}} = S_1; S_{\text{example}} = S_2; S_{\text{example}} = S_3; \)
\( S_{\text{example}} = S_4; S_{\text{example}} = S_5; S_{\text{example}} = S_6; \) and \( S_{\text{example}} = S_7. \) In
other embodiments, \( R^{1-2}, R^{5-7}, \) and \( q, \) and any other generic substituent symbol used herein.

The nomenclature “C_{j-i}” with \( j \geq i, \) when applied
herein to a class of substituents, is meant to refer to embodi-
mements of this invention for which each and every one of
the number of carbon members, from \( i \) to \( j \) including \( i \) and \( j, \) is
independently realized. By way of example, the term \( C_{1-3} \)
refers independently to embodiments that have one carbon
member (\( C_1 \)), embodiments that have two carbon members
(\( C_2 \)), and embodiments that have three carbon members
(\( C_3 \)).

Any disubstituent referred to herein is meant to
compense the various attachment possibilities when more
than one of such possibilities are allowed. For example,
reference to disubstituent \( A-B, \) where \( A \neq B, \) refers herein
to such disubstituent with \( A \) attached to a first substituted
member and \( B \) attached to a second substituted member, and it
also refers to such disubstituent with \( A \) attached to the second
substituted member and \( B \) attached to the first substituted
member.

According to the foregoing interpretive considera-
tions on assignments and nomenclature, it is understood that
explicit reference herein to a set implies, where chemically
meaningful and unless indicated otherwise, independent ref-
erence to embodiments of such set, and reference to each and
every one of the possible embodiments of subsets of the set
referred to explicitly.

In some embodiments of Formula (1), \( R^1 \) is methyl,
ethy1, propyl, isopropyl, butyl, isobutyl, tert-butyl, meth-
oxymethyl, ethoxymethyl, isopropanylmethyl, tert-butoxy-
methy1, 3,3,3-trifluoro-ethyl, cyclopropoxymethyl, benzyl,
4-chlorobenzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl,
pyridin-4-ylmethyl, phenylpropyl, cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, 2-phenyl-cyclopropyl, indan-2-yl,
tetrahydrofuran-3-yl, tetrahydropyran-4-yl, 4-methyl-tet-
rahydro-pyran-4-yl, 2,3-dihydro-benzofuran-2-yl, tetrahy-
drofuran-2-ylmethyl, or adamantyl. In other embodiments,
\( R^1 \) is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In some embodiments, \( R^1 \) is \( H. \)

In some embodiments, \( R^1 \) and \( R^2 \) taken together form
\( -(\text{CH}_2)_3- \). In other embodiments, \( R^1 \) and \( R^2 \) taken together form
\( -(\text{CH}_2)_2\text{OCH}_2- \).

In some embodiments, \(-N(R^3)R^4 \) is:

\[
\begin{align*}
\text{where } R^6, R^b, \text{ and } R^c \text{ are as previously defined. In further embodi-
mements, } -N(R^3)R^4 \text{ is:
}
\end{align*}
\]

\[
\begin{align*}
\text{In still further embodiments, } -N(R^3)R^4 \text{ is:
}
\end{align*}
\]

\[
\begin{align*}
\text{where } R^b \text{ is as previously defined. In still further embodi-
mements, } -N(R^3)R^4 \text{ is:
}
\end{align*}
\]

\[
\begin{align*}
\text{where } R^b \text{ is as previously defined. In still further embodi-
mements, } -N(R^3)R^4 \text{ is:
}
\end{align*}
\]
where \( R' \) is as previously defined. In still further embodiments, \(-N(R')R^*\) is:

\[
\begin{align*}
\text{or}
\end{align*}
\]

where \( R^* \) is as previously defined.

[0063] In some embodiments, \( R^* \) is H.

[0064] In some embodiments, \( R^* \) and \( R^* \) are each independently H or methyl.

[0065] The invention includes also pharmaceutically acceptable salts of the compounds represented by Formula (I), preferably of those described above and of the specific compounds exemplified herein, and methods using such salts.

[0066] A “pharmaceutically acceptable salt” is intended to mean a salt of a free acid or base of a compound represented by Formula (I) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S. M. Berge, et al., “Pharmaceutical Salts”, J. Pharm. Sci., 1977, 66:1-19, and Handbook of Pharmaceutical Salts. Properties, Selection, and Use, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable salts are those that are pharmaceutically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. A compound of Formula (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, phosphonates, phosphonic acids, phosphinic acids, carbonates, hydrogencarbonates, formates, ethanolamines, ethanolammonium, and amino acids.

[0067] If the compound of Formula (I) contains a basic nitrogen, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lauric acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, and pantothenic acid, or with an organic base, such as quaternary ammonium bases, quaternary phosphonium bases, tertiary amines, diethylammonium salts, trimethylammonium salts, and alkali metal salts.

[0068] Where the compound of Formula (I) contains a plurality of basic nitrogens, one skilled in the art will recognize that suitable salts include salts formed with one or more equivalents of an inorganic or organic acid. In preferred embodiments of Formula (I), such salts include bis-hydrochloride salts.

[0069] If the compound of Formula (I) is an acid, such as a carboxylic acid or sulfonic acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal hydroxide, an alkaline earth metal hydroxide, or an amine hydrochloride, such as triethylamine hydrochloride, to yield a pharmaceutically acceptable salt. In some cases, the pharmaceutically acceptable salt may be used in place of the corresponding free acid. In other cases, the pharmaceutically acceptable salt may be converted to the corresponding free acid by treatment with a suitable base. The pharmaceutically acceptable salt may be obtained in a crystalline or amorphous form, or it may be obtained as a mixture of forms.

[0070] The invention also relates to pharmaceutically acceptable produgs of the compounds of Formula (I), and treatment methods employing such pharmaceutically acceptable produgs. The term “produg” means a prodrug derivative of a designated compound that, following administration to a subject, yields the compound in vivo via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula (I)). A “pharmaceutically acceptable produg” is a produg that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable produg derivatives are described, for example, in “Design of Prodrugs”, ed. H. Bundgaard, Elsevier, 1985.

[0071] Examples of produgs include compounds having an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of a compound of Formula (I). Examples of amino acid residues include the twenty naturally occurring amino acids, commonly designated by three letter symbols, as well as 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, betalanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfoxide.

[0072] Additional types of produgs may be produced, for instance, by derivatizing free carboxyl groups of structures of Formula (I) as amides or alkyl esters. Examples of amides include those derived from ammonia, primary \( \text{C}_n\text{-alkyl amine} \) amine and secondary \( \text{di}[	ext{C}_n\text{-alkyl amine}] \) amine. Secondary amides include \( \text{C}_n\text{-} \text{amine} \) or \( \text{C}_n\text{-} \text{amine} \) of \( \text{C}_n\text{-} \text{amine} \), or \( \text{C}_n\text{-} \text{amine} \) of \( \text{C}_n\text{-} \text{amine} \). Examples of amides include those that...

The compounds of Formula (I) and their pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites, whether alone or in combination, (collectively; “active agents”) of the present invention are useful as histamine H\textsubscript{4} receptor modulators in the methods of the invention. Such methods for modulating histamine H\textsubscript{4} receptor activity comprise exposing histamine H\textsubscript{4} receptor to an effective amount of at least one chemical entity selected from compounds of Formula (I), pharmaceutically acceptable salts of compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of compounds of Formula (I). Embodiments of this invention inhibit histamine H\textsubscript{4} receptor activity.

In some embodiments, the histamine H\textsubscript{4} receptor is in a subject diagnosed with or suffering from a disease, disorder, or medical condition mediated through histamine H\textsubscript{4} receptor activity, such as those described herein. Symptoms or disease states are intended to be included within the scope of “medical conditions, disorders, or diseases.”

Accordingly, the invention relates to methods of using the active agents described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through histamine H\textsubscript{4} receptor activity, such as inflammation. Active agents according to the invention may therefore be used as anti-inflammatory agents.
and “activators” are compounds that increase, activate, facilitate, sensitize, or up-regulate histamine $H_4$ receptor expression or activity.

[0082] In treatment methods according to the invention, an effective amount of at least one active agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. An “effective amount” means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the active agents of the present invention may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject’s previous or ongoing therapy, the subject’s health status and response to drugs, and the judgment of the treating physician. An exemplary dose is in the range of about 0.001 to about 200 mg of active agent per kg of subject’s body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, or about 0.1 to 10 mg/kg daily in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, a illustrative range for a suitable dosage amount is from about 1 to 200 mg/day, or about 5 to 50 mg/day.

[0083] Once improvement of the patient’s disease, disorder, or condition has occurred, the dose may be adjusted for preventive or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[0084] In addition, the active agents of the invention may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with an active agent of Formula (1) or included with such an agent in a pharmaceutical composition according to the invention. In an exemplary embodiment, additional active ingredients are those that are known or discovered to be effective in the treatment of conditions, disorders, or diseases mediated by histamine $H_4$ receptor activity, such as another histamine $H_4$ receptor modulator or a compound active against another target associated with the particular condition, disorder, or disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an agent according to the invention), decrease one or more side effects, or decrease the required dose of the active agent according to the invention.

[0085] When referring to modulating the target receptor, an “effective amount” means an amount sufficient to affect the activity of such receptor. Measuring the activity of the target receptor may be performed by routine analytical methods. Target receptor modulation is useful in a variety of settings, including assays.

[0086] The active agents of the invention are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: (a) an effective amount of at least one active agent in accordance with the invention; and (b) a pharmaceutically acceptable excipient.

[0087] A “pharmaceutically acceptable excipient” refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0088] Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

[0089] The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

[0090] For oral administration, the active agents of the invention can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the active agents may be formulated to yield a dosage of, e.g., from about 0.05 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

[0091] Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinylpyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glycercyll monostearate or glycercyl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0092] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0093] Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-ac-
ceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

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

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

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

Exemplary chemical entities useful in methods of the invention will now be described by reference to illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent.

Each of the reactions depicted in Scheme A is preferably run at a temperature from about room temperature to the reflux temperature of the organic solvent used. Unless otherwise specified, the variables are as defined above in reference to Formula (I).

As shown in Scheme A, the present invention includes methods of making compounds of Formula (I), from β-ketoesters A1 (where R is C1-alkyl, preferably methyl or ethyl), which are commercially available or prepared by known methods. β-Ketoesters A1 are reacted with guanidine, or a hydrochloride, carbonate, nitrate, or sulfamate salt thereof, in the presence of an organic base (for example, potassium tert-butoxide or a tertiary amine base, such as triethylamine or diisopropylethylamine) or an inorganic base (for example, K2CO3, Na2CO3, Cs2CO3 or K2PO4, or a mixture thereof), in an organic solvent (for example, methanol, ethanol, isopropanol, tert-amyl alcohol, THF, acetonitrile, or methyl tert-butyl ether (MTBE)), or a mixture thereof, to provide hydroxyxypyrimeridines A2. One skilled in the art will recognize that compounds of formula A2 include hydroxyxypyrimeridines and their pyrimidine tautomers, and mixtures thereof.

Chlorination of compounds A2 with POCl3, neat or in an organic solvent (for example, acetonitrile or toluene, dichloromethane, or MTBE, or a mixture thereof), provides chloro-pyrimeridines A3. In preferred embodiments, the reaction is done in the presence of a tertiary amine base (for example, dimethylamine, diethylamine, or iPyrNEt) and a tetraethylammonium chloride salt (such as Et4NCl).

Displacement of the chloro substituent by reacting a chloro-pyrimeridine A3 with a diamine HNR4, in an organic solvent (for example, methanol, ethanol, isopropanol, tert-amyl alcohol, THF, or acetonitrile, or a mixture thereof), gives compounds of Formula (I). In some embodiments of the displacement reaction, the R4 substituent in diamine HNR4 is a nitrogen protecting group, such as a tert-butoxycarbonyl (Boc) group or benzyl group, and the reaction provides compounds of formula (la) where R4 is a nitrogen protecting group.

Where the R4 group in diamine HNR4 is a nitrogen protecting group, the protecting group is removed by deprotecting compounds of formula (la) to give compounds of Formula (I) where R4 is H. Deprotection may be accomplished using standard deprotection conditions. For example, a tert-butoxycarbonyl group is removed using an organic acid such as TFA (neat or in a solvent such as CH2Cl2) or an
inorganic acid such as HCl (in a solvent such as 1,4-dioxane, isopropanol, or formic acid) to give a compound of Formula (I) where R is H.

[0102] In an alternative embodiment, reaction of hydroxypyrimidinones A2 with protected or unprotected diamines 
HNR of under standard peptide coupling conditions known in the art provide compounds of Formula (I) directly.

[0103] Compounds of Formula (I) may be converted to their corresponding salts using methods described in the art. For example, an amine of Formula (I) is treated with trifluoroacetic acid, HCl, or citric acid in a solvent such as Et2O, CH2Cl2, THF, MeOH, or isopropanol to provide the corresponding salt form. Crystalline forms of pharmaceutically acceptable salts of compounds of Formula (I) may be obtained in crystalline form by recrystallization from polar solvents (including mixtures of polar solvents and aqueous mixtures of polar solvents) or from non-polar solvents (including mixtures of non-polar solvents).

[0104] Compounds prepared according to the schemes described above may be obtained as single enantiomers, diastereomers, or regioisomers, by enantio-, diastereo-, or regiospecific synthesis, or by resolution. Compounds prepared according to the schemes above may alternately be obtained as racemic (1:1) or non-racemic (not 1:1) mixtures or as mixtures of diastereomers or regioisomers. Where racemic and non-racemic mixtures of enantiomers are obtained, single enantiomers may be isolated using conventional separation methods known to one skilled in the art, such as chiral chromatography, recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, single isomers may be separated using conventional methods such as chromatography or crystallization.

[0105] The following specific examples are provided to further illustrate the invention and various preferred embodiments.

EXAMPLES

[0106] In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

[0107] Unless otherwise stated, reaction mixtures were magnetically stirred at room temperature (rt). Where solutions are “dried,” they are generally dried over a drying agent such as Na2SO4 or MgSO4. Where mixtures, solutions, and extracts were “concentrated,” they were typically concentrated on a rotary evaporator under reduced pressure. Silica gel (SiO2) was used for all chromatographic purification unless otherwise noted and the eluent used is listed in parentheses.

[0108] Analytical reversed-phase HPLC was performed on a Hewlett Packard HPLC Series 1100, with a Phenomenex ONYX® monolithic C18 (5 μm, 4.6x100 mm) column. Detection was done at λ=230, 254 and 280 nm. The flow rate was 1 ml/min. The gradient was 10 to 90% acetonitrile/water (20 mM NH4OH) over 5.0 min. Preparative reversed-phase HPLC was performed on a Shimadzu LC-8A equipped with a YMC-Pack ODS 250x30 mm column with a gradient of 10 to 50% TFA in acetonitrile (0.05% water) over 15 min at a flow rate of 70 ml/min.

[0109] Compounds were analyzed in a free base, hydrochloride salt, or trifluoroacetic acid salt form. Hydrochloride salts were obtained either: 1) during the removal of the tert-butylcarbamoyl (Boc) group; or 2) by treatment of a solution of the purified free base in THF or CH2Cl2 with at least two equivalents of a solution of HCl in 1,4-dioxane followed by concentration. TFA salts were obtained following preparative reversed-phase HPLC purification.

[0110] Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model DRX spectrometers. The format of the 1H NMR data below is: chemical shift in ppm downfield of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration).

