

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 October 2007 (18.10.2007)

PCT

(10) International Publication Number
WO 2007/117401 A2

(51) International Patent Classification:
A61K 31/4184 (2006.01) C07D 403/14 (2006.01)
A61K 31/405 (2006.01)

(21) International Application Number:
PCT/US2007/008218

(22) International Filing Date: 30 March 2007 (30.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/790,421 7 April 2006 (07.04.2006) US

(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turn-
houtseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EDWARDS, James,
P. [US/US]; 8723 Hesby Court, San Diego, CA 92129
(US). SAVALL, Brad, M. [US/US]; 9512 Ronda Avenue,
San Diego, CA 92123 (US). SHAH, Chandravadan, R.
[US/US]; 14213 Dalhousie Road, San Diego, CA 92129
(US).

(74) Agent: JUANOS I TIMONEDA, Jesus; Johnson & John-
son, Patent Law Dept., One Johnson & Johnson Plaza, New
Brunswick, NJ 08933 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,
FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN,
IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR,
LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv))

Published:
— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: INDOLES AND BENZOIMIDAZOLES AS MODULATORS OF THE HISTAMINE H4 RECEPTOR

(57) Abstract: Benzoimidazole and indole 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 pruritis.



WO 2007/117401 A2

**INDOLES AND BENZOIMIDAZOLES AS HISTAMINE H₄ RECEPTOR
MODULATORS**

This application claims the benefit of US provisional patent application serial number 60/790,421, filed on April 7, 2006, which is incorporated herein by
5 reference.

Field of the Invention

The present invention relates to certain indole and benzoimidazole compounds, pharmaceutical compositions containing them, and methods of using them for the treatment of disease states, disorders, and conditions mediated by
10 histamine H₄ receptor activity.

Background of the Invention

The histamine H₄ receptor (H₄R) is the most recently identified receptor for histamine (for reviews, see: Fung-Leung, W.-P., et al., *Curr. Opin. Invest. Drugs* 2004, 5(11), 1174-1183; de Esch, I.J.P., et al., *Trends Pharmacol. Sci.* 2005, 26(9), 462-469). The receptor is found in the bone marrow and spleen and is
15 expressed on eosinophils, basophils, mast cells (Liu, C., et al., *Mol. Pharmacol.* 2001, 59(3), 420-426; Morse, K.L., et al., *J. Pharmacol. Exp. Ther.* 2001, 296(3), 1058-1066; Hofstra, C.L., et al., *J. Pharmacol. Exp. Ther.* 2003, 305(3), 1212-1221; Lippert, U., et al., *J. Invest. Dermatol.* 2004, 123(1), 116-123; Voehringer, D., et al., *Immunity* 2004, 20(3), 267-277), CD8⁺ T cells (Gantner, F., et al., *J. Pharmacol. Exp. Ther.* 2002, 303(1), 300-307), dendritic cells, and human
20 synovial cells from rheumatoid arthritis patients (Ikawa, Y., et al., *Biol. Pharm. Bull.* 2005, 28(10), 2016-2018). However, expression in neutrophils and monocytes is less well defined (Ling, P., et al., *Br. J. Pharmacol.* 2004, 142(1), 161-171). Receptor expression is at least in part controlled by various
25 inflammatory stimuli (Coge, F., et al., *Biochem. Biophys. Res. Commun.* 2001, 284(2), 301-309; Morse, et al., 2001), thus supporting that H₄ receptor activation influences inflammatory responses. Because of its preferential expression on immunocompetent cells, the H₄ receptor is closely related with the regulatory
30 functions of histamine during the immune response.

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
5 function, or a combination of these.

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
10 cause the activation, recruitment, and de-granulation 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
15 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; Thurmond, 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 (Thurmond, et al., 2004). The migration of
20 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.,
25 *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 is mediated by histamine H₄
30 receptors.

It has been shown that eosinophils can chemotax towards histamine (O'Reilly, M., et al., *J. Recept. Signal Transduction* 2002, 22(1-4), 431-448; Buckland, 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
5 histamine treatment (Ling, et al., 2004). This increase is blocked by H₄ receptor antagonists but not by H₁, H₂, or H₃ receptor antagonists.

The H₄R also plays a role in dendritic cells and T cells. In human monocyte-derived dendritic cells, H₄R stimulation suppresses IL-12p70 production and drives histamine-mediated chemotaxis (Gutzmer, R., et al., J. Immunol. 2005,
10 174(9), 5224-5232). A role for the H₄ receptor in CD8⁺ T cells has also been reported. Gantner, et al., (2002) showed that both H₄ and H₂ 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
15 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.

In vivo H₄ receptor antagonists were able to block neutrophilia in zymosan-
20 induced peritonitis or pleurisy models (Takeshita, K., et al., J. Pharmacol. Exp. Ther. 2003, 307(3), 1072-1078; Thurmond, 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-
25 inflammatory in vivo.

Another physiological role of histamine is as a mediator of itch and H₁ receptor antagonists are not completely 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
30 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 pruritis.

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.

Examples of textbooks on the subject of inflammation include: 1) Gallin, J.I.; Snyderman, R., *Inflammation: Basic Principles and Clinical Correlates*, 3rd ed.; Lippincott Williams & Wilkins: Philadelphia, 1999; 2) Stvrtnova, V., et al., *Inflammation and Fever. Pathophysiology Principles of Diseases* (Textbook for Medical Students); Academic Press: New York, 1995; 3) Cecil; et al. *Textbook Of Medicine*, 18th ed.; W.B. Saunders Co., 1988; and 4) Stedman's Medical Dictionary.

Background and review material on inflammation and conditions related with inflammation can be found in articles such as the following: Nathan, C., *Nature* 2002, 420(6917), 846-852; Tracey, K.J., *Nature* 2002, 420(6917), 853-859; Coussens, L.M., et al., *Nature* 2002, 420(6917), 860-867; Libby, P., *Nature* 2002, 420, 868-874; Benoist, C., et al., *Nature* 2002, 420(6917), 875-878; Weiner, H.L., et al., *Nature* 2002, 420(6917), 879-884; Cohen, J., *Nature* 2002, 420(6917), 885-891; Steinberg, D., *Nature Med.* 2002, 8(11), 1211-1217.

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, pruritis, and immunodeficiency disorders. Diseases, disorders and medical conditions that are mediated by histamine H₄ receptor activity include those referred to herein.

Indole and benzoimidazole amides were disclosed as histamine H₄ receptor modulators in Intl. Patent Appl. Publ. No. WO02/072548 (Sept. 19, 2002). 4-Pyrrolidino pyrimidines have also been disclosed as histamine H₄ receptor modulators (See, Intl. Patent Appl. Publ. Nos. WO05/014556 (Feb. 17,

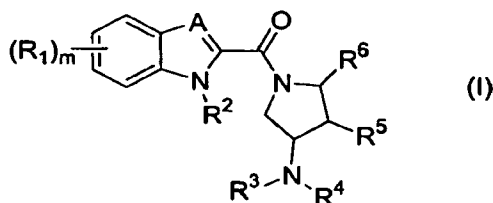
2005) and WO05/054239 (June 16, 2005). However, there still remains a need for potent histamine H₄ receptor modulators with desirable pharmaceutical properties.