[0111] Mass spectra were obtained by using electrospray ionization (ESI) in either positive or negative modes as indicated. The MS data presented is the m/z found (typically [M+H]+) for the molecular ion.

[0112] Chemical names were generated using Chem Draw Version 6.02 (CambridgeSoft, Cambridge, Mass.) or ACD/Name Version 9 (Advanced Chemistry Development, Toronto, Ontario, Canada).

Example 1

4-Cyclopentyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0113]

[0114] Step A: 2-Amino-6-cyclopentyl-3H-pyrimidin-4-one. To a solution of 3-cyclopentyl-3-oxo-propionic acid ethyl ester (5.0 g, 27.4 mmol) and guanidine hydrochloride (3.1 g, 33.0 mmol) in MeOH (50 mL) at 23°C. The reaction was cooled to room temperature (rt) and stirred overnight and the precipitated salt was removed by filtration. The solution was concentrated to approximately 10 mL then diluted with 10 mL of water and added to pH 5 by the addition of 6.0 N HCl (61 mL). The resulting precipitate was filtered and dried via suction then vacuum to yield a white solid (4.3 g, 87%) that was used without further purification.

[0115] Step B: 2-Amino-4-chloro-6-cyclopentyl-pyrimidine. A suspension of 2-amino-6-cyclopentyl-pyrimidine (1.52 g, 8.4 mmol), tetraethyl ammonium chloride (2.8 g 16.9 mmol) and dimethylaniline (1.1 mL, 8.4 mmol) in acetonitrile (16 mL) was treated with phosphorous oxychloride (4.7 mL, 51 mmol) and heated at 110°C for 20 min. The resulting solution was cooled to rt and concentrated to minimum volume then diluted with CHCl3 and ice and stirred for 30 min. The layers were separated and the organic layer was washed with water (3x50 mL) and 5% NaHCO3, dried, and concentrated to yield 2.0 g of crude product that was used without purification.

[0116] Step C: 4-Cyclopentyl-6-piperazin-1-yl-pyrimidin-2-ylamine. A solution of crude 2-amino-4-chloro-6-cyclopentyl-pyrimidine (150 mg, 0.76 mmol), N—BOC piperazine (184 mg, 0.99 mmol) and Et3N (210 ul., 1.5 mmol) in EtOH (2 mL) was heated at 70°C for 16 h. The reaction was cooled to rt and concentrated and the crude residue purified (2 M NH4 in MeOH/CH2Cl2) to yield a white solid (34 mg, 11%). MS (ESI): mass calcld. for C18H23N3O2, 347.2; m/z found,
348.3 [M+H]+. 1H NMR (MeOD): 6.01 (s, 1H), 3.66-3.58 (m, 4H), 3.53-3.43 (m, 4H), 3.33 (td, J=3.3, 1.6, 1H), 2.90-2.75 (m, 1H), 2.05-1.90 (m, 2H), 1.87-1.77 (m, 2H), 1.77-1.62 (m, 4H), 1.53-1.46 (m, 9H).

[0117] Step D: 4-Cyclopentyl-6-piperazin-1-yl-pyrimidine-2-ylamine. A solution of 4-cyclopentyl-6-piperazin-1-yl-pyrimidin-2-ylamine (34 mg, 0.10 mmol) in formic acid (3 mL) was treated with 6.0 N HCl (0.1 mL) and stirred for 2 h. The reaction was diluted with MeOH and concentrated. This process was repeated twice to remove the formic acid to yield a white solid (30 mg, 97%). MS (ESI): mass calcld. for C14H23N5, 247.2; m/z found, 248.2 [M+H]+. 1H NMR (MeOD): 6.45 (s, 1H), 4.34-4.16 (m, 2H), 4.13-3.96 (m, 2H), 3.42-3.34 (m, 4H), 3.03 (p, J=8.0, 1H), 2.22-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.83-1.65 (m, 4H).

Example 2
4-Cyclopentyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0118]

[0119] A solution of crude 2-amino-4-chloro-6-cyclopentyl-pyrimidine (92 mg, 0.47 mmol), and N-methyl piperazine (0.15 mL, 1.4 mmol) in EtOH (2 mL) was heated at 70°C for 2 h. The reaction was cooled to rt and concentrated and the crude residue chromatographed (2 M NH3 in MeOH/CH2Cl2) to yield an oil (81 mg, 66%). MS (ESI): mass calcld. for C14H23N5, 261.2; m/z found, 262.3 [M+H]+. 1H NMR (CDCl3): 5.85 (s, 1H), 4.78 (s, 2H), 3.59 (t, J=5.0, 4H), 2.81 (q, J=8.7, 1H), 2.44 (t, J=5.0, 4H), 2.32 (s, 3H), 2.04-1.89 (m, 2H), 1.82-1.59 (m, 6H).

[0120] The compounds in Examples 3-36 were prepared using methods analogous to those described for Examples 1 and 2. Where amines used in Example 1, Step C or Example 2 were not protected, the deprotection step described in Example 1, Step D was omitted.

Example 3
(R)-4-(3-Amino-piperidin-1-yl)-6-cyclopentyl-pyrimidin-2-ylamine

[0121]

[0122] MS (ESI): mass calcld. for C14H23N5, 261.2; m/z found, 262.2 [M+H]+.

Example 4
(R)-4-Cyclopentyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0123]

[0124] MS (ESI): mass calcld. for C14H23N5, 261.4; m/z found, 262.3 [M+H]+. 1H NMR (MeOD): 5.75 (s, 1H), 3.74-3.51 (m, 2H), 3.52-3.39 (m, 1H), 3.37-3.30 (m, 2H), 2.86-2.75 (m, 1H), 2.41 (s, 3H), 2.27-2.14 (m, 1H), 2.05-1.92 (m, 2H), 1.93-1.83 (m, 1H), 1.84-1.73 (m, 2H), 1.73-1.60 (m, 4H).

Example 5
trans-1-(2-Amino-6-cyclopentyl-pyrimidin-4-yl)-4-methylamino-pyrrolidin-3-ol

[0125]

[0126] MS (ESI): mass calcld. for C14H23N5O, 277.2; m/z found, 278.1 [M+H]+. 1H NMR (CDCl3): 5.52 (s, 1H), 5.34-5.17 (m, 2H), 4.17-4.07 (m, 1H), 3.75-3.56 (m, 2H), 3.40-3.08 (m, 4H), 3.10-3.02 (m, 1H), 2.78-2.65 (m, 1H), 2.37 (s, 3H), 1.96-1.84 (m, 2H), 1.75-1.63 (m, 2H), 1.63-1.49 (m, 4H).

Example 6
4-Cyclopentyl-6-(cis-hexahydro-pyrrolol[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine

[0127]

[0128] MS (ESI): mass calcld. for C15H23N5, 273.2; m/z found, 274.2 [M+H]+. 1H NMR (CDCl3): 5.63 (s, 1H), 5.36-
Example 7

4-Cyclopentyl-6-(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

[0129]

[0130] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 235.2; m/z found, 236.2 [M+H]^+.

Example 8

4-Isopropyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0131]

[0132] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 221.2; m/z found, 222.1 [M+H]^+; 1H NMR (MeOD): 5.99 (s, 1H), 3.66-3.62 (m, 4H), 2.93-2.84 (m, 4H), 2.67 (q, J=7.0, 1H), 1.21 (d, J=6.9, 6H).

Example 9

(R)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine

[0133]

[0134] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 235.2; m/z found, 236.2 [M+H]^+.

Example 10

(S)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine

[0135]

[0136] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 235.2; m/z found, 236.2 [M+H]^+.

Example 11

(R)-4-Isopropyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0137]

[0138] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 235.2; m/z found, 236.2 [M+H]^+; 1H NMR (CDCl3): 5.66 (s, 1H), 5.00-4.87 (m, 2H), 3.75-3.56 (m, 2H), 3.56-3.43 (m, 1H), 3.43-3.23 (m, 2H), 2.71 (q, J=6.9, 1H), 2.53 (s, 3H), 2.22 (dt, J=13.4, 6.1, 1H), 1.98-1.81 (m, 1H), 1.25 (d, J=6.9, 6H).

Example 12

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine

[0139]

[0140] MS (ESI): mass calcd. for C_{13}H_{21}N_{5}, 221.16; m/z found, 222.2 [M+H]^+; 1H NMR (MeOD; mixture of forms): 6.10 (s, 0.67H), 6.08 (s, 0.33H), 4.16-3.68 (m, 5H), 2.89 (sept, J=6.9, 1H), 2.60-2.50 (m, 0.67H), 2.50-2.42 (m, 0.33H), 2.32-2.22 (m, 0.67H), 2.22-2.14 (m, 0.33H), 1.33 (d, J=7.0, 6H).
Example 13
trans-1-(2-Amino-6-isopropyl-pyrimidin-4-yl)-4-methylamino-pyrrolidin-3-ol

Example 14
(S,S)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 15
(R,R)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 16
4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 17
(R,R)-4-(Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 18
4-Isopropyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine
Example 19

4-Isopropyl-6-[(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-yl]amine

Example 20

(R,R)-4-Isopropyl-6-[(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-yl]amine

Example 21

4-Methyl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 22

4-Methyl-6-[(4-methyl-piperazin-1-yl)-pyrimidin-2-yl]amine

Example 23

(R)-4-Methyl-6-[(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-yl]amine

Example 24

4-Methyl-6-[(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-yl]amine
Example 25
4,5-Dimethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

**Example 25**
4,5-Dimethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

**[0165]**

**[0166]** MS (ESI): mass calcd. for C_{10}H_{11}N_{6}, 207.1; m/z found, 208.2 [M+H]^+.

Example 26
4,5-Dimethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

**Example 26**
4,5-Dimethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

**[0167]**

**[0168]** MS (ESI): mass calcd. for C_{11}H_{12}N_{6}, 221.2; m/z found, 222.2 [M+H]^+.

Example 27
(R)-4-(3-Amino-pyridolin-1-yl)-5,6-dimethyl-pyrimidin-2-ylamine

**Example 27**
(R)-4-(3-Amino-pyridolin-1-yl)-5,6-dimethyl-pyrimidin-2-ylamine

**[0169]**

**[0170]** MS (ESI): mass calcd. for C_{10}H_{11}N_{6}, 207.1; m/z found, 208.2 [M+H]^+.

Example 28
(R)-4,5-Dimethyl-6-(3-methylamino-pyridolin-1-yl)-pyrimidin-2-ylamine

**Example 28**
(R)-4,5-Dimethyl-6-(3-methylamino-pyridolin-1-yl)-pyrimidin-2-ylamine

**[0171]**

**[0172]** MS (ESI): mass calcd. for C_{11}H_{12}N_{6}, 221.2; m/z found, 222.2 [M+H]^+.

Example 29
4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5,6-dimethyl-pyrimidin-2-ylamine

**Example 29**
4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5,6-dimethyl-pyrimidin-2-ylamine

**[0173]**

**[0174]** MS (ESI): mass calcd. for C_{13}H_{16}N_{6}, 233.2; m/z found, 234.2 [M+H]^+.

Example 30
4,5-Dimethyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

**Example 30**
4,5-Dimethyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

**[0175]**

**[0176]** MS (ESI): mass calcd. for C_{13}H_{22}N_{6}, 247.2 m/z found, 248.2 [M+H]^+.

Example 31
4,5-Dimethyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrimidin-6-yl)-pyrimidin-2-ylamine

**Example 31**
4,5-Dimethyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrimidin-6-yl)-pyrimidin-2-ylamine

**[0177]**
[0178] MS (ESI): mass calc’d. for C\textsubscript{13}H\textsubscript{12}N\textsubscript{5}, 247.2; m/z found, 248.2 [M+H]\textsuperscript{+}.

Example 32
(S,S)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-5,6-dimethyl-pyrimidin-2-ylamine

[0179]

[0180] MS (ESI): mass calc’d. for C\textsubscript{11}H\textsubscript{15}N\textsubscript{6}, 219.2; m/z found, 220.2 [M+H]\textsuperscript{+}.

Example 33
4-Ethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0181]

[0182] MS (ESI): mass calc’d. for C\textsubscript{13}H\textsubscript{12}N\textsubscript{5}, 207.15; m/z found, 208.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): 13.51 (s, 1H), 9.68 (s, 2H), 7.76 (s, 2H), 6.53-6.42 (m, 4H), 3.99 (s, 4H), 3.19 (s, 4H), 2.61-2.53 (m, 2H), 1.28-1.19 (m, 3H).

Example 34
4-Ethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0183]

[0184] MS (ESI): mass calc’d. for C\textsubscript{11}H\textsubscript{15}N\textsubscript{6}, 221.16; m/z found, 222.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 5.8 (s, 1H), 5.1 (s, 2H), 3.7-3.5 (m, 5H), 2.5-2.4 (m, 6H), 2.3 (s, 3H), 1.2 (t, J=7.0, 3H).

Example 35
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-ethyl-pyrimidin-2-ylamine

[0185]

[0186] MS (ESI): mass calc’d. for C\textsubscript{13}H\textsubscript{12}N\textsubscript{5}, 207.15; m/z found, 208.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): 8.85-8.58 (m, 2H), 8.42-7.18 (m, 1H), 6.17-6.10 (m, 1H), 4.04-3.85 (m, 1H), 3.85-3.53 (m, 4H), 2.66-2.53 (q, J=7.5, 2H), 2.41-2.09 (m, 2H), 1.28-1.19 (t, J=7.5, 3H).

Example 36
(R)-4-Ethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0187]

[0188] MS (ESI): mass calc’d. for C\textsubscript{13}H\textsubscript{12}N\textsubscript{5}, 221.16; m/z found, 222.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 5.61 (s, 1H), 5.21 (s, 2H), 3.72-3.12 (m, 5H), 2.55-2.41 (m, 5H), 2.22-2.09 (m, 1H), 1.93-1.77 (m, 1H), 1.27-1.15 (t, J=7.3, 3H).

Example 37
(R,R)-(4-Ethyl-6-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine

[0189]


To a solution of 4-chloro-6-ethyl-pyrimidin-2-ylamine (200 mg, 1.27 mmol) in EtOH (2.4 mL) was added pyridine (210 mL, 2.54 mmol) and 1-(1-phenyl-ethyl)-octahydro-pyrrolo[3, 4-b]pyrrole (360 mg, 1.65 mmol). The solution was stirred for
2 h at 90°C. The compound was purified directly with reversed-phase HPLC to yield 115 mg (28%) of the desired compound as a yellow oil.

Step B: (R,R)-(4-Ethyl-6-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)pyrimidin-2-ylamine. To a solution of 4-ethyl-6-[1-(1-phenyl-ethyl)-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl]pyrimidin-2-ylamine (110 mg, 0.33 mmol) in EtOH (1.0 mL) at 23°C, was added palladium hydroxide on carbon (22 mg). The reaction mixture was placed on a Parr hydrogenator and reacted with hydrogen gas at 60 psi for 6 h. The mixture was filtered through diatomaceous earth, rinsing with EtOAc (3 x 10 mL). The resulting solution was concentrated and purified with reversed-phase HPLC to yield the desired compound as a colorless oil (65 mg, 86%). MS (ESI): mass calcd. for C_{12}H_{21}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.61 (s, 1H), 5.22 (s, 2H), 3.99-3.54 (m, 4H), 3.55-3.42 (m, 1H), 3.38-3.23 (m, 1H), 3.16-3.05 (m, 1H), 3.05-2.94 (m, 1H), 2.92-2.80 (m, 1H), 2.53-2.42 (q, J=7.1, 2H), 2.08-1.96 (m, 1H), 1.83-1.67 (m, 1H), 1.28-1.16 (t, J=7.0, 3H).