5

Summary of the Invention

Certain indole and benzimidazole derivatives have now been found to have histamine H₄ receptor-modulating activity.

In one general aspect, the invention relates to compounds of the following Formula (I):



10

wherein:

A is CH or N;

each R¹ is independently Cl, Br, methyl, ethyl, NO₂, or CF₃;

m is 0, 1, or 2;

15 R² is H;

R³ is H, methyl, or ethyl; and

1) R⁴ is H, methyl, or ethyl; one of R⁵ and R⁶ is H, methyl, or ethyl and the other is H; or

2) R⁴ and R⁵ together form -(CH₂)₃-; and R⁶ is H; or

20 3) R⁴ and R⁶ together form -CH₂-; and R⁵ is H.

This invention also relates to any of the following: 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).

25

In other embodiments, the compound of Formula (I) is a compound selected from those species described or exemplified in the detailed description below.

In a further general aspect, the invention relates to pharmaceutical compositions comprising an effective amount of at least one of an agent selected from compounds of Formula (I) and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites thereof. Some embodiments of pharmaceutical compositions according to the invention further comprise a pharmaceutically acceptable excipient.

In another general 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 compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite of such compound. 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.

In another general aspect, the invention is directed to a method for modulating histamine H₄ receptor activity, comprising exposing histamine H₄ receptor to an effective amount of at least one of a compound of Formula (I) and a salt thereof.

In other embodiments of methods and compositions according to this invention, the compound of Formula (I) is a compound selected from those species described or exemplified in the detailed description below.

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

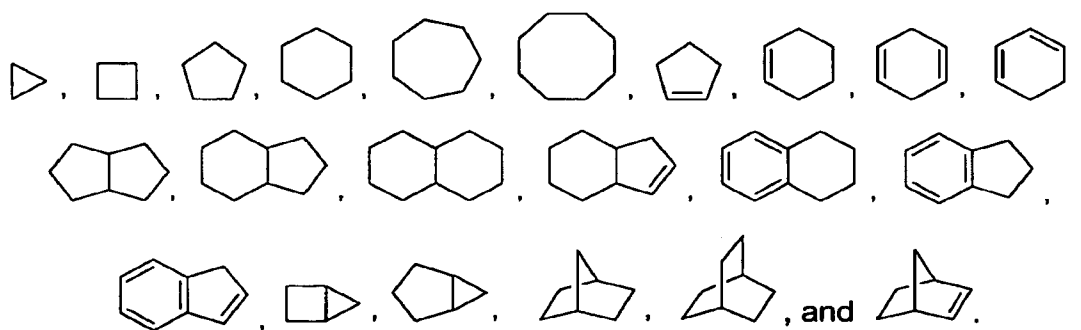
The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications, including patents, cited in this specification are herein incorporated by reference.

As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

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 the symbol "/"), 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.

The term "alkenyl" refers to a straight- or branched-chain alkenyl group having from 2 to 12 carbon atoms in the chain. (The double bond of the alkenyl group is formed by two sp^2 hybridized carbon atoms.) Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, 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.

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:

25

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 atropisomers. Additionally, any formula given herein is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

The symbols  and  are used as meaning the same spatial arrangement in chemical structures shown herein. Analogously, the symbols  and  are used as meaning the same spatial arrangement in chemical structures shown herein.

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_(s), R-COOH_(sol), and R-COO⁻_(sol). In this example, R-COOH_(s) refers to the solid compound, as it could be for example in a tablet or some other solid pharmaceutical composition or preparation; R-COOH_(sol) refers to the undissociated form of the compound in a solvent; and R-COO⁻_(sol) 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 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-COOH_(aq) and/or R-COO⁻_(aq), 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
5 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,
10 phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed
15 tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C 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
20 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
25 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.

30 By way of a first example on substituent terminology, if substituent S^1_{example} is one of S_1 and S_2 , and substituent S^2_{example} is one of S_3 and S_4 , then these assignments refer to embodiments of this invention given according to the choices S^1_{example} is S_1 and S^2_{example} is S_3 ; S^1_{example} is S_1 and S^2_{example} is S_4 ; S^1_{example}

is S_2 and S_{example}^2 is S_3 ; S_{example}^1 is S_2 and S_{example}^2 is S_4 ; and equivalents of each one of such choices. The shorter terminology " S_{example}^1 is one of S_1 and S_2 , and S_{example}^2 is one of S_3 and S_4 " 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 applicable, to members such as R^{1-6} , A, and m, 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 equivalents thereof. By way of a second example on substituent terminology, if it is herein described that substituent S_{example} is one of S_1 , S_2 , and S_3 , this listing refers to embodiments of this invention for which S_{example} is S_1 ; S_{example} is S_2 ; S_{example} is S_3 ; S_{example} is one of S_1 and S_2 ; S_{example} is one of S_1 and S_3 ; S_{example} is one of S_2 and S_3 ; S_{example} is one of S_1 , S_2 and S_3 ; and S_{example} is any equivalent of each one of these choices. The shorter terminology " S_{example} is one of S_1 , S_2 , and S_3 " is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing second 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 applicable, to members such as R^{1-6} , A, and m, and any other generic substituent symbol used herein.

The nomenclature " C_{i-j} " with $j > i$, when applied herein to a class of substituents, is meant to refer to embodiments 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).

The term C_{n-m} alkyl refers to an aliphatic chain, whether straight or branched, with a total number N of carbon members in the chain that satisfies $n \leq N \leq m$, with $m > n$.

Any disubstituent referred to herein is meant to encompass the various attachment possibilities when more than one of such possibilities are allowed. For example, reference to disubstituent –A-B-, where A ≠ 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 considerations on assignments and nomenclature, it is understood that explicit reference herein to a set implies, where chemically meaningful and unless indicated otherwise, independent reference 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 (I), A is CH. In other embodiments, A is N.

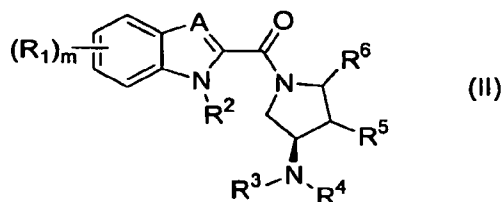
In some embodiments, R¹ is Cl.

In some embodiments, m is 0 or 1.

In some embodiments, R³ is H or methyl.

In some embodiments, R⁴ is methyl, R⁵ is H, and R⁶ is H. In other embodiments, R⁴ and R⁵ together form –(CH₂)₃–, and R⁶ is H. In still other embodiments, R⁴ and R⁶ together form –CH₂–, and R⁵ is H.

In some embodiments, the structure given by Formula (I) is given by Formula (II):



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.