The compounds in Examples 38-55 were prepared using methods analogous to those described in the preceding examples.

**Example 38**
4-Ethyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)pyrimidin-2-ylamine

**Example 39**
(R,R)-(4-Ethyl-6-octahydro-pyrrolo[3,4-b]pyridin-6-yl)pyrimidin-2-ylamine

**Example 40**
4-Cyclopropyl-6-(4-methyl-piperazin-1-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.81 (s, 1H), 4.75 (s, 2H), 3.63-3.54 (t, J=4.9, 4H), 2.46-2.40 (t, J=5.0, 4H), 2.32 (s, 3H), 1.75-1.67 (m, 1H), 1.00-0.94 (m, 2H), 0.89-0.82 (m, 2H).

**Example 41**
(R)-(4-Cyclopropyl-6-3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine

**Example 42**
4-Cyclopropyl-6-(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.58 (s, 1H), 5.30 (s, 1H), 4.73-4.63 (m, 1H), 3.75-3.11 (m, 5H), 2.46 (s, 3H), 2.21-2.10 (m, 1H), 2.04-2.00 (m, 1H), 1.88-1.77 (m, 1H), 1.77-1.67 (m, 1H), 1.00-0.91 (m, 2H), 0.89-0.82 (m, 2H).

**Example 43**
4-Cyclopropyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.81 (s, 1H), 4.75 (s, 2H), 3.63-3.54 (t, J=4.9, 4H), 2.46-2.40 (t, J=5.0, 4H), 2.32 (s, 3H), 1.75-1.67 (m, 1H), 1.00-0.94 (m, 2H), 0.89-0.82 (m, 2H).

**Example 44**
4-Cyclopropyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.81 (s, 1H), 4.75 (s, 2H), 3.63-3.54 (t, J=4.9, 4H), 2.46-2.40 (t, J=5.0, 4H), 2.32 (s, 3H), 1.75-1.67 (m, 1H), 1.00-0.94 (m, 2H), 0.89-0.82 (m, 2H).

**Example 45**
4-Cyclopropyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.81 (s, 1H), 4.75 (s, 2H), 3.63-3.54 (t, J=4.9, 4H), 2.46-2.40 (t, J=5.0, 4H), 2.32 (s, 3H), 1.75-1.67 (m, 1H), 1.00-0.94 (m, 2H), 0.89-0.82 (m, 2H).

**Example 46**
4-Cyclopropyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{19}N_3, 233.16; m/z found, 234.2 [M+H]^+. ^1H NMR (CDCl_3): 5.81 (s, 1H), 4.75 (s, 2H), 3.63-3.54 (t, J=4.9, 4H), 2.46-2.40 (t, J=5.0, 4H), 2.32 (s, 3H), 1.75-1.67 (m, 1H), 1.00-0.94 (m, 2H), 0.89-0.82 (m, 2H).
Example 43

4-Cyclobutyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0203]

Example 44

4-Cyclobutyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0205]

Example 45

(R)-4-(3-Amino-piperidin-1-yl)-6-cyclobutyl-pyrimidin-2-ylamine

[0207]

Example 46

(R)-4-Cyclobutyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0209]

MS (ESI): mass calcld. for C_{14}H_{16}N_{5}, 233.16; m/z found, 234.2 [M+H]^+;
1H NMR (DMF-d_7): 12.67 (s, 1H), 9.45 (s, 2H), 8.33-7.25 (m, 1H), 6.43 (s, 1H), 4.16-3.88 (m, 4H), 3.28-3.15 (m, 4H), 2.37-2.19 (m, 4H), 2.10-1.95 (m, 1H), 1.90-1.78 (m, 1H).

Example 47

4-Cyclobutyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrolo-5-yl)-pyrimidin-2-ylamine

[0211]

MS (ESI): mass calcld. for C_{14}H_{16}N_{5}, 259.18; m/z found, 260.2 [M+H]^+;
1H NMR (CDCl_3): 5.82 (s, 1H), 4.81 (s, 2H), 3.60 (t, J=4.9, 4H), 2.44 (t, J=5.0, 4H), 2.32 (s, 3H), 2.28-2.18 (m, 5H), 2.07-1.93 (m, 1H), 1.91-1.78 (m, 1H).

Example 48

4-Cyclobutyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrolo-2-yl)-pyrimidin-2-ylamine

[0213]

MS (ESI): mass calcld. for C_{14}H_{16}N_{5}, 259.18; m/z found, 260.2 [M+H]^+;
1H NMR (CDCl_3): 5.84 (s, 1H), 4.91 (s, 2H), 4.32-4.16 (m, 1H), 4.09-3.98 (m, 1H), 3.49-3.43 (m, 1H), 3.40-3.26 (m, 1H), 3.11-2.64 (m, 4H), 2.36-2.15 (m, 4H), 2.12-1.93 (m, 2H), 1.91-1.71 (m, 2H), 1.65-1.48 (m, 1H), 1.44-1.22 (m, 1H).

MS (ESI): mass calcld. for C_{14}H_{16}N_{5}, 247.18; m/z found, 248.2 [M+H]^+;
1H NMR (CDCl_3): 5.62 (s, 1H), 4.71 (s, 2H), 3.75-3.52 (m, 2H), 3.50-3.39 (m, 1H), 3.38-3.20 (m, 3H), 2.52-2.44 (s, 3H), 2.33-2.10 (m, 5H), 2.09-1.76 (m, 5H).
Example 49
4-Cyclobutyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

Example 50
4-Cyclobutyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrimidin-6-yl)-pyrimidin-2-ylamine

Example 51
(R,R)-(4-Cyclobutyl-6-cis-octahydro-pyrrolo[3,4-b]pyrimidin-6-yl)-pyrimidin-2-ylamine

Example 52
4-Cyclohexyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 53
(R)-(4-Cyclohexyl-6-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 54
4-Cyclohexyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine
Example 55
(R,R)-4-Cyclohexyl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

\[
\text{NH}_2
\]

[0227]

Example 56
4-piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

[0229]

Step A: 2-Amino-6-(tetrahydro-furan-3-yl)-3H-pyrimidin-4-one. To a solution of 3-oxo-3-(tetrahydro-furan-3-yl)propionic acid ethyl ester (4.0 g, 21.5 mmol) and guanidine hydrochloride (2.6 g, 27.2 mmol) in MeOH (125 mL) at 23°C, was added potassium tert-butoxide in portions (3.4 g, 30.3 mmol) over 5 min. The reaction was heated at 80°C for 18 h. The mixture was filtered while warm to remove insoluble salts, and the filtrate was concentrated to afford an oil which was diluted with water (25 mL) and extracted with EtOAc (8x50 mL). The combined organic layers were washed with satd. aq. NaCl, dried, and concentrated to give a residue. The aqueous portion was concentrated to afford a solid residue that was collected and rinsed with MeOH. The residue and solid materials were combined and chromatographed (2 M NH₃ in MeOH/EtOAc) to provide 0.2 g of product as a white solid (51%).

[0230]

Step B: 4-Chloro-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine. A suspension of 2-amino-6-(tetrahydro-furan-3-yl)-3H-pyrimidin-4-one (1.5 g, 8.28 mmol), tetramethyl ammonium chloride (2.7 g, 16.3 mmol) and dimethylamine (1.4 mL, 11.1 mmol) in acetonitrile (15 mL) was treated with phosphorous oxychloride (2.4 mL, 26.2 mmol) and heated at 110°C for 20 min. The resulting solution was cooled to rt and concentrated to minimum volume and pipetted onto ice chips. The aqueous portion was extracted with EtOAc (3x50 mL). The combined organic layers were basified with satd. aq. NaHCO₃ solution to pH ~7. The organic portion was separated, dried, and concentrated. The crude material was chromatographed (MeOH/CH₂Cl₂) to yield 680 mg (42%) of product as a light orange foam.

[0231]
Example 58

4-piperazin-1-yl-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

\[ \text{MS (ESI): mass calcd. for } C_{13}H_{15}N_2O, 263.17; m/z found, 264.2 } [\text{M+H}]^+ \]. \[ ^1\text{H NMR (CDCl}_3\text{): } 5.80 \text{ (s, 1H), 5.16 (br s, 2H), 4.03-4.08 (m, 2H), 3.56-3.60 (m, 4H), 3.50 (dt, J=11.4, 3.0, 2H), 2.90-2.94 (m, 4H), 2.58-2.67 (m, 4H), 1.73-1.85 (m, 4H).} \]

Example 59

4-(4-Methyl-piperazin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

\[ \text{MS (ESI): mass calcd. for } C_{13}H_{15}N_2O, 277.19; m/z found, 278.2 } [\text{M+H}]^+ \]. \[ ^1\text{H NMR (CDCl}_3\text{): } 5.81 \text{ (s, 1H), 4.74 (br s, 2H), 4.05 (dt, J=11.2, 3.2, 2H), 3.59-3.62 (m, 4H), 3.45-3.52 (m, 2H), 2.54-2.62 (m, 1H), 2.43-2.46 (m, 4H), 2.33 (s, 3H), 1.76-1.82 (m, 4H).} \]

Example 60

(R)-4-(3-Methylamino-pyrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

\[ \text{MS (ESI): mass calcd. for } C_{10}H_{14}N_2O, 283.37; m/z found, 284.2 } [\text{M+H}]^+ \]. \[ ^1\text{H NMR (CDCl}_3\text{): } 7.20-7.32 \text{ (m, 5H),} \]
5.73 (s, 1H), 4.75 (br s, 2H), 3.78 (s, 2H), 3.5-3.55 (m, 4H), 2.38-2.45 (m, 4H), 2.32 (s, 3H).

Example 64
(R)-Benzyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0249]

[0250] MS (ESI): mass calcd. for C_{19}H_{21}N_{5}s, 283.37; m/z found, 284.2 [M+H]^+; 1H NMR (CDCl_3): 7.18-7.32 (m, 5H), 5.50 (s, 1H), 4.83-4.85 (br s, 2H), 3.78 (s, 3H), 3.2-3.7 (m, 4H), 2.44 (s, 3H), 2.05-2.15 (m, 1H), 1.74-1.84 (m, 1H).

Example 65
(R,R)-4-Benzyl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

[0251]

[0252] MS (ESI): mass calcd. for C_{17}H_{23}N_{5}s, 309.41; m/z found, 310.2 [M+H]^+; 1H NMR (DMSO-d_6): 12.90-12.95 (br s, 1H), 10.10-10.22 (m, 1H), 9.0-9.10 (m, 1H), 7.25-7.45 (m, 5H), 6.24 (s, 1H), 3.65-3.95 (br m, 6H), 3.48-3.58 (m, 11H), 3.12-3.16 (m, 1H), 2.60-2.90 (m, 2H), 1.60-1.80 (m, 4H).

Example 66
4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

[0253]

[0254] Steps A: 4-Chloro-5,6,7,8-tetrahydro-quinazolin-2-ylamine. The title compound was prepared from 3-cyclohexyl-3-oxo-propionic acid ethyl ester, using methods analogous to those described in Example 1, Steps A-B.

[0255] Step B: 4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine. A solution of 4-chloro-5,6,7,8-tetrahydro-quinazolin-2-ylamine (100 mg, 0.55 mmol), N-methyl piperazin (91 μL, 1.5 mmol) and Et_3N (140 μL, 1.1 mmol) in EtOH (2 ml) was heated at 70°C for 16 h. The mixture was cooled to rt and concentrated, and the crude residue was purified (2 M NH_3 in MeOH/CH_2Cl_2) to yield a white solid (31 mg, 23%). MS (ESI): mass calcd. for C_{19}H_{21}N_{5}s, 247.3; m/z found, 248.2 [M+H]^+; 1H NMR (MeOD): 3.30-3.23 (m, 4H), 3.21 (dt, J=3.3, 1.6, 1H), 2.49 (t, J=6.7, 2H), 2.47-2.41 (m, 4H), 2.36 (t, J=5.9, 2H), 2.23 (s, 3H), 1.77-1.67 (m, 2H), 1.62-1.52 (m, 2H).

[0256] The compounds in Examples 67-75 were prepared using methods analogous to those described in Example 66.

Example 67
4-(4-piperazin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

[0257]

[0258] MS (ESI): mass calcd. for C_{16}H_{22}N_{5}s, 233.2; m/z found, 234.2 [M+H]^+; 1H NMR (MeOD): 2.85 (t, J=4.8, 4H), 2.53 (t, J=6.6, 2H), 2.39 (t, J=5.9, 2H), 1.80-1.71 (m, 2H), 1.65-1.56 (m, 2H).

Example 68
(R)-4-(3-Amino-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

[0259]

[0260] MS (ESI): mass calcd. for C_{12}H_{18}N_{5}s, 233.2; m/z found, 234.2 [M+H]^+.

Example 69
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

[0261]

[0262] MS (ESI): mass calcd. for C_{13}H_{22}N_{5}s, 248.4; m/z found, 248.2 [M+H]^+; 1H NMR (MeOD): 3.67-3.55 (m, 2H), 3.53-3.45 (m, 11H), 3.28 (dd, J=11.0, 5.5, 1H), 3.06 (p, J=6.0,
Example 70
(R, R)-4-(Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5, 6, 7, 8-tetrahydro-quinazolin-2-ylamine

0264] MS (ESI): mass calcd. for C_{16}H_{21}N_{5}, 259.2; m/z found, 260.2 [M+H]^+.

Example 71
4-(cis-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-5, 6, 7, 8-tetrahydro-quinazolin-2-ylamine

0265]

0266] MS (ESI): mass calcd. for C_{15}H_{23}N_{5}, 273.4; m/z found, 274.3 [M+H]^+. 1H NMR (MeOD): 3.87-3.74 (m, 2H), 3.66-3.59 (m, 1H), 3.54 (dd, J=11.7, 1.6, 1H), 3.32-3.28 (m, 1H), 2.96 (dt, J=12.2, 3.6, 1H), 2.78-2.68 (m, 2H), 2.67-2.58 (m, 1H), 2.58-2.50 (m, 2H), 2.34-2.24 (m, 1H), 1.92-1.80 (m, 2H), 1.80-1.73 (m, 2H), 1.73-1.60 (m, 2H), 1.60-1.44 (m, 2H).

Example 72
(R, R)-4-(Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-5, 6, 7, 8-tetrahydro-quinazolin-2-ylamine

0267]

0268] MS (ESI): mass calcd. for C_{15}H_{23}N_{5}, 273.4; m/z found, 274.3 [M+H]^+. 1H NMR (MeOD): 3.87-3.74 (m, 2H), 3.66-3.59 (m, 1H), 3.54 (dd, J=11.7, 1.6, 1H), 3.32-3.28 (m, 1H), 2.96 (dt, J=12.2, 3.6, 1H), 2.78-2.68 (m, 2H), 2.67-2.58 (m, 1H), 2.58-2.50 (m, 2H), 2.34-2.24 (m, 1H), 1.92-1.80 (m, 2H), 1.80-1.73 (m, 2H), 1.73-1.60 (m, 2H), 1.60-1.44 (m, 2H).

Example 73
(S, S)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

0269] [Image]

0270] MS (ESI): mass calcd. for C_{13}H_{19}N_{6}, 245.2; m/z found, 246.2 [M+H]^+.

Example 74
4-(4-Methyl-piperazin-1-yl)-6,7-dihydro-5H-cyclopentapyrimidin-2-ylamine

0271] [Image]

0272] MS (ESI): mass calcd. for C_{13}H_{13}N_{6}, 233.16; m/z found, 234.2 [M+H]^+. 1H NMR (CDCl3): 4.75 (s, 2H), 3.68 (t, J=9.8, 4.8, 4H), 2.91-2.85 (t, J=14.4, 7.0, 2H), 2.73-2.66 (t, J=15.6, 7.7, 2H), 2.47-2.42 (t, J=10.0, 5.0, 4H), 2.31 (s, 3H), 2.03-1.94 (qt, J=15.5, 7.9, 2H).

Example 75
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopentapyrimidin-2-ylamine

0273] [Image]

0274] MS (ESI): mass calcd. for C_{13}H_{19}N_{5}, 233.16; m/z found, 234.2 [M+H]^+. 1H NMR (CDCl3): 4.88 (s, 2H), 3.84-3.74 (m, 2.7H), 3.72-3.61 (m, 1.3H), 3.49-3.41 (m, 2H), 3.27-3.20 (m, 1H), 3.08-2.92 (m, 2H), 2.82-2.61 (m, 2H), 2.46 (s, 3H), 2.14-2.04 (m, 1H), 2.02-1.90 (m, 2H), 1.83-1.74 (m, 2H).
The compounds in Examples 76-79 were prepared using methods analogous to those described in the preceding examples.

Example 76

4-tert-Butyl-6-piperazin-1-yl-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{13}H_{23}N_{4}, 235.18; m/z found, 236.2 [M+H]^+.

Example 77

4-tert-Butyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{13}H_{23}N_{4}, 249.20; m/z found, 250.3 [M+H]^+.

Example 78

(R)-4-tert-Butyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{13}H_{23}N_{5}, 249.20; m/z found, 250.3 [M+H]^+.

Example 79

(R,R)-4-tert-Butyl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{13}H_{23}N_{5}, 275.21; m/z found, 276.3 [M+H]^+.

Intermediate 1

3-(4-Methyl-tetrahydro-pyran-4-yl)-3-oxo-propionic acid ethyl ester

Step A: (4-Methyl-tetrahydro-pyran-4-yl)-methanol. A -78°C solution of 4-methyl-tetrahydro-pyran-4-carboxylic acid methyl ester (Regan, J. et al. J. Med. Chem. 2002, 45, 2994-3008; 9.9 g, 63 mmol) in CH_2Cl_2 (400 mL) was treated with DIBAL-H (1.0 M in CH_2Cl_2; 125 mL, 125 mmol). The resulting mixture was stirred for 1 h, and then was diluted with EtOAc (200 mL) and satd. aq. NH_4Cl. The mixture was treated with satd. aq. sodium potassium tartrate, allowed to warm to r.t., and stirred for 45 min. The mixture was extracted with CH_2Cl_2 (4x), and the combined extracts were washed with satd. aq. NaCl, dried, and concentrated. Chromatography (EtOAc/hexanes) afforded the title compound as a colorless oil (5.6 g, 69%). The spectral data matched that reported in PCT Intl. Pat. Appl. Publ. No. WO 2006/001752.

Step B: 4-Methyl-tetrahydro-pyran-4-carboxaldehyde. To a solution of (4-methyl-tetrahydro-pyran-4-yl)-methanol (1.5 g, 11.5 mmol) in CH_2Cl_2 was added a suspension of Dess-Martin periodinane (5.8 g, 14 mmol) in CH_2Cl_2 (30 mL). After 70 min, the heterogenous mixture was diluted with EtO (100 mL), stirred for 10 min, treated with 1 N NaOH (10 mL), and stirred for another 10 min. The mixture was filtered, and the filtrate was concentrated. The residue was purified by chromatography (EtOAc/CH_2Cl_2) to give the title compound (1.01 g, 68%) as a colorless volatile oil. The spectral data matched that reported in PCT Intl. Pat. Appl. Publ. No. WO 2006/001752.

Step C: 3-(4-Methyl-tetrahydro-pyran-4-yl)-3-oxo-propionic acid ethyl ester. To a solution of BF_3·OEt_2 (0.350 mL, 2.50 mmol) and ethyl diazoacetate (0.390 mL, 3.42 mmol) was added a solution of 4-methyl-tetrahydro-pyran-4-carboxaldehyde (350 mg, 2.73 mmol) in CH_2Cl_2 (15 mL). After 20 min, the mixture was poured into half-saturated aq.
NaCl and extracted with CH₂Cl₂. The combined organic layers were dried and concentrated. Chromatography (EtOAc/hexanes) afforded the title compound (461 mg, 79%) as a colorless oil. MS (ESI): mass calcd. for C₁₉H₁₈O₂, 214.1; m/z found, 215.2 [M+H]+. ¹H NMR (mixture of tautomers; CDCl₃): 12.5 (s, 0.5H), 5.05 (s, 0.5H), 4.25-4.17 (m, 2H), 3.76-3.53 (m, 2H), 5.52 (s, 3H), 2.05-1.92 (m, 2H), 1.56-1.47 (m, 2H), 1.26-1.22 (m, 3H), 1.38-1.34 (m, 3H).

**Intermediate 2**
3-Cyclopentyl-2-methoxy-3-oxo-propionic acid methyl ester

The title compound was prepared using a method analogous to that described in Tetrhedron 1998, 44, 1603-1607. To a suspension of iodosobenzene disulfonate (5.2 g, 16.3 mmol) in MeOH (40 mL) was added BF₃·OEt₂ (2.1 mL, 16.3 mmol). The resulting mixture was added to 3-cyclopentyl-3-oxo-propionic acid ethyl ester (3.0 g, 16.3 mmol) and stirred at rt overnight. The mixture was concentrated to half the total volume, quenched with satd. aq. NaCl, and extracted with CHCl₃ (2x). The combined organic layers were dried and concentrated and the crude residue purified (EtOAc/hexanes) to yield a colorless oil (1.5 g, 43%). ¹H NMR (MeOD): 4.4 (s, 1H), 3.8 (s, 3H), 3.5 (s, 3H), 3.3-3.2 (m, 2H), 1.9-1.5 (m, 3H).

**Intermediate 3**
3-Oxo-4-pyridin-4-yl-butyric acid ethyl ester

A solution of pyridin-4-yl-acetic acid hydrochloride salt (1.73 g, 10 mmol) in CH₂Cl₂ (50 mL) was treated with triethylamine (2.09 mL, 15 mmol), followed by 1.1'-carbonodimimidazole (2.43 g, 15 mol). After 4 h, the solution was added dropwise to a 0°C solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; 1.73 g, 12 mmol) and pyridine (1.63 mL, 20 mmol) in CH₂Cl₂ (50 mL). The reaction mixture was allowed to warm slowly to rt and was stirred for 18 h. The mixture was washed with H₂O (2x), and the organic layer was dried and concentrated. The crude residue was dissolved in EtOH (100 mL) and heated at reflux for 4 h. The mixture was allowed to cool to rt and was concentrated. The residue was purified by chromatography (EtOAc/hexanes) to give the title compound (411 mg, 15%) as a pale yellow oil. MS (ESI): mass calcd. for C₁₉H₁₈N₂O₂, 247.2; m/z found, 248.2 [M+H]+. ¹H NMR (MeOD): 5.72 (s, 1H), 3.85-3.54 (m, 3H), 3.54-3.32 (m, 1H), 3.32-3.15 (m, 1H), 2.92-2.71 (m, 1H), 2.24 (ddd, J=12.8, 12.7, 6.4, 1H), 2.03-1.94 (m, 2H), 1.95-1.75 (m, 3H), 1.74-1.63 (m, 4H).

**Example 80**
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopentyl-pyrimidin-2-ylamine

**Example 81**
(R,R)-4-Cyclopentyl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine
4-Cyclopentyl-6-(cis-1,7-diaza-spiro[4.4]non-7-yl)-pyrimidin-2-ylamine

Example 85

4-(3-Amino-azetidin-1-yl)-6-cyclopentyl-pyrimidin-2-ylamine

Example 86

4-Cyclopentyl-6-(trans-hexahydro-pyrrrolo[3,4-b][1,4]oxazin-6-yl)-pyrimidin-2-ylamine

Example 87

4-Cyclopentyl-6-(trans-hexahydro-pyrrrolo[3,4-b][1,4]oxazin-6-yl)-pyrimidin-2-ylamine

Example 88

4-Cyclopentyl-6-(trans-hexahydro-pyrrrolo[3,4-b][1,4]oxazin-6-yl)-pyrimidin-2-ylamine

Example 89

4-Cyclopentyl-6-(trans-hexahydro-pyrrrolo[3,4-b][1,4]oxazin-6-yl)-pyrimidin-2-ylamine

Example 90

4-Cyclopentyl-6-(trans-hexahydro-pyrrrolo[3,4-b][1,4]oxazin-6-yl)-pyrimidin-2-ylamine
Example 87
4-Cyclopentyl-6-(hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

Example 88
4-Cyclopentyl-6-(cis-hexahydro-pyrrolo[3,4-b][1,4] oxazin-6-yl)-pyrimidin-2-ylamine

Example 89
(2-Amino-ethyl)-6-isopropyl-pyrimidine-2,4-diamine

Example 90
4-(3-Amino-azetidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 91
4-(1,7-Diaza-spiro[4.4]non-7-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 92
N^2-(2-Amino-ethyl)-6-isopropyl-N^4-methyl-pyrimidine-2,4-diamine
Example 93
4-(cis-Hexahydro-pyrrolo[3,4-b][1,4]oxazin-6-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 94
4-(trans-Hexahydro-pyrrolo[3,4-b][1,4]oxazin-6-yl)-6-isopropyl-pyrimidin-2-ylamine

Example 95
4-Isopropyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 96
4-(4-Methyl-piperazin-1-yl)-7,8-dihydro-5H-pyran-[4,3-d]pyrimidin-2-ylamine

Example 97
(R,R)-4-(Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-7,8-dihydro-5H-pyran-[4,3-d]pyrimidin-2-ylamine

Example 98
(R)-4-(3-Amino-pyrrolidin-1-yl)-7,8-dihydro-5H-pyran-[4,3-d]pyrimidin-2-ylamine
Example 99
(R)-4-((3-Methylamino-pyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-yl)amine

Example 102
4-Butyl-6-(1,4-diazepan-1-yl)-5-methoxy-pyrimidin-2-ylamine

Example 100
4-piperazin-1-yl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine

Example 103
4-(3-Amino-azetidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine

Example 101
4-Butyl-5-methoxy-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 104
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine

[0332] MS (ESI): mass calcd. for C₁₁H₁₂N₅O, 235.14; m/z found, 236.2 [M+H]⁺.

Example 99
(s, 3H), 3.43-3.37 (m, 4H), 2.73-2.66 (m, 2H), 1.68 (td, J=15.5, 7.6, 2H), 1.51-1.39 (m, 2H), 0.99 (t, J=7.3, 3H).

[0333] MS (ESI): mass calcd. for C₁₂H₁₆N₅O, 249.16; m/z found, 250.3 [M+H]⁺.

Example 100
4-piperazin-1-yl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine

[0334] MS (ESI): mass calcd. for C₁₄H₂₆N₅O, 279.21; m/z found, 280.2 [M+H]⁺.

Example 103
4-(3-Amino-azetidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine

[0335] MS (ESI): mass calcd. for C₁₂H₁₆N₅O, 235.14; m/z found, 236.2 [M+H]⁺.

Example 101
4-Butyl-5-methoxy-6-piperazin-1-yl-pyrimidin-2-ylamine

[0336] MS (ESI): mass calcd. for C₁₁H₁₂N₅O, 235.14; m/z found, 236.2 [M+H]⁺.

Example 104
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine

[0337] MS (ESI): mass calcd. for C₁₄H₂₆N₅O, 265.2; m/z found, 266.1 [M+H]⁺. ¹H NMR (MeOD): 4.30 (s, 4H), 3.69

[0338] MS (ESI): mass calcd. for C₁₄H₂₆N₅O, 265.2; m/z found, 266.1 [M+H]⁺.

[0339] MS (ESI): mass calcd. for C₁₄H₂₆N₅O, 279.21; m/z found, 280.2 [M+H]⁺.
Example 105
(S)-4-(3-Amino-pyridin-1-yl)-6-buty1-5-methoxy-pyrimidin-2-ylamine

[0345]

Example 108
4-Butyl-5-methoxy-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0351]

Example 106
(R)-4-Butyl-5-methoxy-6-(3-methylamino-pyrroli-
din-1-yl)-pyrimidin-2-ylamine

[0347]

Example 109
N<sup>4</sup>-(2-Amino-ethyl)-6-buty1-5-methoxy-N<sup>4</sup>-methyl-
pyridine-2,4-diamine

[0353]

Example 107
(S)-4-Butyl-5-methoxy-6-(3-methylamino-pyrroli-
din-1-yl)-pyrimidin-2-ylamine

[0349]

Example 110
N<sup>4</sup>-(2-Amino-ethyl)-6-buty1-5-methoxy-pyrimidine-
2,4-diamine

[0355]

[0346] MS (ESI): mass calcd. for C<sub>1</sub>H<sub>2</sub>N<sub>2</sub>O, 265.2; m/z found, 266.1 [M+H]<sup>+</sup>.

[0348] MS (ESI): mass calcd. for C<sub>1</sub>4H<sub>2</sub>N<sub>2</sub>O, 279.2; m/z found, 280.2 [M+H]<sup>+</sup>.

[0354] MS (ESI): mass calcd. for C<sub>1</sub>2H<sub>2</sub>N<sub>2</sub>O, 253.2; m/z found, 254.2 [M+H]<sup>+</sup>.

[0356] MS (ESI): mass calcd. for C<sub>1</sub>1H<sub>2</sub>N<sub>2</sub>O, 239.2; m/z found, 240.2 [M+H]<sup>+</sup>.
Example 111
4-(3-Amino-azetidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine

[0357]

[0358] MS (ESI): mass calcd. for C₁₃H₂₆N₄O, 263.2; m/z found, 264.2 [M+H]⁺. ¹H NMR (MeOD): 4.97-4.88 (m, 1H), 4.64-4.52 (m, 2H), 4.33-4.23 (m, 2H), 3.70 (s, 3H), 3.48-3.35 (m, 1H), 2.11-2.01 (m, 2H), 1.99-1.89 (m, 2H), 1.84-1.67 (m, 4H).

Example 112
4-Cyclopentyl-6-[1,4]diazepan-1-yl-5-methoxy-pyrimidin-2-ylamine

[0359]

[0360] MS (ESI): mass calcd. for C₁₃H₂₆N₄O, 291.2; m/z found, 292.2 [M+H]⁺. ¹H NMR (MeOD): 4.33-3.99 (m, 4H), 3.69 (s, 3H), 3.58-3.44 (m, 3H), 3.41-3.34 (m, 2H), 2.27-2.17 (m, 2H), 2.16-2.03 (m, 2H), 2.02-1.91 (m, 2H), 1.86-1.66 (m, 4H).

Example 113
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine

[0361]

[0362] MS (ESI): mass calcd. for C₁₄H₂₃N₅O, 277.2; m/z found, 278.2 [M+H]⁺.