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. Examples of pharmaceutically acceptable salts are those that are

5 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, 10 pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, 15 malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methane-sulfonates, 20 propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

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, 25 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, lactic 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, 30 oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic

acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level
5 of skill in this technology.

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
10 hydroxide, alkaline earth metal hydroxide, any compatible mixture of bases such as those given as examples herein, and any other base and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia,
15 carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine, and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

The invention also relates to treatment methods employing
20 pharmaceutically acceptable prodrugs of the compounds of Formula (I). The term "prodrug" means a precursor 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
25 converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is not toxic, biologically intolerable, or otherwise biologically unsuitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

30 Examples of prodrugs include compounds having an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino, 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, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs 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 C₁₋₆alkyl amines and secondary di(C₁₋₆alkyl) amines. Secondary amines include 5- or 6-membered heterocycloalkyl or heteroaryl ring moieties. Examples of amides include those that are derived from ammonia, C₁₋₃alkyl primary amines, and di(C₁₋₂alkyl)amines. Examples of esters of the invention include C₁₋₇alkyl, C₅₋₇cycloalkyl, phenyl, and phenyl(C₁₋₆alkyl) esters. Preferred esters include methyl esters. Prodrugs may also be prepared by derivatizing free hydroxy groups using groups including hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, following procedures such as those outlined in *Adv. Drug Delivery Rev.* 1996, 19, 115. Carbamate derivatives of hydroxy and amino groups may also yield prodrugs. Carbonate derivatives, sulfonate esters, and sulfate esters of hydroxy groups may also provide prodrugs. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group may be an alkyl ester, optionally substituted with one or more ether, amine, or carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, is also useful to yield prodrugs. Prodrugs of this type may be prepared as described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphoramides. All of these prodrug moieties may incorporate groups including ether, amine, and carboxylic acid functionalities.

Pharmaceutically active metabolites may also be used in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I) or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini, et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan, et al., *J. Pharm. Sci.* 1997, 86 (7),

765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 224-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen, et al., eds., Harwood Academic Publishers, 1991).

5 The compounds of Formula (I) and their pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites (collectively, "agents") of the present invention are useful as histamine H₄ receptor modulators in the methods of the invention. The agents may be used in the inventive methods for the treatment or prevention of medical conditions,
10 diseases, or disorders mediated through modulation of the histamine H₄ receptor, such as those described herein. Agents according to the invention may therefore be used as an anti-inflammatory agents. Symptoms or disease states are intended to be included within the scope of "medical conditions, disorders, or diseases."

15 Accordingly, the invention relates to methods of using the pharmaceutical agents described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through histamine H₄ receptor activity, such as inflammation.

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

 Illustrative types of inflammation treatable with a histamine H₄ receptor-modulating agent according to the invention include inflammation due to any one
30 of a plurality of conditions such as allergy, asthma, chronic obstructed pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (including colitis, Crohn's disease, and ulcerative colitis), psoriasis, pruritis, itchy skin, atopic dermatitis, urticaria (hives), ocular

inflammation, conjunctivitis, nasal polyps, allergic rhinitis, nasal itch, scleroderma, autoimmune thyroid diseases, immune-mediated (also known as type 1) diabetes mellitus and lupus, which are characterized by excessive or prolonged inflammation at some stage of the disease. Other autoimmune diseases that lead to inflammation include Myasthenia gravis, autoimmune neuropathies, such as Guillain-Barré, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, such as Wegener's granulomatosis, Behcet's disease, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland, polymyositis, dermatomyositis, spondyloarthropathies, such as ankylosing spondylitis, and Sjogren's syndrome.

Pruritis with a histamine H₄ receptor-modulating agent according to the invention includes that which is a symptom of allergic cutaneous diseases (such as atopic dermatitis and hives) and other metabolic disorders (such as chronic renal failure, hepatic cholestasis, and diabetes mellitus).

In another preferred embodiment, an agent of the present invention is administered to treat allergy, asthma, autoimmune diseases, or pruritis.

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

In treatment methods according to the invention, an effective amount of at least one pharmaceutical 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 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 example of a dose is in the range of from about 0.001 to about 200 mg of 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, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

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

In addition, the agents of the invention may be used in combination with additional active compounds in the treatment of the above conditions. The additional compounds may be coadministered separately with an agent of Formula (I) or included with such an agent as an additional active ingredient in a pharmaceutical composition according to the invention. In an illustrative embodiment, additional active compounds are those that are known or discovered to be effective in the treatment of conditions, disorders, or diseases mediated by histamine H₄ receptor activity, such as another histamine H₄ receptor modulator

or a compound active against another target associated with the particular condition, disorder, or disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an agent according to the invention), decrease one or more side effects, or decrease the required dose of the agent according to the invention.

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.

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

A "pharmaceutically acceptable excipient" refers to a substance that is not toxic, biologically intolerable, or otherwise biologically unsuitable 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 pharmaceutical agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

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

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

For oral administration, the compounds 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 agents may be formulated to yield a dosage of, e.g., from about 0.05 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

Oral tablets may include the agent and any other active ingredients mixed
5 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,
10 and the like. Examples of liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are examples of 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
15 coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

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

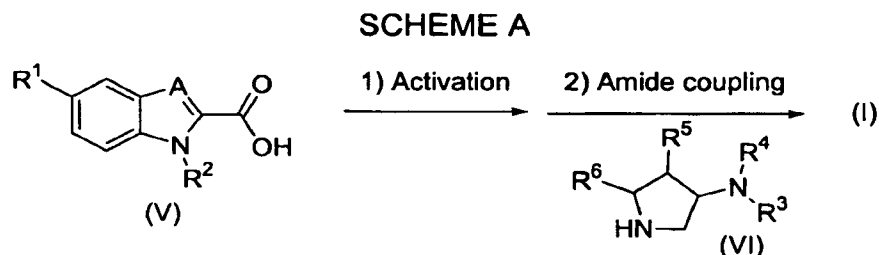
Liquids for oral administration may be in the form of suspensions,
25 solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil
30 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, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the agents of the invention
5 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
10 withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 $\mu\text{g}/\text{kg}/\text{minute}$ 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
15 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.

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

Examples of agents 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
25 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.
30 Unless otherwise specified, the variables are as defined above in reference to Formula (I).



Referring to Scheme A, compounds of Formula (I) are prepared by amide coupling procedures known to one skilled in the art. For example, acids (V) are coupled with amines (VI) directly, in the presence of an activating agent such as 1,1'-carbonyl-diimidazole (CDI), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium phosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide/1-hydroxybenzotriazole (EDC/HOBt), and the like.

Alternatively, acids (V) are activated as mixed anhydrides or acid chlorides, and then coupled with amines (VI) in the presence of a suitable base such as triethylamine (TEA), iPr₂NEt, pyridine, imidazole, or the like. Suitable amino protecting groups may be used in place of R³ and/or R⁴ and removed following the coupling.