Example 114
(S)-4-Cyclopentyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0363]

[0364] MS (ESI): mass calcd. for C₁₄H₂₃N₅O, 291.2; m/z found, 292.2 [M+H]⁺.

Example 115
N⁴-(2-Amino-ethyl)-6-cyclopentyl-5-methoxy-N⁴-methyl-pyrimidine-2,4-diamine

[0365]

[0366] MS (ESI): mass calcd. for C₁₅H₂₆N₅O, 265.2; m/z found, 266.2 [M+H]⁺.

Example 116
N⁴-(2-Amino-ethyl)-6-cyclopentyl-5-methoxy-pyrimidine-2,4-diamine

[0367]

[0368] MS (ESI): mass calcd. for C₁₃H₂₁N₄O, 251.2; m/z found, 252.2 [M+H]⁺.
Example 117

4-[1,4]Diazepan-1-yl-6-methoxymethyl-pyrimidin-2-ylamine

[0369]

[0370] MS (ESI): mass calc'd. for C_{12}H_{18}N_{2}O, 237.2; m/z found, 238.2 [M+H]^+.

\(^1\)H NMR (MeOD): 6.50 (s, 1H), 4.48-4.42 (m, 2H), 4.24-4.17 (m, 1.5H), 4.11-3.99 (m, 1.5H), 3.86-3.77 (m, 1.5H), 3.48 (s, 3H), 3.46-3.41 (m, 1.5H), 3.44-3.33 (m, 2H), 2.29-2.12 (m, 2H).

Example 120

4-Cyclopropyl-6-(cis-5-methyl-hexahydro-pyrorolo[3, 4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

[0375]

[0376] MS (ESI): mass calc'd. for C_{14}H_{22}N_{2}, 259.18; m/z found, 260.3 [M+H]^+.

\(^1\)H NMR (CDCl\textsubscript{3}): 5.60 (s, 1H), 4.66 (s, 2H), 3.67-3.54 (m, 2H), 3.42-3.31 (m, 2H), 2.98-2.88 (m, 2H), 2.73-2.67 (m, 2H), 2.45-2.36 (m, 2H), 2.32 (s, 3H), 1.71-1.65 (m, 1H), 0.98-0.90 (m, 2H), 0.90-0.82 (m, 2H).

Example 118

(S)-4-(3-Amino-pyrrolidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine

[0371]

[0372] MS (ESI): mass calc'd. for C_{10}H_{14}N_{3}O, 223.14; m/z found, 224.2 [M+H]^+.

Example 121

4-Cyclopropyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0377]

[0378] MS (ESI): mass calc'd. for C_{11}H_{17}N_{3}, 219.15; m/z found, 220.3 [M+H]^+.

\(^1\)H NMR (MeOD): 6.21 (s, 1H), 4.32-3.88 (m, 4H), 3.36-3.32 (m, 4H), 1.97-1.89 (m, 1H), 1.27-1.20 (m, 2H), 1.13-1.08 (m, 2H).

Example 119

(S)-4-Methoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0373]

[0374] MS (ESI): mass calc'd. for C_{10}H_{14}N_{3}O, 237.2; m/z found, 238.2 [M+H]^+.

Example 122

4-(3-Amino-azetidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine

[0379]
**Example 123**

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine

\[
\text{NH}_2
\]

**Example 124**

4-Cyclopropyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

**Example 125**

(S)-4-Isopropyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

**Example 126**

(S)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine

**Example 127**

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine

**Example 128**

4-tert-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

**Example 129**

4-tert-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

**Example 130**

4-tert-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine
(s, 1H), 3.66-3.57 (m, 2H), 3.43-3.34 (m, 2H), 2.96-2.90 (m, 2H), 2.73-2.66 (m, 2H), 2.47-2.41 (m, 2H), 2.32 (s, 3H), 1.23 (s, 9H).

Example 129
(S)-4-(3-Amino-pyrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{11}H_{17}N_{5}, 223.18; m/z found, 224.4 [M+H]^*.

Example 130
(S)-4-tert-Butyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{12}H_{21}N_{5}, 261.20; m/z found, 262.3 [M+H]^*.

Example 131
N^4-(2-Amino-ethyl)-6-tert-butyl-N^4-methyl-pyrimidine-2,4-diamine

MS (ESI): mass calcd. for C_{11}H_{17}N_{5}, 249.20; m/z found, 250.2 [M+H]^*; ^1H NMR (CDCl_3): 6.71 (s, 1H), 4.80 (s, 1H), 3.72-3.51 (m, 2H), 3.49-3.40 (m, 1H), 3.38-3.22 (m, 2H), 2.47 (s, 3H), 2.21-2.10 (m, 1H), 1.91-1.76 (m, 1H), 1.25 (s, 9H).

Example 132
4-tert-Butyl-6-((cis-hexahydro-pyrrrolo[3,4-c]pyrrolo-2-yl)-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{14}H_{23}N_{5}, 221.16; m/z found, 222.3 [M+H]^*.

Example 133
4-(3-Amino-azetidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine

MS (ESI): mass calcd. for C_{14}H_{23}N_{5}, 261.20; m/z found, 262.3 [M+H]^*.
Example 135
(R)-4-(3-Amino-pyrroolidin-1-yl)-6-butyl-pyrimidin-2-ylamine

Example 136
4-Butyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 137
(R)-4-Butyl-6-(3-methylamino-pyrroolidin-1-yl)-pyrimidin-2-ylamine

Example 138
N^4-(2-Amino-ethyl)-6-butyl-N^4-methyl-pyrimidine-2,4-diamine

Example 139
4-Butyl-6-(cis-5-methyl-hexahydro-pyrrrolo[3,4-c]pyrroll-2-yl)-pyrimidin-2-ylamine

Example 140
Butyl-6-(cis-hexahydro-pyrrrolo[3,4-c]pyrroll-2-yl)-pyrimidin-2-ylamine

Example 141
N^4-(2-Amino-ethyl)-6-butyl-N^4-methyl-pyrimidine-2,4-diamine
Example 141

4-Butyl-6-(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

[0417]

Example 142

4-Butyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0419]

Example 143

4-Butyl-6-(3,8-diazabicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

[0421]

Example 144

4-(4-Methyl-piperazin-1-yl)-6-propyl-pyrimidin-2-ylamine

[0423]

Example 145

4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-propyl-pyrimidin-2-ylamine

[0425]

Example 146

4-Isobutyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0427]

Example 147

4-(4-Methyl-piperazin-1-yl)pyrazin-2-ylamine

[0429]
Example 147
4-Isobutyl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 150
(S)-4-Ethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 148
(R)-4-Isobutyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 151
(R)-4-Adamantan-1-yl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 149
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isobutyl-pyrimidin-2-ylamine

Example 152
4-Adamantan-1-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 144
MS (ESI): mass calcd. for C_{14}H_{19}N_{2}O_{2}, 235.18; m/z found, 236.2 [M+H]^+.
1H NMR (MeOD): 6.15 (s, 0.7H), 6.14 (s, 0.3H), 4.18-3.64 (m, 5H), 2.50 (s, 1H), 2.48 (s, 1H), 2.34-2.14 (m, 1H), 2.12-2.00 (m, 1H), 1.00 (d, J=6.6, 6H).

Example 150
MS (ESI): mass calcd. for C_{14}H_{19}N_{2}, 221.16; m/z found, 222.2 [M+H]^+.
1H NMR (CDCl3): 5.61 (s, 1H), 5.21 (s, 2H), 3.72-3.12 (m, 5H), 2.55-2.41 (m, 5H), 2.22-2.09 (m, 1H), 1.93-1.77 (m, 1H), 1.27-1.15 (t, J=7.3, 3H).

Example 151
MS (ESI): mass calcd. for C_{14}H_{19}N_{2}, 327.24; m/z found, 328.4 [M+H]^+.
1H NMR (CDCl3): 5.92 (s, 1H), 4.71 (s, 2H), 3.71-3.17 (m, 5H), 2.48 (s, 3H), 1.99-1.92 (m, 6H), 1.81-1.72 (m, 6H), 1.38 (s, 3H), 1.15 (s, 1H).
Example 153
4-(4-Methyl-tetrahydro-pyran-4-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 154
4-(4-Methyl-piperazin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

Example 155
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

Example 156
4-(trans-2-Phenyl-cyclopropyl)-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 157
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine

Example 158
4-(4-Methyl-piperazin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine
Example 159

$N^2$-(2-Amino-ethyl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidine-2,4-diamine

Example 160

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine

Example 161

4-(3-Amino-azetidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine salt

Example 162

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine

Example 163

4-Indan-2-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 164

(R)-4-Indan-2-yl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine
Example 165

4-Indan-2-yl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 166

4-(3-Amino-azetidin-1-yl)-6-benzyl-pyrimidin-2-ylamine

Example 167

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-benzyl-pyrimidin-2-ylamine

Example 168

N^4-(2-Amino-ethyl)-6-indan-2-yl-pyrimidine-2,4-diamine

Example 169

(R)-4-(2,3-Dihydro-benzofuran-2-yl)-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 170

4-(cis-Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine
Example 171
4-(2,3-Dihydro-benzofuran-2-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 174
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

Example 172
4-(3-Amino-azetidin-1-yl)-6-(2,3-dihydro-benzofuran-2-yl)-pyrimidin-2-ylamine

Example 175
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

Example 173
4-(cis-Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-indan-2-yl-pyrimidin-2-ylamine

Example 176
N^2-(2-Amino-ethyl)-6-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
Example 177

N^4-(2-Amino-ethyl)-N^2-methyl-6-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine

Example 178

(R)-4-(3-Amino-pyrolidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine

Example 179

4-(4-Methyl-piperazin-1-yl)-6-phenethyl-pyrimidin-2-ylamine

Example 181

4-(4-Methyl-piperazin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine

Example 182

4-piperazin-1-yl-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine
Example 183

(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine

Example 184

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine

Example 185

4-Cyclopentyl-5-methoxy-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 186

4-Cyclopentyl-5-methoxy-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 187

(R)-4-Cyclopentyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 188

(R,R)-4-Cyclopentyl-5-methoxy-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine
Example 189

N\textsuperscript{2}-(2-Amino-ethyl)-N\textsuperscript{3}-methyl-6-(tetrahydro-furan-3-yl)-pyrimidine-2,4-diamine

Example 190

4-(cis-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

Example 191

(R)-4-(3-Methylamino-pyrroolidin-1-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

Example 192

4-[1,4]Diazepan-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

Example 193

(-)-4-piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

Example 194

(+)-4-piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine

Example 195

MS (ESI): mass calcld. for C\textsubscript{11}H\textsubscript{18}N\textsubscript{4}O, 237.2; m/z found, 238.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 5.71 (s, 1H), 4.98 (s, 2H), 4.19-3.93 (m, 2H), 3.90-3.80 (m, 2H), 3.65-3.51 (m, 1H), 3.44 (s, 3H), 3.31-3.07 (m, 1H), 2.88-2.84 (m, 2H), 2.49 (s, 3H), 2.30-2.04 (m, 2H).

Example 196

MS (ESI): mass calcld. for C\textsubscript{11}H\textsubscript{18}N\textsubscript{4}O, 260.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 5.77 (s, 1H), 5.10 (s, 2H), 4.09-3.97 (m, 2H), 3.88-3.82 (m, 2H), 3.72-3.59 (m, 4H), 3.24-3.16 (m, 1H), 2.99-2.94 (m, 2H), 2.88-2.79 (m, 2H), 2.32-2.05 (m, 2H), 2.04-1.88 (m, 1H), 1.89-1.78 (m, 2H).

Example 197

The compounds in Examples 193-194 were obtained by chiral HPLC separation of the enantiomers of Example 56 (column, ADH; eluent, 95% (hexanes/0.2% TEA)/5% [1:1 MeOH/EtOH/0.2% TEA]).
Example 195

N^4-(2-Amino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidine-2,4-diamine

Example 196

N^4-(3-Amino-propyl)-6-(tetrahydro-furan-3-yl)-pyrimidine-2,4-diamine

Example 197

N^4-Methyl-N^4-(2-methylamino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidine-2,4-diamine

Example 198

N^4-(2-Methylamino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidine-2,4-diamine

Example 199

5-Fluoro-4-methyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 200

5-Fluoro-4-methyl-6-(octahydro-pyrrolo[3,4-b]pyrimidin-6-yl)-pyrimidin-2-ylamine
Example 201
5-Fluoro-4-methyl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 202
(R)-5-Fluoro-4-methyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 203
N^4-(2-Amino-ethyl)-5-fluoro-6,N^4-dimethyl-pyrimidine-2,4-diamine

Example 204
4-piperazin-1-yl-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine

Example 205
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine

Example 206
4-(4-Methyl-piperazin-1-yl)-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine
Example 207
4-(4-Methyl-piperazin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine

Example 208
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine

Example 209
4-piperazin-1-yl-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine

Example 210
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine

Example 211
4-(cis-Octahydro-pyrido[3,4-b]pyridin-6-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine

Example 212
N^4-(2-Amino-ethyl)-6-thiophen-3-ylmethyl-pyrimidine-2,4-diamine
Example 213

4-(4-Methyl-piperazin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine

[0562]

Example 215

4-piperazin-1-yl-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine

[0566]

Example 216

(R)-4-(3-Amino-pyrrolidin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine

[0568]

Example 217

4-(cis-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine

[0570]
Example 218
N^4-(2-Amino-ethyl)-6-thiophen-2-ylmethyl-pyrimidine-2,4-diamine

[0572]

MS (ESI): mass calcd. for C_{15}H_{22}N_{2}S, 249.1; m/z found, 250.1 [M+H]^+.
^1H NMR (CDCl_3): 7.19 (dd, J=5.1, 1.1, 1H), 6.93 (dd, J=5.1, 3.5, 1H), 6.90-6.88 (m, 1H), 5.71 (s, 1H), 4.76 (s, 5H), 3.89 (s, 2H), 3.41-3.31 (m, 2H), 2.81 (t, J=6.0, 2H).

Example 219
N^4-(2-Amino-ethyl)-6-methoxymethyl-pyrimidine-2,4-diamine

[0574]

MS (ESI): mass calcd. for C_{16}H_{24}N_{2}O, 197.1; m/z found, 198.1 [M+H]^+.

Example 220
4-(3-Amino-azetidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine

[0576]

MS (ESI): mass calcd. for C_{16}H_{18}N_{2}O, 209.1; m/z found, 210.1 [M+H]^+.
^1H NMR (MeOD): 5.77 (s, 1H), 4.25 (t, J=8.2, 2H), 4.18-4.15 (m, 2H), 3.95-3.85 (m, 1H), 3.76-3.68 (m, 2H), 3.41 (s, 3H).

Example 221
(R)-4-Methoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0578]

MS (ESI): mass calcd. for C_{17}H_{20}N_{2}O, 237.2; m/z found, 238.1 [M+H]^+.
^1H NMR (MeOD): 5.92 (s, 1H), 4.23-4.15 (m, 2H), 3.84-3.44 (m, 3H), 3.42 (s, 3H), 3.38-3.25 (m, 2H), 2.40 (s, 3H), 2.28-2.15 (m, 3H), 1.96-1.78 (m, 1H).