Compounds prepared according to the schemes described above may be obtained as single enantiomers, diastereomers, or regioisomers, or as racemic mixtures or mixtures of enantiomers, diastereomers, or regioisomers. Where regioisomeric or diastereomeric mixtures are obtained, isomers may be separated using conventional methods such as chromatography or crystallization. Where racemic (1:1) and non-racemic (not 1:1) mixtures of enantiomers are obtained, single enantiomers may be isolated using conventional separation methods known to one skilled in the art. Particularly useful separation methods may include chiral chromatography, recrystallization, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

The following examples are provided to further illustrate aspects of the invention and various preferred embodiments.

EXAMPLES

Chemistry:

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.

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.

Thin-layer chromatography was performed using Merck silica gel 60 F₂₅₄ 2.5 cm x 7.5 cm 250 μm or 5.0 cm x 10.0 cm 250 μm pre-coated silica gel plates. Preparative thin-layer chromatography was performed using EM Science silica gel 60 F₂₅₄ 20 cm x 20 cm 0.5 mm pre-coated plates with a 20 cm x 4 cm concentrating zone.

Normal-phase flash column chromatography (FCC) was performed on silica gel (SiO₂) eluting with 2 M NH₃ in MeOH/DCM, unless otherwise noted.

Reversed-phase analytical HPLC was performed on a Hewlett Packard HPLC Series 1100, with a Phenomenex Luna C18 (5 μm, 4.6x150 mm) column. Detection was done at λ = 254 nm. The flow rate was 1 mL/min. The gradient was 10 to 99% CH₃CN/H₂O (0.05% trifluoroacetic acid (TFA)) over 5.0 min.

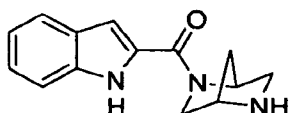
Reversed-phase preparative HPLC (preparative HPLC) was performed on a Shimadzu LC-8A equipped with a Gemini C18 column (5 μm, 21.2 x 180 mm). Detection was done at λ = 254 nm. The gradient was 10 to 100% acetonitrile/water (0.05% TFA) over 15 min at a flow rate of 25 mL/min.

Mass spectra (MS) were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

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).

Chemical names were generated using ChemDraw Version 6.0.2 (CambridgeSoft, Cambridge, MA).

5 Example 1: (S,S)-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-methanone hydrochloride salt.

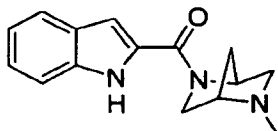


Step A: 1H-Indole-2-carbonyl chloride. To a suspension of indole-2-carboxylic acid (800 mg, 4.9 mmol) in CH₂Cl₂ was added oxalyl chloride (1.28 mL, 14.9 mmol) and N,N-dimethylformamide (DMF; 0.05 mL). After 1.5 h at 40 °C, the mixture was concentrated to give a yellow solid (874 mg, 98%), which was used without purification in subsequent reactions.

10 Step B: (S,S)-5-(1H-Indole-2-carbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester. To a 0 °C suspension of indole-2-carbonyl chloride (100 mg, 0.56 mmol) in CH₂Cl₂ was added a solution of TEA (235 µL, 1.67 mmol) and (S,S)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (156 mg, 0.84 mmol) in CH₂Cl₂. After 1.5 h at 0 °C, the mixture was diluted with saturated aqueous (satd. aq.) NaHCO₃ and extracted with CH₂Cl₂ (3x15 mL). The combined organic layers were washed with satd. aq. NaCl (20 mL), dried (Na₂SO₄), and concentrated to give a yellow liquid, which was purified by FCC to give a yellow solid (130 mg, 46%). ¹H NMR (CDCl₃): 9.37-9.17 (m, 1H), 7.70-7.64 (m, 1H), 7.47-7.41 (m, 1H), 7.35-7.28 (m, 1H), 7.19-7.10 (m, 1H), 6.86-6.78 (m, 1H), 5.13 (s, 1H), 4.77-4.50 (m, 1H), 4.02-3.80 (m, 1H), 3.80-3.39 (m, 2H), 2.08-1.88 (m, 2H), 1.54-1.35 (m, 9H).

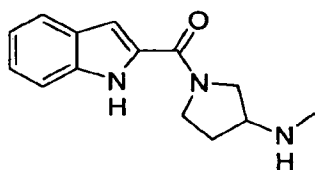
25 Step C. To a solution of (S,S)-5-(1H-indole-2-carbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (124 mg, 0.36 mmol) in formic acid was added 5.0 N HCl (75 µL, 1.82 mmol). After 1 h at rt, the solution was diluted with MeOH (30 mL) and concentrated to give a purple solid (87 mg, 99%). MS (ESI): mass calcd. for C₁₄H₁₅N₃O, 241.12; m/z found, 242.3 [M+H]⁺. ¹H NMR (MeOD): 7.67-7.63 (m, 1H), 7.49-7.44 (m, 1H), 7.28-7.22 (m, 1H), 7.12-7.05 (m, 1H), 7.01-6.97 (m, 1H), 5.49 (s, 1H), 5.41-5.02 (m, 1H), 4.58 (s, 1H), 4.28-3.39 (m, 4H), 3.33-3.29 (m, 1H), 2.32-2.21 (m, 1H), 2.13-2.04 (m, 1H).

Example 2: (S,S)-(1H-Indol-2-yl)-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-methanone.



To a solution of (S,S)-(2,5-diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-
 5 methanone hydrochloride (50 mg, 0.18 mmol), TEA (50 μ L, 0.36 mmol), and
 formaldehyde (6 μ L, 0.22 mmol) in dichloroethane (DCE)/MeOH (10:1, 3 mL) was
 added NaB(OAc)₃H (115 mg, 0.54 mmol). After 2 h at rt, the mixture was diluted
 with satd. aq. NaHCO₃ and extracted with CH₂Cl₂ (3x). The combined organic
 layers were washed with satd aq. NaCl, dried (Na₂SO₄), and concentrated to yield
 10 an orange solid (44 mg, 96%). MS (ESI): mass calcd. for C₁₅H₁₇N₃O, 255.14;
 m/z found, 256.4 [M+H]⁺. ¹H NMR (mixture of rotamers; CDCl₃): 10.34-10.08 (m,
 1H), 7.64-7.54 (m, 1H), 7.44-7.35 (m, 1H), 7.24-7.16 (m, 1H), 7.09-7.00 (m, 1H),
 6.80 (s, 0.5H), 6.67 (s, 0.5H), 4.99-4.86 (m, 1H), 4.05-3.95 (m, 0.7H), 3.84-3.77
 15 (m, 0.3H), 3.71-3.62 (m, 1H), 3.55-3.46 (m, 1H), 3.18-3.10 (m, 0.3H), 2.98-2.88
 (m, 0.7H), 2.82-2.69 (m, 1H), 2.46-2.31 (m, 3H), 1.98-1.88 (m, 1H), 1.79-1.70 (m,
 1H).

Example 3: (1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone trifluoroacetic acid salt.

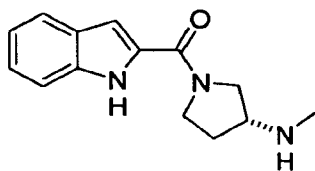


20 **Step A: [1-(1H-Indole-2-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester.** To a solution of indole-2-carboxylic acid (388 mg, 2.40 mmol) and
 methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester (401 mg, 2.00 mmol) in THF
 (16 mL) was added CDI (356 mg, 2.20 mmol). After 18 h at rt, the mixture was
 concentrated, diluted with CH₂Cl₂, washed with satd. aq. Na₂CO₃ and water, dried
 25 (Na₂SO₄), and concentrated. The residue was purified by FCC to give the title
 compound (565 mg, 69%). MS (ESI): mass calcd. for C₁₉H₂₅N₃O₃, 343.19; m/z
 found, 344 [M+H]⁺. ¹H NMR (CDCl₃): 9.73 (s, 1H), 7.67 (d, J = 8.0, 1H), 7.46 (dd,
 J = 8.3, 0.8, 1H), 7.29 (t, J = 8.2, 1H), 6.89 (d, J = 1.3, 1H), 4.89 (br s, 1H), 4.26-

3.49 (m, 4H), 2.85 (s, 3H), 2.36-1.96 (m, 2H), 1.76 (s, 1H), 1.49 (s, 9H). Anal. Calcd for C₁₉H₂₅N₃O₃: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.42; H, 7.55; N, 12.10.

Step B. A solution of [1-(1H-indole-2-carbonyl)-pyrrolidin-3-yl]-methyl-
 5 carbamic acid tert-butyl ester (0.500 g, 1.46 mmol) in CH₂Cl₂ (20 mL) was treated with TFA (8 mL). After 18 h at rt, the mixture was concentrated to give the title compound (520 mg, 99%). MS (ESI): mass calcd. for C₁₆H₁₇N₃O, 243.14; m/z found, 244.4 [M+H]⁺. MS (ESI): mass calcd. for C₁₄H₁₆N₃O, 243.43; m/z found, 244.3 [M+H]⁺. ¹H NMR (MeOD): 7.68-7.63 (m, 1H), 7.48-7.43 (m, 1H), 7.28-7.21
 10 (m, 1H), 7.11-7.05 (m, 1H), 7.05-7.00 (m, 1H), 4.44-3.76 (m, 5H), 2.85-2.74 (m, 3H), 2.67-2.08 (m, 2H).

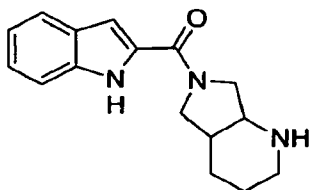
Example 4: (R)-(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone hydrochloride salt.



Step A: [1-(1H-Indole-2-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid
 15 tert-butyl ester. The title compound was prepared from (R)-methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester as described in Example 1, Step B, to give a yellow solid (30 mg, 16%). ¹H NMR (CDCl₃): 10.06-9.90 (m, 1H), 7.70-7.64 (m, 1H), 7.50-7.44 (m, 1H), 7.33-7.27 (m, 1H), 7.16-7.10 (m, 1H), 6.90-6.87 (m, 1H), 5.10-
 20 4.64 (m, 1H), 4.20-3.83 (m, 2.5H), 3.79-3.58 (m, 1.5 H), 2.89-2.80 (m, 1H), 2.31-2.00 (m, 2H), 1.55-1.44 (m, 9H).

Step B. The title compound was prepared as described in Example 1, Step C, to give a pale pink solid (21 mg, 99%). MS (ESI): mass calcd. for C₁₄H₁₆N₃O, 243.14; m/z found, 244.3 [M+H]⁺. ¹H NMR (MeOD): 7.68-7.63 (m,
 25 1H), 7.48-7.43 (m, 1H), 7.28-7.21 (m, 1H), 7.11-7.05 (m, 1H), 7.05-7.00 (m, 1H), 4.44-3.76 (m, 5H), 2.85-2.74 (m, 3H), 2.67-2.08 (m, 2H).

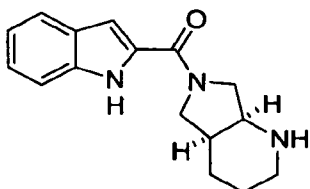
Example 5: cis-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone trifluoroacetic acid salt.



Step A: 6-(1H-Indole-2-carbonyl)-octahydro-pyrrolo[3,4-b]pyridine-1-carboxylic acid tert-butyl ester. To a solution of indole-2-carboxylic acid (67.4 mg, 0.42 mmol) in THF (2.8 mL) was added CDI (68.3 mg, 0.42 mmol) and cis-octahydro-pyrrolo[3,4-b]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.44 mmol). After 72 h at rt, the mixture was diluted with satd. aq. NaHCO₃ and extracted with CH₂Cl₂ (3x). The combined organic layers were washed with satd. aq. NaCl, dried (Na₂SO₄), and concentrated to give a yellow liquid, which was purified by FCC (EtOAc/hexanes) to give a yellow solid (50 mg, 44%). ¹H NMR (mixture of rotamers; CDCl₃): 7.79-7.72 (m, 1H), 7.72-7.64 (m, 1H), 7.49-7.39 (m, 1H), 7.34-7.29 (m, 1H), 7.25-7.19 (m, 1H), 7.17-7.09 (m, 1H), 6.94-6.89 (m, 1H), 6.89-6.85 (m, 1H), 4.20-3.95 (m, 2H), 3.95-3.86 (m, 0.5H), 3.86-3.69 (m, 2H), 3.69-3.59 (m, 0.5H), 2.91-2.71 (m, 1H), 2.40-2.30 (m, 0.4H), 2.30-2.19 (m, 0.6H), 1.89-1.67 (m, 2H), 1.54-1.42 (m, 9H), 1.41-1.21 (m, 2H).

Step B. The title compound was prepared as described in Example 1, Step C, to give a blue oil, which was purified by preparative HPLC to give the title compound (18 mg, 60%). MS (ESI): mass calcd. for C₁₆H₁₉N₃O, 269.15; m/z found, 270.4 [M+H]⁺. ¹H NMR (mixture of rotamers; DMSO): 11.78-11.69 (m, 1H), 7.68 (s, 1H), 7.47-7.42 (m, 1H), 7.22-7.16 (m, 1H), 7.01-6.97 (m, 0.5H), 6.90-6.87 (m, 0.5H), 3.94-3.76 (m, 2H), 3.70-3.42 (m, 3H), 2.89-2.77 (m, 1H), 2.38-2.17 (m, 1.5 H), 1.80-1.47 (m, 3.5 H), 1.42-1.32 (m, 1H).

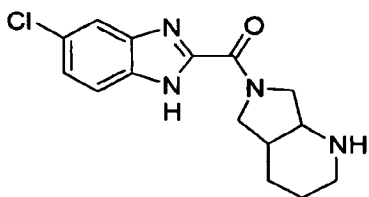
Example 6: (S,S)-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone trifluoroacetic acid salt.