Example 222
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine

[0580]

MS (ESI): mass calcd. for C_{17}H_{20}N_{2}O, 223.1; m/z found, 224.1 [M+H]^+.
^1H NMR (MeOD): 6.10 (s, 1H), 4.31 (s, 2H), 3.99 (s, 1H), 3.91-3.81 (m, 1H), 3.80-3.57 (m, 3H), 3.45 (s, 3H), 2.53-2.35 (m, 1H), 2.21-2.09 (m, 1H).

Example 223
4-Methoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0582]

MS (ESI): mass calcd. for C_{17}H_{20}N_{2}O, 237.2; m/z found, 238.1 [M+H]^+.
^1H NMR (MeOD): 6.15 (s, 1H), 4.19-4.18 (m, 2H), 3.67-3.62 (m, 4H), 3.41 (s, 3H), 2.51-2.41 (m, 4H), 2.51 (s, 3H).
Example 224
4-Methoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0584]

Example 225
(R)-4-(3-Amino-piperidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine

[0586]

Example 226
(R,R)-4-Methoxymethyl-6-(octahydro-pyrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

[0587]

Example 227
4-(4-Methyl-piperazin-1-yl)-6-tetrahydro-furan-2-ylmethyl-pyrimidin-2-ylamine

[0590]

Example 228
(R)-4-(3-Methylenamino-pyrrolin-1-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine

[0592]

Example 229
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine

[0594]

Example 230
4-(cys-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine

[0595]
Example 230
4-piperazin-1-yl-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine

[0596]

Example 231
4-(cis-Octahydro-pyrrololo[3,4-b]pyridin-6-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine

[0598]

Example 232
4-(4-Chloro-benzyl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0599]

Example 233
4-(4-Chloro-benzyl)-6-piperazin-1-yl-pyrimidin-2-ylamine

[0602]

Example 234
(R)-4-(4-Chloro-benzyl)-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0604]

Example 235
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(4-chloro-benzyl)-pyrimidin-2-ylamine

[0606]
[0607] MS (ESI): mass caled. for C_{13}H_{18}ClN_{5}, 303.79; m/z found, 304.1 [M+H]^+.

Example 236

4-(4-Chloro-benzyl)-6-(cis-5-methyl-hexahydro-pyrrrolo[3,4][pyrrol-2-y])-pyrimidin-2-ylamine

[0614]

Example 239

4-Ethoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0608]  

[0609] MS (ESI): mass caled. for C_{18}H_{22}ClN_{5}, 343.14; m/z found, 344.1 [M+H]^+.

Example 237

4-(4-Chloro-benzyl)-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine

[0616]

Example 240

4-Ethoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0610]

[0611] MS (ESI): mass caled. for C_{17}H_{20}ClN_{5}, 329.14; m/z found, 330.1 [M+H]^+.

Example 238

N^2-(2-Amino-ethyl)-6-(4-chloro-benzyl)-N^4-methyl-pyrimidine-2,4-diamine

[0618]

Example 241

(R)-Ethoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0612]

[0613] MS (ESI): mass caled. for C_{14}H_{18}ClN_{5}, 291.13; m/z found, 292.1 [M+H]^+.

[0619] MS (ESI): mass caled. for C_{19}H_{23}N_{5}O, 251.3; m/z found, 252.2 [M+H]^+; 1H NMR (MeOD): 6.22 (s, 1H), 4.46 (s, 2H), 4.03-3.88 (m, 3H), 3.82 (m, 1H), 3.74 (m, 0.5H), 3.64 (m, 2H), 3.58-3.39 (m, 0.5H), 2.79 (m, 3H), 2.61-2.19 (m, 2H), 1.28 (t, J=7.0, 3H).
Example 242

(R)-Ethoxymethyl-6-(3-amino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0620]

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
&\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

[0621] MS (ESI): mass calcd. for C_{13}H_{18}N_{3}O, 209.1; m/z found, 215.1 [M+H]^+; \text{H NMR (MeOD):} 6.27 (m, 1H), 4.49 (s, 2H), 4.10 (m, 1H), 3.98 (m, 1H), 3.93-3.70 (m, 3H), 3.66 (s, 1H), 3.65 (q, J=7.0, 2H), 2.55 (m, 1H), 2.28 (m, 1H), 1.28 (t, J=7.0, 3H).

Example 243

Isopropoxymethyl-6-((R)-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0622]

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
&\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

[0623] MS (ESI): mass calcd. for C_{13}H_{18}N_{3}O, 265.4; m/z found, 265.3 [M+H]^+; \text{H NMR (MeOD):} 6.27 (m, 1H), 4.50 (s, 2H), 4.00 (m, 3H), 3.79 (m, 3H), 3.66 (s, 2H), 2.79 (m, 3H), 2.63-2.22 (m, 2H), 1.25 (m, 6H).

Example 244

4-Isopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0624]

[0625] MS (ESI): mass calcd. for C_{13}H_{18}N_{3}O, 251.3; m/z found, 252.2 [M+H]^+; \text{H NMR (MeOD):} 5.94 (s, 1H), 4.23 (s, 2H), 3.68 (quintet, J=6.1, 1H), 3.62 (m, 4H), 3.56-3.32 (m, 1H), 3.25-2.90 (m, 1H), 2.50-2.15 (m, 1H), 1.91-1.75 (m, 1H), 1.21 (m, 6H).

Example 245

(R)-Isopropoxymethyl-6-(3-amino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

[0626]

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
&\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

[0627] MS (ESI): mass calcd. for C_{13}H_{18}N_{3}O, 251.3; m/z found, 252.2 [M+H]^+; \text{H NMR (MeOD):} 6.27 (m, 1H), 4.24 (s, 2H), 3.68 (quintet, J=6.1, 1H), 3.66-3.58 (m, 4H), 3.49-3.38 (m, 1H), 2.82 (m, 4H), 1.23 (m, 6H).

Example 246

4-Isopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

[0628]

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
&\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

[0629] To a solution of 2-amino-6-isopropoxymethyl-3H-pyrimidin-4-one (0.050 g, 0.27 mmol) in acetonitrile (2.37 ml) was added benzotriazol-1-yl-oxytris(dimethylamino) phosphonium hexafluorophosphate (0.157 g, 0.355 mmol), DBU (0.82 mL, 5.55 mmol), and 1-methyl-piperazine (0.091 mL, 0.82 mmol). The reaction mixture was stirred at rt for 12 h, then at 60 °C for 3 h. The mixture was concentrated and the resultant residue was purified (2 M NH₃ in MeOH/CH₂Cl₂) to yield a white solid (10 mg, 14%). MS (ESI): mass calcd. for C_{13}H_{18}N_{3}O, 265.4; m/z found, 266.3 [M+H]^+; \text{H NMR (MeOD):} 6.55 (s, 1H), 4.49 (s, 2H), 3.78 (quintet, J=6.1, 1H), 3.70-3.00 (m, 8H), 2.95 (s, 3H), 1.25 (d, J=6.1, 6H).

Example 247

4-Phenethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

[0630]

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
&\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]
Example 248
4-(3-Amino-azetidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine

Example 249
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine

Example 250
N^2-(2-Amino-ethyl)-6-benzyl-N^2-methyl-pyrimidine-2,4-diamine

Example 251
4-Indan-2-yl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine

Example 252
4-(3-Amino-azetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine

Example 253
4-(3-Amino-azetidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine

[0631] MS (ESI): mass calcd. for C_{14}H_{12}N_{3}O, 283.18; m/z found, 284.2 [M+H]^+.

[0632] Example 248

[0633] MS (ESI): mass calcd. for C_{15}H_{19}N_{3}, 269.16; m/z found, 270.2 [M+H]^+.

[0634] Example 249

[0635] MS (ESI): mass calcd. for C_{13}H_{21}N_{3}O, 263.17; m/z found, 264.2 [M+H]^+.

[0636] Example 250

[0637] MS (ESI): mass calcd. for C_{14}H_{10}N_{3}, 257.1; m/z found, 258.2 [M+H]^+.

[0638] Example 251

[0639] MS (ESI): mass calcd. for C_{20}H_{25}N_{5}, 335.21; m/z found, 336.2 [M+H]^+.

[0640] Example 252

[0641] MS (ESI): mass calcd. for C_{16}H_{23}N_{3}O, 221.1; m/z found, 222.2 [M+H]^+.

[0642] Example 253

[0643] MS (ESI): mass calcd. for C_{11}H_{17}N_{3}, 219.2; m/z found, 220.2 [M+H]^+. 

Sep. 8, 2011
Example 254
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-7,8-dihydro-5H-pyranol[4,3-d]pyrimidin-2-ylamine

Example 255
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine (diastereomer 1)

Example 256
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine (diastereomer 2)

Example 257
4-Cyclopentyl-6-(cis-1,7-diaza-spiro4.4non-7-yl)-pyrimidin-2-ylamine (enantiomer 1)

Example 258
4-Cyclopentyl-6-(cis-1,7-diaza-spiro4.4non-7-yl)-pyrimidin-2-ylamine (enantiomer 2)

Example 259
(R)-4-Isopropoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine
Example 260
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropanoxymethyl-pyrimidin-2-ylamine

Example 264
4-Isopropanoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

Example 261
4-Isopropanoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 265
(R)-4-Cyclopropoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine

Example 262
4-Isopropanoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine

Example 266
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopropoxymethyl-pyrimidin-2-ylamine

Example 263
4-(3-Amino-azetidin-1-yl)-6-isopropanoxymethyl-pyrimidin-2-ylamine

Example 267
4-Cyclopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine
Example 268
4-Cyclopropoxymethyl-6-[4-methyl-piperazin-1-yl]-pyrimidin-2-ylamine

Example 270
4-Cyclopropoxymethyl-6-[8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-pyrimidin-2-ylamine

Example 272
(R)-4-(3-Aminopyrrolidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine

Example 273
4-tert-Butoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine

Example 274
4-tert-Butoxymethyl-6-[4-methyl-piperazin-1-yl]-pyrimidin-2-ylamine

Example 275
4-(3-Aminopyrrolidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine
Example 276
4-tert-Butoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

Example 277
4-Ethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

Example 278
4-(8-Methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-6-propyl-pyrimidin-2-ylamine

Example 279
4-Isopropyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

Example 280
4-Cyclopentyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine

Crystal Forms

Bis hydrochloride salts of compounds of Formula (I) were dissolved in methanol (40 mg/mL concentration) and aliquots (125 μL) were dispensed into 96-well plates. The aliquots were evaporated to leave a 5 mg sample of compound in each well. An aliquot (400 μL) of a polar or a non-polar solvent, neat or as a mixture (1:1 or 2.25:1), were added to each well. Plates were covered, sonicated, and heated to 40°C for 15 min. Solvents were allowed to evaporate. Residual solids were analyzed for crystallinity. Crystalline forms were obtained from polar solvents, including methanol, ethanol, propanol, isopropanol, butanol, ethyl acetate, propyl acetate, butyl acetate, acetone, and 2-butanol, and aqueous mixtures thereof, and from mixtures of polar solvents, including mixtures of methanol, ethanol, propanol, isopropanol, butanol, 2-butanol, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, acetone, and 2-butanol. Crystalline forms were obtained from non-polar solvents, including heptane, methyl ethyl ketone, chlorobenzene, chloroform, dichloromethane, isobutyl acetate, and toluene, and from mixtures of non-polar solvents, including mixtures of methyl tert-butyl ether, isobutyl acetate, toluene, dichlorobenzene, hexane, cyclohexane, heptane, methyl ethyl ketone, acetonitrile, pentane, THF, chloroform, and chlorobenzene.

Binding assay on Recombinant Human Histamine H4 Receptor.

Cell pellets from SK-N-MC cells stably or transiently transfected with human H4 receptor were used for the binding assays. Cell pellets were homogenized in 50 mM Tris/5 mM EDTA buffer and supernatants from an 800 g spin were collected and recentrifuged at 30,000 g for 30 min. Pellets were rehomogenized in 50 mM Tris/5 mM EDTA buffer. For competition binding studies, cell membranes were incubated with 2xKg(10 nM), [3H]histamine (Specific activity: 23 Ci/mmol), with or without test compounds for 45 min at 25°C. Compounds were tested in free base, hydrochloride salt, or trifluoroacetic acid form. Nonspecific binding was defined with 100 μM cold histamine. Ks values were calculated based on an experimentally determined appropriate Ks values according to Cheng and Prusoff (Biochem. Pharmacol. 1973, 22 (23): 3099-3108). Membranes were harvested by rapid filtration using the 96 well Brandel system or a cell harvester using a Whatman GF/C filter or filter plates treated with 0.5% polyethyleneimine (PEI), and washed 4 times with
ice-cold 50 mM Tris/5 mM EDTA buffer. Filters were then dried, mixed with scintillant and radioactive counts were determined. Results for the compounds tested in these assays are presented in Tables 1 and 2 as an average of results obtained (NT=not tested). Data marked with an asterisk (*) were obtained by the cell harvester method. Where activity is shown as greater than (> ≥) a particular value, the value is the highest concentration tested.

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While the invention has been illustrated by reference to examples, it is understood that the invention is intended not to be limited to the foregoing detailed description.

What is claimed is:

1. A chemical entity selected from compounds of Formula (I):

![Chemical Structure](attachment:image.png)
wherein R¹ is:

a) a C₁₋₉ alkyl group, optionally substituted with —OH, —OC₁₋₉ alkyl, —CF₃, or —O— (monocyclic cycloalkyl);

b) a benzyl, —CH₂-(monocyclic heteroaryl), or phenylethyl group, each optionally substituted with halo;

c) a monocyclic cycloalkyl, —(CH₂)ₙ₋₁-tetrahydrofuranyl, or —(CH₂)ₙ₋₁-tetrahydropyranyl group, each optionally fused to a phenyl ring, and each optionally substituted with C₁₋₉ alkyl or phenyl; or

d) an adamantyl group;

R² is H, F, methyl, or methoxy;

or R¹ and R² taken together form —(CH₂)ₙ₋₅— or —(CH₂)ₙ₋₁-OCH₂—; and —N(R³)R⁴ is one of the following acyclic, monocyclic, spirocyclic, bridged, or fused ring systems:

where q is 0 or 1;

R³ and R⁴ are taken together as defined by the structure of each one of such moieties;

R⁵ is H or OH;

R⁶ and R⁷ are each independently H or C₁₋₉ alkyl; and each R⁸ substituent is methyl or two R⁸ substituents taken together form a methylene or ethylene bridge; provided that when R¹ is methyl, then —N(R³)R⁴ is selected from said spirocyclic, bridged, and fused ring systems;

and pharmaceutically acceptable salts of compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of Formula (I).

2. A chemical entity as in claim 1, wherein R¹ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, methoxyethyl, ethoxyethyl, isopropanoxymethyl, tert-butoxymethyl, 3,3,3-trifluoropropyl, cyclopropoxymethyl, benzyl, 4-chlorobenzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridin-4-ylmethyl, phenethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-phenyl-cyclopropyl, indan-2-yl, tetrahydrofur-3-yl, tetrahydropyran-4-yl, 4-methyl-tetrahydro-pyran-4-yl, 2,3-dihydro-benzofuran-2-yl, tetrahydrofur-an-2-ylmethyl, or adamantyl.