The title compound was prepared from commercially available (S,S)-octahydro-pyrrolo[3,4-b]pyridine (Haorui Pharma-Chem, Inc., Batch #050312, 95% enantiomeric excess (ee)) as described in Example 5. The crude material

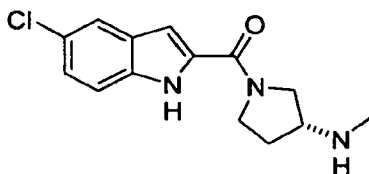
was purified by preparative HPLC. MS (ESI): mass calcd. for $C_{16}H_{19}N_3O$, 269.15; m/z found, 270.4 $[M+H]^+$. 1H NMR (mixture of rotamers; DMSO): 11.78-11.69 (m, 1H), 7.68 (s, 1H), 7.47-7.42 (m, 1H), 7.22-7.16 (m, 1H), 7.01-6.97 (m, 0.5H), 6.90-6.87 (m, 0.5H), 3.94-3.76 (m, 2H), 3.70-3.42 (m, 3H), 2.89-2.77 (m, 1H), 2.38-2.17 (m, 1.5 H), 1.80-1.47 (m, 3.5 H), 1.42-1.32 (m, 1H).

Example 7: cis-(5-Chloro-1H-benzoimidazol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone.



To a suspension of 5-chloro-2-trichloromethyl-1H-benzimidazole (30 mg, 0.11 mmol) and K_2CO_3 (46 mg, 0.33 mmol) in CH_3CN/H_2O (10:1, 3 mL) was added cis-octahydro-pyrrolo[3,4-b]pyridine (28 mg, 0.22 mmol). After 1 h at 100 °C, the mixture was filtered and extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4) and concentrated to give a yellow oil, which was purified by FCC to give a brown solid (14 mg, 40%). MS (ESI): mass calcd. for $C_{15}H_{17}ClN_4O$, 304.11; m/z found, 305.4 $[M+H]^+$. 1H NMR (mixture of rotamers; MeOD): 7.70-7.58 (m, 2H), 7.35-7.25 (m, 1H), 4.43-4.28 (m, 0.6H), 4.19-4.09 (m, 0.6H), 3.77-3.69 (m, 1H), 3.46-3.40 (m, 0.3H), 3.38-3.33 (m, 0.3H), 3.33-3.28 (m, 2H), 3.04-2.82 (m, 1.5H), 2.71-2.53 (m, 1H), 2.50-2.31 (m, 1.5H), 1.95-1.43 (m, 4H).

Example 8: (R)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.

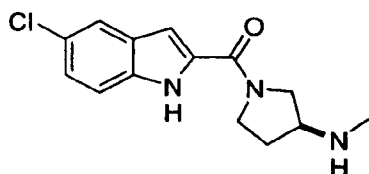


Step A: 5-Chloroindole-2-carbonyl chloride. The title compound was prepared from 5-chloroindole-2-carboxylic acid as described in Example 1, Step A, to give a brown solid (810 mg, 98%), which was used without purification in subsequent reactions.

Step B. The title compound was prepared from (R)-methyl-pyrrolidin-3-yl-amine as in Example 1, Step B, to give a pale yellow solid, which was purified by

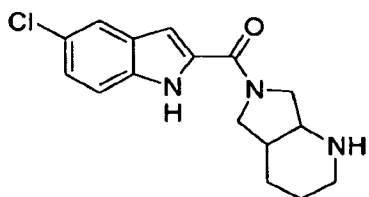
FCC to give a yellow solid (26 mg, 24%). MS (ESI): mass calcd. for $C_{14}H_{16}ClN_3O$, 277.10; m/z found, 278.3 $[M+H]^+$. 1H NMR ($CDCl_3$): 10.08-9.85 (m, 1H), 7.66-7.58 (m, 1H), 7.42-7.35 (m, 1H), 7.25-7.19 (m, 1H), 6.82-6.76 (m, 1H), 4.11-3.98 (m, 1H), 3.97-3.84 (m, 1.6 H), 3.83-3.73 (m, 0.4 H), 3.72-3.59 (m, 1H), 3.50-3.40 (m, 0.5 H), 3.40-3.33 (m, 0.5 H), 2.29-2.12 (m, 1H), 2.07-1.93 (m, 0.5 H), 1.90-1.78 (m, 0.5 H), 1.46-1.10 (m, 1H).

Example 9: (S)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.



The title compound was prepared from (S)-methyl-pyrrolidin-3-yl-amine as described in Example 7, Step B, to give a yellow solid (48 mg, 44%). MS (ESI): mass calcd. for $C_{14}H_{16}ClN_3O$, 277.10; m/z found, 278.3 $[M+H]^+$. 1H NMR (mixture of rotamers; $CDCl_3$): 10.02-9.74 (m, 1H), 7.62 (s, 1H), 7.41-7.35 (m, 1H), 7.25-7.20 (m, 1H), 6.80 (s, 1H), 4.12-3.99 (m, 1.5H), 3.98-3.84 (m, 0.5H), 3.83-3.73 (m, 1H), 3.72-3.57 (m, 1H), 3.49-3.40 (m, 0.4H), 3.40-3.28 (m, 0.6H), 2.54-2.45 (m, 3H), 2.28-2.12 (m, 0.6H), 2.06-1.93 (m, 0.4H), 1.91-1.78 (m, 1H), 1.55-1.30 (m, 1H).

Example 10: cis-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone.



Step A: 6-(5-Chloro-1H-indole-2-carbonyl)-octahydro-pyrrolo[3,4-b]pyridine-1-carboxylic acid tert-butyl ester. The title compound (50 mg, 45%) was prepared as in Example 1, Step B. 1H NMR (mixture of rotamers; DMSO): 7.69-7.58 (m, 1H), 7.46-7.34 (m, 1H), 7.26-7.20 (m, 1H), 6.83 (s, 0.5H), 6.79 (s, 0.5H), 5.07-4.63 (m, 1H), 4.18-3.85 (m, 2.5H), 3.84-3.78 (m, 0.5H), 3.77-3.69 (m, 1.5H), 3.68-3.59 (m, 0.5H), 2.91-2.72 (m, 1H), 2.41-2.20 (m, 1H), 1.93-1.62 (m, 2H), 1.59-1.43 (m, 9H), 1.42-1.27 (m, 2H), 0.98-0.73 (m, 1H).

Step B. The title compound was prepared as described in Example 1, Step C, to give a pale yellow solid, which was purified by preparative HPLC (18 mg, 60%). The resulting trifluoroacetic acid salt was dissolved in satd. aq. NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated to give the title compound. MS (ESI): mass calcd. for C₁₆H₁₈ClN₃O, 303.11; m/z found, 304.4 [M+H]⁺. ¹H NMR (mixture of rotamers; DMSO): 11.78-11.69 (m, 1H), 7.68 (s, 1H), 7.47-7.42 (m, 1H), 7.22-7.16 (m, 1H), 7.01-6.97 (m, 0.5H), 6.90-6.87 (m, 0.5H), 3.94-3.76 (m, 2H), 3.70-3.42 (m, 3H), 2.89-2.77 (m, 1H), 2.38-2.17 (m, 1.5H), 1.80-1.47 (m, 3.5H), 1.42-1.32 (m, 1H).

Racemic 6-(5-chloro-1H-indole-2-carbonyl)-octahydro-pyrrolo[3,4-b]pyridine-1-carboxylic acid tert-butyl ester was separated into enantiomers by supercritical fluid chromatography (SFC) on a Jasco SFC equipped with an AS-H column, and using an isocratic gradient of 15% MeOH/0.2% TEA/85% CO_{2(l)} at a rate of 2 mL/min at 25 °C and 100 bar. The individual enantiomers were deprotected as in Example 1, Step C, to provide Examples 11 and 12, each greater than 99% ee.

Example 11: (R,R)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.

MS (ESI): mass calcd. for C₁₆H₁₈ClN₃O, 303.11; m/z found, 304.4 [M+H]⁺. ¹H NMR (mixture of rotamers; DMSO): 7.68-7.59 (m, 1H), 7.47-7.41 (m, 1H), 7.24-7.17 (m, 1H), 7.07 (s, 0.5H), 6.96 (s, 0.5H), 4.34-4.23 (m, 0.5H), 4.21-4.11 (m, 1H), 4.05-3.83 (m, 3H), 3.72-3.61 (m, 0.5H), 3.41-3.33 (m, 1H), 3.25-3.15 (m, 0.6H), 3.13-2.98 (m, 1.4H), 2.96-2.76 (m, 1H), 2.00-1.76 (m, 4H).

Example 12: (S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.

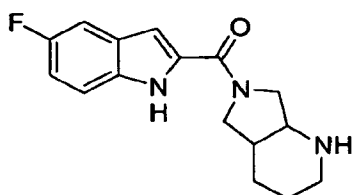
MS (ESI): mass calcd. for C₁₆H₁₈ClN₃O, 303.11; m/z found, 304.4 [M+H]⁺. ¹H NMR (mixture of rotamers; DMSO): 7.68-7.59 (m, 1H), 7.47-7.41 (m, 1H), 7.24-7.17 (m, 1H), 7.07 (s, 0.5H), 6.96 (s, 0.5H), 4.34-4.23 (m, 0.5H), 4.21-4.11 (m, 1H), 4.05-3.83 (m, 3H), 3.72-3.61 (m, 0.5H), 3.41-3.33 (m, 1H), 3.25-3.15 (m, 0.6H), 3.13-2.98 (m, 1.4H), 2.96-2.76 (m, 1H), 2.00-1.76 (m, 4H).

Example 12A: (S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone.

The title compound was prepared from commercially available (S,S)-octahydro-pyrrolo[3,4-b]pyridine (Haorui Pharma-Chem, Inc., Batch #050312, 95% ee) as described in Example 6.

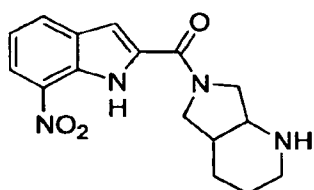
5 The compounds in Examples 13-31 were prepared using methods analogous to those described in the preceding examples.

Example 13: cis-(5-Fluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.



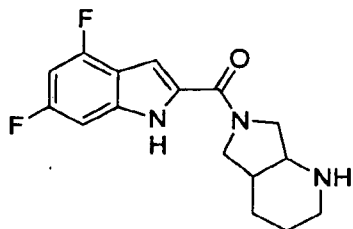
10 MS (ESI): mass calcd. for $C_{16}H_{18}FN_3O$, 287.14; m/z found, 288.4 $[M+H]^+$.
 1H NMR (mixture of rotamers; DMSO): 11.80-11.69 (m, 1H), 9.96-9.76 (m, 1H), 8.87-8.63 (m, 1H), 7.51-7.33 (m, 1H), 7.12-7.04 (m, 1H), 7.04-6.99 (m, 0.7H), 6.95-6.90 (m, 0.3H), 4.23-4.14 (m, 0.4H), 4.07-3.96 (m, 1H), 3.93-3.83 (m, 1.6H), 3.82-3.67 (m, 2H), 3.23-3.11 (m, 1H), 2.97-2.82 (m, 1H), 2.82-2.71 (m, 0.7H),
 15 2.71-2.61 (m, 0.3H), 1.87-1.58 (m, 4H).

Example 14: cis-(7-Nitro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.



20 MS (ESI): mass calcd. for $C_{16}H_{18}N_4O_3$, 314.14; m/z found, 315.4 $[M+H]^+$.
 1H NMR (mixture of rotamers; DMSO): 11.00-10.88 (m, 1H), 9.79-9.59 (m, 1H), 8.96-8.72 (m, 1H), 8.31-8.17 (m, 2H), 7.42-7.31 (m, 2H), 4.24-4.15 (m, 0.4H), 4.03-3.94 (m, 1H), 3.93-3.85 (m, 1.6H), 3.85-3.71 (m, 1.6H), 3.64-3.51 (m, 0.4H), 3.26-3.12 (m, 1H), 2.99-2.85 (m, 1H), 2.83-2.73 (m, 0.6H), 2.72-2.63 (m, 0.4H), 1.88-1.58 (m, 4H).

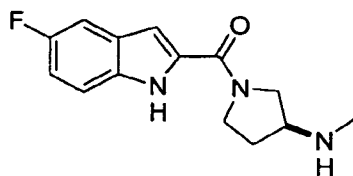
25 Example 15: cis-(4,6-Difluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.



MS (ESI): mass calcd. for $C_{16}H_{17}F_2N_3O$, 305.13; m/z found, 306.4 $[M+H]^+$.

1H NMR (mixture of rotamers; DMSO): 9.78-9.67 (m, 1H), 8.82-8.67 (m, 1H), 7.12-7.08 (m, 0.6H), 7.08-7.03 (m, 1H), 7.03-6.99 (m, 0.4H), 6.97-6.88 (m, 1H), 4.27-4.18 (m, 0.4H), 4.09-3.97 (m, 1H), 3.94-3.83 (m, 1.6H), 3.82-3.66 (m, 1.6H), 3.60-3.50 (m, 0.4H), 3.24-3.12 (m, 1H), 2.98-2.82 (m, 1H), 2.81-2.72 (m, 0.6H), 2.70-2.59 (m, 0.4H), 1.87-1.59 (m, 4H).

Example 16: (S)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.

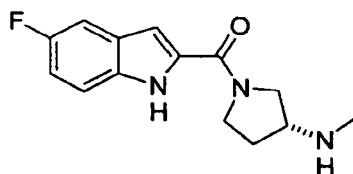


10

MS (ESI): mass calcd. for $C_{14}H_{16}FN_3O$, 261.13; m/z found, 262.4 $[M+H]^+$.