3. A chemical entity as in claim 1, wherein R¹ is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

4. A chemical entity as in claim 1, wherein R² is H.

5. A chemical entity as in claim 1, wherein R¹ and R² taken together form —(CH₂)₆—.

6. A chemical entity as in claim 1, wherein R¹ and R² taken together form —(CH₂)₆-OCH₂—.

7. A chemical entity as in claim 1, wherein —N(R³)R⁴ is:
8. A chemical entity as in claim 1, wherein \(-N(R^2)R^4-\) is:

9. A chemical entity as in claim 1, wherein \(-N(R^3)R^4-\) is:

10. A chemical entity as in claim 1, wherein \(-N(R^3)R^4-\) is:

11. A chemical entity as in claim 1, wherein \(-N(R^3)R^4-\) is:

12. A chemical entity as in claim 1, wherein \(-N(R^3)R^4-\) is:

13. A chemical entity as in claim 1, wherein \(-N(R^3)R^4-\) is:

14. A chemical entity as in claim 1, wherein \(R^8\) is H.

15. A chemical entity as in claim 1, wherein \(R^6\) and \(R^7\) are each independently H or methyl.

16. A chemical entity selected from the group consisting of:

- 4-Cyclopentyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
- 4-Cyclopentyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
- (R)-4-(3-Amino-piperidin-1-yl)-6-cyclohexyl-pyrimidin-2-ylamine;
- (R)-4-Cyclopentyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
- trans-1-(2-Amino-6-cyclohexyl-pyrimidin-4-yl)-4-methylamino-pyrrolidin-3-ol;
- 4-Cyclopentyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine;
- 4-Cyclopentyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine;
- 4-Isopropyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
- (R)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine;
- (S)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine;
- (R)-4-Isopropyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
- (R)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine;
- trans-1-(2-Amino-6-isopropyl-pyrimidin-4-yl)-4-methylamino-pyrrolidin-3-ol;
- (S,S)-4-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-6-isopropyl-pyrimidin-2-ylamine;
- (R,R)-4-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-6-isopropyl-pyrimidin-2-ylamine;
- 4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-6-isopropyl-pyrimidin-2-ylamine;
- (R,R)-4-(Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-6-isopropyl-pyrimidin-2-ylamine;
- 4-Isopropyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
- 4-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine;
- (R)-4-Isopropyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine;
- (R)-4-Methyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
- 4-Methyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine;
- 4,5-Dimethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
- 4,5-Dimethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
- (R)-4-(3-Amino-pyrrolidin-1-yl)-5,6-dimethyl-pyrimidin-2-ylamine;
- (R)-4,5-Dimethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
- 4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5,6-dimethyl-pyrimidin-2-ylamine;
- 4,5-Dimethyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
- 4,5-Dimethyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine;
- (S,S)-4-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-5,6-dimethyl-pyrimidin-2-ylamine;
- (R)-4-(3-Amino-pyrrolidin-1-yl)-6-ethyl-pyrimidin-2-ylamine;
4-Butyl-6-(1,4) diazepan-1-yl-5-methoxy-pyrimidin-2-ylamine;  
4-(3-Amino-azetidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;  
(S)-4-(3-Amino-pyrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;  
(R)-4-Butyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
(S)-4-Butyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
4-Butyl-5-methoxy-6-(4-methylpiperazin-1-yl)pyrimidin-2-ylamine;  
N4-(2-Amino-ethyl)-6-butyl-N4-methyl-pyrimidine-2,4-diamine;  
N4-(2-Amino-ethyl)-6-butyl-5-methoxy-pyrimidine-2,4-diamine;  
4-(3-Amino-azetidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine;  
4-Cyclopentyl-6-[1,4] diazepan-1-yl-5-methoxy-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopropyl-5-methoxy-pyrimidin-2-ylamine;  
(S)-4-Cyclopentyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
N4-(2-Amino-ethyl)-6-cyclopropyl-5-methoxy-N4-methyl-pyrimidine-2,4-diamine;  
N4-(2-Amino-ethyl)-6-cyclopropyl-5-methoxy-pyrimidine-2,4-diamine;  
4-Butyl-6-(1,4) diazepan-1-yl-6-methoxymethyl-pyrimidin-2-ylamine;  
(S)-4-(3-Amino-pyrrolidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine;  
(S)-4-Methoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
4-Cyclopropyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
4-Cyclopropyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-(3-Amino-azetidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine;  
4-Cyclopropyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
(S)-4-Isopropyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
(S)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;  
4-tert-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
(S)-4-(3-Amino-pyrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;  
(S)-4-tert-Butyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
N4-(2-Amino-ethyl)-6-tert-butyl-N4-methyl-pyrimidine-2,4-diamine;  
4-tert-Butyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
4-(3-Amino-azetidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;  
4-tert-Butyl-6-(3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-butyl-pyrimidin-2-ylamine;  
4-Butyl-6-(4-methyl-piperazin-1-yl)pyrimidin-2-ylamine;  
(R)-4-Butyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine;  
N4-(2-Amino-ethyl)-6-butyl-N4-methyl-pyrimidine-2,4-diamine;  
4-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)pyrimidin-2-ylamine;  
Butyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)pyrimidin-2-ylamine;  
4-Butyl-6-(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)pyrimidin-2-ylamine;  
4-Butyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-Butyl-6-(3,8-diaza-bicyclo[3.2.1]oct-3-yl)pyrimidin-2-ylamine;  
4-(4-Methyl-piperazin-1-yl)-6-propyl-pyrimidin-2-ylamine;  
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-propyl-pyrimidin-2-ylamine;  
4-Isobutyl-6-(4-methyl-piperazin-1-yl)pyrimidin-2-ylamine;  
4-Isobutyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
(R)-4-Isobutyl-6-(3-methylamino-pyrrolidin-1-yl)pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isobutyl-pyrimidin-2-ylamine;  
(S)-4-Ethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
4-Adamantan-1-yl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
4-Adamantan-1-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
4-(4-Methyl-tetrahydro-pyran-4-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-(4-Methyl-piperazin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;  
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;  
4-(trans-2-Phenyl-cyclopropyl)-6-piperazin-1-yl-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;  
4-(4-Methyl-piperazin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;  
N4-(2-Amino-ethyl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidine-2,4-diamine;  
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(trans-2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;  
4-(3-Amino-azetidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine;  
4-Indan-2-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
(R)-4-Indan-2-yl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;  
4-Indan-2-yl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-(3-Amino-azetidin-1-yl)-6-benzyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-benzyl-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(Amino-ethyl)-6-indan-2-yl-pyrimidin-2,4-diamine; 
(R)-4-(2,3-Dihydro-benzo-furan-2-yl)-6-(3-methy lamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 
4-(cis-Hexahydro-pyrorlo[3,4-c]pyrorl-2-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; 
(R)-4-(2,3-Dihydro-benzo-furan-2-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine; 
4-(3-Amino-acetidin-1-yl)-6-(2,3-dihydro-benzo-furan-2-yl)-pyrimidin-2-ylamine; 
4-(cis-Hexahydro-pyrorlo[3,4-c]pyrorl-2-yl)-6-indan-2-yl-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(Amino-ethyl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2,4-diamine; 
N\textsuperscript{2}-(Amino-ethyl)-N\textsuperscript{4}-methyl-6-(tetrahydro-pyran-4-yl)-pyrimidin-2,4-diamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine; 
4-(4-Methyl-piperazin-1-yl)-6-phenethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine; 
4-(Methyl-piperazin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine; 
4-Piperazin-1-yl-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine; 
4-Cyclopentyl-5-methoxy-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; 
4-Cyclopentyl-5-methoxy-6-piperazin-1-yl-pyrimidin-2-ylamine; 
(R)-4-Cyclopentyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 
(R)-4-Cyclopentyl-5-methoxy-6-(3,4-bipyrindin-6-yl)-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-N\textsuperscript{4}-methyl-6-(tetrahydro-furan-3-yl)-pyrimidin-2,4-diamine; 
4-(cis-Octahydro-pyrorlo[3,4-b]pyrorl-6-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 
[1,4]Diazepan-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 
(-)-4-Piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 
(+)-4-Piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2,4-diamine; 
N\textsuperscript{2}-(3-Amino-propyl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2,4-diamine; 
N\textsuperscript{2}-(Methyl)-N\textsuperscript{4}-(2-methylamino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2,4-diamine; 
N\textsuperscript{2}-(2-Methylamino-ethyl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2,4-diamine; 
5-Fluoro-4-methyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; 
5-Fluoro-4-methyl-6-(octahydro-pyrorlo[3,4-b]pyrorl-6-yl)-pyrimidin-2-ylamine; 
5-Fluoro-4-methyl-6-piperazin-1-yl-pyrimidin-2-ylamine; 
(R)-5-Fluoro-4-methyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-5-fluoro-6,N\textsuperscript{4}-dimethyl-pyrimidin-2,4-diamine; 
4-Piperazin-1-yl-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine; 
4-(4-Methyl-piperazin-1-yl)-6-pyridin-4-ylmethyl-pyrimidin-2-ylamine; 
4-(4-Methyl-piperazin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine; 
4-Piperazin-1-yl-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine; 
4-(cis-Octahydro-pyrorlo[3,4-b]pyrorl-6-yl)-6-thiophen-3-ylmethyl-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-6-thiophen-3-ylmethyl-pyrimidin-2,4-diamine; 
4-(4-Methyl-piperazin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
4-Piperazin-1-yl-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
4-(4-Methyl-piperazin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
4-(cis-Octahydro-pyrorlo[3,4-b]pyrorl-6-yl)-6-thiophen-2-ylmethyl-pyrimidin-2-ylamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-6-thiophen-2-ylmethyl-pyrimidin-2,4-diamine; 
N\textsuperscript{2}-(2-Amino-ethyl)-6-methoxymethyl-pyrimidin-2-4-diamine; 
4-(3-Amino-acetidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine; 
(R)-4-Methoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 
4-(3-Amino-pyrrolidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine; 
4-Methoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; 
4-Methoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine; 
(R)-4-Methoxymethyl-6-(octahydro-pyrorlo[3,4-b]pyrorl-6-yl)-pyrimidin-2-ylamine; 
4-(4-Methyl-piperazin-1-yl)-6-(tetrahydro-furan-2-ylmethyl-pyrimidin-2-ylamine; 
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(tetrahydro-furan-2-ylmethyl-pyrimidin-2-ylamine; 
4-(cis-5-Methyl-hexahydro-pyrorlo[3,4-c]pyrorl-2-yl)-6-(tetrahydro-furan-2-ylmethyl-pyrimidin-2-ylamine; 
4-Piperazin-1-yl-6-(tetrahydro-furan-2-ylmethyl-pyrimidin-2-ylamine;
4-(cis-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;
4-(4-Chloro-benzyl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-(4-Chloro-benzyl)-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-4-(4-Chloro-benzyl)-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(4-chloro-benzyl)-pyrimidin-2-ylamine;
4-(4-Chloro-benzyl)-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrole-2-yl)-pyrimidin-2-ylamine;
4-(4-Chloro-benzyl)-6-(cis-hexahydro-pyrrolo[3.4-c]pyrrole-2-yl)-pyrimidin-2-ylamine;
N^+-(2-Amino-ethyl)-6-(4-chloro-benzyl)-N^4-methyl-pyrimidin-2-4-diamine;
4-Ethoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-Ethoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-Ethoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-Ethoxymethyl-6-(3-amino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
Isopropoxymethyl-6-(R)-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
4-Isopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-Isopropoxymethyl-6-(3-amino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
4-Isopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-Phenethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
N^+-(2-Amino-ethyl)-6-benzyl-N^4-methyl-pyridine-2,4-diamine;
4-Indan-2,6-dihydro-pyrrolo[3,4-b]pyridin-6-yl-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-7,8-dihydro-SH-pyrano[4,3-d]pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine;
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrole-2-yl)-7,8-dihydro-SH-pyrano[4,3-d]pyrimidin-2-ylamine;
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(2-phenyl-cyclopropyl)-pyrimidin-2-ylamine (diastereomer 1);
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(2-phenyl-cyclopropyl)-pyrimidin-2-ylamine (diastereomer 2);
4-Cyclopentyl-6-(cis,1,7-diaza-spiro[4,4]non-7-yl)-pyrimidin-2-ylamine (enantomer 1);
4-Cyclopentyl-6-(cis,1,7-diaza-spiro[4,4]non-7-yl)-pyrimidin-2-ylamine (enantomer 2);
(R)-4-Isopropoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropoxymethyl-pyrimidin-2-ylamine;
4-Isopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-Isopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-isopropoxymethyl-pyrimidin-2-ylamine;
4-Isopropoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
(R)-4-Cyclopropoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-cyclopropoxymethyl-pyrimidin-2-ylamine;
4-Cyclopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-Cyclopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-cyclopropoxymethyl-pyrimidin-2-ylamine;
4-Cyclopropoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
(R)-4-tert-Butoxymethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine;
4-tert-Butoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-tert-Butoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine;
4-tert-Butoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
4-Ethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
4-(8-Methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-6-propyl-pyrimidin-2-ylamine;
4-Isopropyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
4-Cyclopentyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
and pharmaceutically acceptable salts thereof.

17. A pharmaceutical composition for treating a disease, disorder, or medical condition mediated by histamine H4 receptor activity, comprising an effective amount of at least one chemical entity selected from compounds of Formula (I):

![Chemical Structure Image]

wherein
R^1: is:

a) a C^1-alkyl group, optionally substituted with —OH, —OC^1-alkyl, —CF_3, or —O— (monocyclic cycloalkyl);
b) a benzyl, —CH_2— (monocyclic heteroary1), or phenethyl group, each optionally substituted with halo;
c) a monocyclic cycloalkyl, or (CH_2)_n-tetrahydrofuranyl, or —(CH_2)_n-1-tetrahydropyranyl group, each optionally fused to a phenyl ring, and each optionally substituted with C_1-alkyl or phenyl; or
d) an adamantyl group;
R² is H, F, methyl, or methoxy; or R¹ and R² taken together form —(CH₂)₃— or —(CH₂)₂OCH₃—; and
—N(R³)R⁴ is one of the following acyclic, monocyclic, spirocyclic, bridged, or fused ring systems:

where q is 0 or 1;
R³ and R⁴ are taken together as defined by the structure of each one of such moieties;
R⁵ is H or OH;
R² and R⁴ are each independently H or C₁₃ alkyl, and each R⁶ substituent is methyl or two R⁶ substituents taken together form a methylene or ethylene bridge; provided that when R⁴ is methyl, then —N(R³)R⁴ is selected from said spirocyclic, bridged, and fused ring systems;
and pharmaceutically acceptable salts of compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of compounds of Formula (I).

18. A pharmaceutical composition as in claim 17, wherein said chemical entity is selected from the group consisting of:
- 4-Cyclopentyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
- 4-Cyclopentyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-piperidin-1-y1)-6-cyclopentyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-piperidin-1-y1)-6-cyclopentyl-pyrimidin-2-ylamine;
(R)-4-Cyclopentyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
trans-1-(2-Amino-6-cyclopentyl-pyrrolidin-4-yl)-4-methylamino-pyrrolidin-3-ol;
- 4-Cyclopentyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrrol-5-yl)-pyrrolidin-2-ylamine;
- 4-Cyclopentyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrrol-6-yl)-pyrrolidin-2-ylamine;
- 4-Isopropyl-6-piperazin-1-yl-pyrrolidin-2-ylamine;
(R)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrrolidin-2-ylamine;
(S)-4-(3-Amino-piperidin-1-yl)-6-isopropyl-pyrrolidin-2-ylamine;
(R)-4-Isopropyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrrolidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-isopropyl-pyrrolidin-2-ylamine;
trans-1-(2-Amino-6-isopropyl-pyrrolidin-4-yl)-4-methylamino-pyrrolidin-3-ol;
(S,S)-4-(2,5-Diaza-bicycle[2.2.1]hept-2-yl)-6-isopropyl-pyrrolidin-2-ylamine;
(R,R)-4-(2,5-Diaza-bicycle[2.2.1]hept-2-yl)-6-isopropyl-pyrrolidin-2-ylamine;
4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrrol-5-yl)-6-isopropyl-pyrrolidin-2-ylamine;
(R,R)-4-(Hexahydro-pyrrolo[3,4-b]pyrrrol-5-yl)-6-isopropyl-pyrrolidin-2-ylamine;
- 4-Isopropyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrrol-2-yl)-pyrrolidin-2-ylamine;
4-Isopropyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrrol-6-yl)-pyrrolidin-2-ylamine;
(R,R)-4-Isopropyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrrol-6-yl)-pyrrolidin-2-ylamine;
(R)-4-Methyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrrolidin-2-ylamine;
- 4-Methyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrrol-6-yl)-pyrrolidin-2-ylamine;
4,5-Dimethyl-6-piperazin-1-yl-pyrrolidin-2-ylamine;
4,5-Dimethyl-6-(4-methyl-piperazin-1-yl)-pyrrolidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-5,6-dimethyl-pyrrolidin-2-ylamine;
(R)-4,5-Dimethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamidine; 4-(cis-Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5,6-dimethyl-pyrimidin-2-ylamidine; 4,5-Dimethyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamidine; 4,5-Dimethyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamidine; (S,S)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-5,6-dimethyl-pyrimidin-2-ylamidine; (R)-4-(3-Amino-pyrrolidin-1-yl)-6-ethyl-pyrimidin-2-ylamidine; (R)-4-Ethyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; (R,R)-4-Ethyl-6-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine; 4-Ethyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine; (R,R)-4-Ethyl-6-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Cyclopropyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; (R)-4-(4-Cyclopropyl-6-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 4-Cyclopropyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Cyclobutyl-6-piperazin-1-yl-pyrimidin-2-ylamine; 4-Cyclobutyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; (R)-4-(3-Amino-piperidin-1-yl)-6-cyclobutyl-pyrimidin-2-ylamine; (R)-4-(4-Cyclobutyl-6-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 4-Cyclobutyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine; 4-Cyclobutyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine; 4-Cyclobutyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine; 4-Cyclobutyl-6-(cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; (R,R)-4-(4-Cyclobutyl-6-cis-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Cyclohexyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; (R)-4-(4-Cyclohexyl-6-3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; 4-Cyclohexyl-6-(cis-hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine; (R,R)-4-(4-Cyclohexyl-6-octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Piperazin-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 4-(Methyl-piperazin-1-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine; 4-Piperazin-1-yl-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; 4-(Methyl-piperazin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; (R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine; (R,R)-4-(3,4-Hexahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Benzy1-6-piperazin-1-yl-pyrimidin-2-ylamine; 4-Benzy1-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; (R)-Benzy1-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; (R,R)-4-Benzy1-6-(octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; 4-(4-Piperazin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (R)-4-(3-Amino-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (R)-4-(3-Methylamino-pyrrolidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (R)-4-(Hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; 4-(cis-Octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (R,R)-4-(Octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (S,S)-4-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine; (R)-4-(4-Methyl-piperazin-1-yl)-6,7-dihydro-5H-cyclopentapyrimidin-2-ylamine; (R)-4-(4-Methylamino-pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopentapyrimidin-2-ylamine; 4-tet-Butyl-6-piperazin-1-yl-pyrimidin-2-ylamine; 4-tet-Butyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine; (R)-4-tet-Butyl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine; (R)-4-tet-Butyl-6-(octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-(3-Amino-pyrrolidin-1-yl)-6-cyclopentyl-pyrimidin-2-ylamine; (R,R)-4-Cyclopentyl-6-(octahydro-pyrrolo[3,4-b]pyrrol-6-yl)-pyrimidin-2-ylamine; 4-Cyclopentyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine; (R,R)-4-Cyclopentyl-6-(hexahydro-pyrrolo[3,4-b]pyrrol-5-yl)-pyrimidin-2-ylamine; 4-Cyclopentyl-6-(cis-1,7-diaza-spiro[4.4.4][7.7]-pyrrol-6-yl)pyrimidin-2-ylamine; 4-(3-Amino-azetidin-1-yl)-6-cyclopentyl-pyrimidin-2-ylamine; 4-Cyclopentyl-6-(trans-hexahydro-pyrrolo[3,4-b][1.4]oxazin-6-yl)-pyrimidin-2-ylamine; 4-Cyclopentyl-6-(hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine; 4-Cyclopentyl-6-(cis-hexahydro-pyrrolo[3,4-b][1.4]oxazin-6-yl)-pyrimidin-2-ylamine; (2-Amino-ethyl)-6-isopropyl-pyrimidin-2-4-diamine; 4-(3-Amino-azetidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine; 4-(1,7-Diaza-spiro[4.4.4][7.7]-pyrrol-6-yl)-isopropyl-pyrimidin-2-ylamine; N"(2-Amino-ethyl)-6-isopropyl-N"-methyl-pyrimidine-2,4-diamine; 4-(cis-Hexahydro-pyrrolo[3,4-b][1.4]oxazin-6-yl)-6-isopropyl-pyrimidin-2-ylamine; 4-(trans-Hexahydro-pyrrolo[3,4-b][1.4]oxazin-6-yl)-6-isopropyl-pyrimidin-2-ylamine; 4-Isopropyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-(4-Methyl-piperazin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;
(R,R)-4-(Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;
(R)-4-(3-Methylamino-pyrrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;
4-Piperazin-1-yl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;
4-Butyl-5-methoxy-2-piperazin-1-yl-pyrimidin-2-ylamine;
4-Butyl-6-[1,4]diazepan-1-yl-5-methoxy-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;
(S)-4-(3-Amino-pyrrrolidin-1-yl)-6-butyl-5-methoxy-pyrimidin-2-ylamine;
(R)-4-Butyl-5-methoxy-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
(S)-4-Butyl-5-methoxy-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
Butyl-5-methoxy-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-butyl-5-methoxy-N<sup>4</sup>-methyl-pyrimidin-2,4-diamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-butyl-5-methoxy-pyrimidine-2,4-diamine;
4-(3-Amino-azetidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine;
4-Cyclopentyl-6-[1,4]diazepan-1-yl-5-methoxy-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine;
(S)-4-(3-Amino-pyrrrolidin-1-yl)-6-cyclopentyl-5-methoxy-pyrimidin-2-ylamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-cyclopentyl-5-methoxy-N<sup>4</sup>-methyl-pyrimidine-2,4-diamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-cyclopentyl-5-methoxy-pyrimidine-2,4-diamine;
4-[1,4]Diazepan-1-yl-6-methoxymethyl-pyrimidin-2-ylamine;
(S)-4-(3-Amino-pyrrrolidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine;
(S)-4-Methoxymethyl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
4-Cyclopentyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
4-Cyclopentyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-cyclopropyl-pyrimidin-2-ylamine;
(R)-4-Cyclopentyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
(S)-4-Isopropyl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
(S)-4-(3-Amino-pyrrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;
4-tert-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
(S)-4-(3-Amino-pyrrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;
2-(2-Amino-ethyl)-6-0-tert-butyl-N<sup>4</sup>-methyl-pyrimidine-2,4-diamine;
4-tert-Butyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;
4-tert-Butyl-6-(3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-tert-butyl-pyrimidin-2-ylamine;
4-Butyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
(R)-4-Butyl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-butyl-N<sup>4</sup>-methyl-pyrimidine-2,4-diamine;
4-Butyl-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
Butyl-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;
4-Butyl-6-(cis-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine;
4-Butyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-Butyl-6-(3,8-diaza-bicycle[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;
4-(4-Methyl-piperazin-1-yl)-6-propyl-pyrimidin-2-ylamine;
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-propyl-pyrimidin-2-ylamine;
4-Isobutyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-Isobutyl-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-4-Isobutyl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-isobutyl-pyrimidin-2-ylamine;
(S)-4-Ethyl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-Adamantan-1-yl-6-(3-methylamino-pyrrrolidin-1-yl)-pyrimidin-2-ylamine;
4-Adamantan-1-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
(R)-4-(4-Methyl-tetrahydro-pyran-4-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-4-(4-Methyl-piperazin-1-yl)-6-(4-Methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Methylamino-pyrrrolidin-1-yl)-6-(4-Methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
(R)-4-(2-Phenyl-cyclopropyl)-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrrolidin-1-yl)-6-(2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;
(R)-4-(4-Methyl-piperazin-1-yl)-6-(2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;
N<sup>2</sup>-(2-Amino-ethyl)-6-(2-phenyl-cyclopropyl)-pyrimidine-2,4-diamine;
(R)-4-(3-Methylamino-pyrrrolidin-1-yl)-6-(2-phenyl-cyclopropyl)-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-indan-2-yl-pyrimidin-2-ylamine;
4-Indan-2-yl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
(R)-4-Indan-2-yl-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
4-Indan-2-yl-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-benzyl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-benzyl-pyrimidin-2-ylamine;
N4-(2-Amino-ethyl)-6-indan-2-yl-pyrimidine-2,4-diamine;
(R)-4-(2,3-Dihydro-benzo[4,5]furan-2-yl)-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
4-(cis-Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
(2,3-Dihydro-benzofuran-2-yl)-6-piperazin-1-yl-pyrimidin-2-ylamine;
4-(3-Amino-azetidin-1-yl)-6-(2,3-dihydro-benzo[4,5]furan-2-yl)-pyrimidin-2-ylamine;
4-(cis-Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-indan-2-yl-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(4-methyl-tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2-ylamine;
N4-(2-Amino-ethyl)-6-(tetrahydro-pyran-4-yl)-pyrimidin-2,4-diamine;
N4-(2-Amino-ethyl)-N4-methyl-6-(tetrahydro-pyran-4-yl)-pyrimidin-2,4-diamine;
N4-(2-Amino-ethyl)-N4-methyl-6-(tetrahydro-pyran-4-yl)-pyrimidin-2,4-diamine;
N4-(2-Amino-ethyl)-6-phenethyl-pyrimidin-2-ylamine;
(4-Methyl-piperazin-1-yl)-6-phenethyl-pyrimidin-2-ylamine;
N4-(3-Amino-pyrrolidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine;
(4-Methyl-piperazin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine;
Piperazin-1-yl-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine;
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-pyrrolidin-1-yl)-6-(3,3,3-trifluoro-propyl)-pyrimidin-2-ylamine;
4-Cyclopentyl-5-methoxy-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;
4-Cyclopentyl-5-methoxy-6-piperazin-1-yl-pyrimidin-2-ylamine;
(R)-4-Cyclopentyl-5-methoxy-6-(3-methylamino-pyrrolidin-1-yl)-pyrimidin-2-ylamine;
(R)-4-Cyclopentyl-5-methoxy-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine;
N4-(2-Amino-ethyl)-N4-methyl-6-(octahydro-furan-3-yl)-pyrimidin-2,4-diamine;
4-(cis-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Methylamino-pyrrolidin-1-yl)-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine;
4-[1,4]Diazepan-1-yl-6-(tetrahydro-furan-3-yl)-pyrimidin-2-ylamine;
(R)-4-(3-Amino-piperidin-1-yl)-6-methoxymethyl-pyrimidin-2-ylamine;  
(R,R)-4-Methoxymethyl-6-(octahydro-pyrrol[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine;  
(4-Methyl-piperazin-1-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;  
(R)-4-(3-Methylamino-pyrroloidin-1-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;  
(3-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;  
Piperazin-1-yl-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;  
(4-Octahydro-pyrrolo[3,4-b]pyridin-6-yl)-6-(tetrahydro-furan-2-ylmethyl)-pyrimidin-2-ylamine;  
(4-Chloro-benzyl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
(4-Chloro-benzyl)-6-piperazin-1-yl-pyrimidin-2-ylamine;  
(R)-4-(4-Chloro-benzyl)-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(R,R)-4-(3-Amino-pyrroloidin-1-yl)-6-(4-chloro-benzyl)-pyrimidin-2-ylamine;  
(4-Chloro-benzyl)-6-(cis-5-methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
(4-Chloro-benzyl)-6-(cis-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyrimidin-2-ylamine;  
N^4-(2-Amino-ethyl)-6-(4-chlorobenzyl)-N^4-methyl-pyrimidine-2,4-diamine;  
Ethoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
Ethoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
Ethoxymethyl-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(R)-Ethoxymethyl-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
Ethoxymethyl-6-(3-amino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
Isopropoxymethyl-6-(R)-3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(4-Isopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
(R)-Isopropoxymethyl-6-(3-amino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
Isopropoxymethyl-6-(4-methyl-piperazin-1-yl-pyrimidin-2-ylamine;  
Phenethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-6-phenethyl-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrroloidin-1-yl)-6-(tetrahydro-pyrann-4-yl)-pyrimidin-2-ylamine;  
N^4-(2-Amino-ethyl)-6-benzyl-N^4-methyl-pyrimidine-2,4-diamine;  
Indan-2-yl-6-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-5,6,7,8-tetrahydro-quinazolin-2-ylamine;  
4-(cis-5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-7,8-dihydro-5H-pyrrano[4,3-d]pyrimidin-2-ylamine;  
(R)-4-(3-Methylamino-pyrroloidin-1-yl)-6-(2-phenyl-cyclopentyl)-pyrimidin-2-ylamine (dastereomer 1);  
(R)-4-(3-Methylamino-pyrroloidin-1-yl)-6-(2-phenyl-cyclopentyl)-pyrimidin-2-ylamine (dastereomer 2);  
4-Cyclopentyl-6-(cis-1,7-diaza-spiro[4.4]non-7-yl)-pyrimidin-2-ylamine (enantiomer 1);  
4-Cyclopentyl-6-(cis-1,7-diaza-spiro[4.4]non-7-yl)-pyrimidin-2-ylamine (enantiomer 2);  
(R)-4-Isopropoxymethyl-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrroloidin-1-yl)-6-isopropoxymethyl-pyrimidin-2-ylamine;  
4-Isopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-Isopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-6-isopropoxymethyl-pyrimidin-2-ylamine;  
4-Isopropoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;  
(R)-4-Cyclopropoxymethyl-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrroloidin-1-yl)-6-cyclopropoxymethyl-pyrimidin-2-ylamine;  
4-Cyclopropoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-Cyclopropoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-6-cyclopropoxymethyl-pyrimidin-2-ylamine;  
4-Cyclopropoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;  
(R)-4-tert-Butoxymethyl-6-(3-methylamino-pyrroloidin-1-yl)-pyrimidin-2-ylamine;  
(R)-4-(3-Amino-pyrroloidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine;  
4-tert-Butoxymethyl-6-piperazin-1-yl-pyrimidin-2-ylamine;  
4-tert-Butoxymethyl-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamine;  
(3-Amino-azetidin-1-yl)-6-tert-butoxymethyl-pyrimidin-2-ylamine;  
4-tert-Butoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;  
4-tert-Butoxymethyl-6-(8-methyl-3,8-diaza-bicyclo[3.2.1]oct-3-yl)-pyrimidin-2-ylamine;  
and pharmaceutically acceptable salts thereof.  
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