1H NMR (MeOD): 7.48-7.39 (m, 1H), 7.35-7.27 (m, 1H), 7.07-6.99 (m, 1H), 6.99-6.94 (m, 1H), 4.18-4.01 (m, 1H), 4.00-3.58 (m, 3H), 3.55-3.42 (m, 1H), 2.58-2.42 (m, 3H), 2.40-2.17 (m, 1H), 2.13-2.02 (m, 0.5H), 1.99-1.85 (m, 0.5H).

Example 17: (R)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.

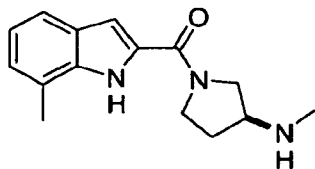


20

MS (ESI): mass calcd. for $C_{14}H_{16}FN_3O$, 261.13; m/z found, 262.4 $[M+H]^+$.

1H NMR (MeOD): 7.48-7.39 (m, 1H), 7.35-7.27 (m, 1H), 7.07-6.99 (m, 1H), 6.99-6.94 (m, 1H), 4.18-4.01 (m, 1H), 4.00-3.58 (m, 3H), 3.55-3.42 (m, 1H), 2.58-2.42 (m, 3H), 2.40-2.17 (m, 1H), 2.13-2.02 (m, 0.5H), 1.99-1.85 (m, 0.5H).

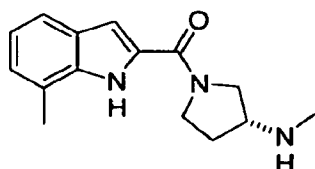
Example 18: (S)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone.



MS (ESI): mass calcd. for $C_{15}H_{19}N_3O$, 257.15; m/z found, 258.4 $[M+H]^+$.

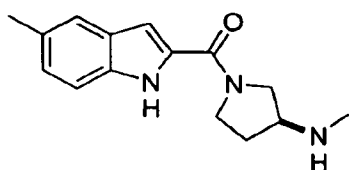
1H NMR (MeOD): 7.50-7.43 (m, 1H), 7.05-6.95 (m, 3H), 4.12-3.98 (m, 1H), 3.96-3.75 (m, 1.5H), 3.73-3.59 (m, 1H), 3.57-3.48 (m, 0.5H), 3.36-3.33 (m, 1H), 2.52 (s, 3H), 2.43-2.37 (m, 3H), 2.28-2.13 (m, 1H), 2.02-1.90 (m, 0.5H), 1.90-1.77 (m, 0.5H).

Example 19: (R)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone.



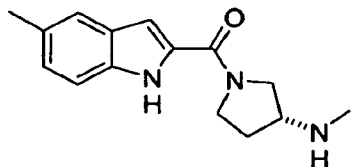
10 MS (ESI): mass calcd. for $C_{15}H_{19}N_3O$, 257.15; m/z found, 258.4 $[M+H]^+$.
 1H NMR (MeOD): 7.47 (d, $J = 7.5$, 1H), 7.05-6.94 (m, 2H), 6.91 (s, 1H), 3.99-3.85 (m, 1H), 3.82-3.67 (m, 1.5H), 3.63-3.50 (m, 1H), 3.47-3.38 (m, 0.5H), 3.23-3.09 (m, 1H), 2.50 (s, 3H), 2.38-2.28 (m, 3H), 2.15-2.00 (m, 1H), 1.87-1.77 (m, 0.5H), 1.76-1.65 (m, 0.5H).

15 Example 20: (S)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone.



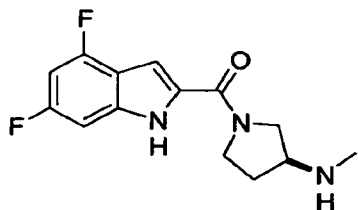
20 MS (ESI): mass calcd. for $C_{15}H_{19}N_3O$, 257.15; m/z found, 258.4 $[M+H]^+$. 1H NMR (MeOD): 7.40 (s, 1H), 7.37-7.31 (m, 1H), 7.11-7.02 (m, 1H), 6.85 (s, 1H), 4.06-3.91 (m, 1H), 3.89-3.71 (m, 1.5H), 3.69-3.55 (m, 1H), 3.53-3.43 (m, 0.5H), 3.34-3.17 (m, 1H), 2.46-2.31 (m, 6H), 2.25-2.04 (m, 1H), 1.97-1.84 (m, 0.5H), 1.83-1.71 (m, 0.5H).

Example 21: (R)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone.



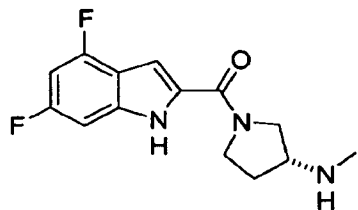
MS (ESI): mass calcd. for $C_{15}H_{19}N_3O$, 257.15; m/z found, 258.4 $[M+H]^+$. 1H NMR (MeOD): 7.40 (s, 1H), 7.37-7.31 (m, 1H), 7.11-7.02 (m, 1H), 6.85 (s, 1H), 4.06-3.91 (m, 1H), 3.89-3.71 (m, 1.5H), 3.69-3.55 (m, 1H), 3.53-3.43 (m, 0.5H), 3.34-3.17 (m, 1H), 2.46-2.31 (m, 6H), 2.25-2.04 (m, 1H), 1.97-1.84 (m, 0.5H), 1.83-1.71 (m, 0.5H).

Example 22: (S)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.



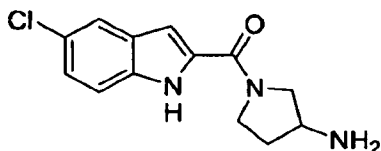
MS (ESI): mass calcd. for $C_{14}H_{15}F_2N_3O$, 279.12; m/z found, 280.4 $[M+H]^+$. 1H NMR (MeOD): 7.04-6.96 (m, 2H), 6.69-6.61 (m, 1H), 4.12-3.97 (m, 1H), 3.96-3.87 (m, 0.5H), 3.86-3.76 (m, 1H), 3.72-3.60 (m, 1H), 3.58-3.50 (m, 0.5H), 3.43-3.35 (m, 0.5H), 3.34-3.28 (m, 0.5H), 2.45-2.36 (m, 3H), 2.31-2.13 (m, 1H), 2.05-1.94 (m, 0.5H), 1.92-1.80 (m, 0.5H).

Example 23: (R)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone.



MS (ESI): mass calcd. for $C_{14}H_{15}F_2N_3O$, 279.12; m/z found, 280.4 $[M+H]^+$. 1H NMR (MeOD): 7.04-6.96 (m, 2H), 6.69-6.61 (m, 1H), 4.12-3.97 (m, 1H), 3.96-3.87 (m, 0.5H), 3.86-3.76 (m, 1H), 3.72-3.60 (m, 1H), 3.58-3.50 (m, 0.5H), 3.43-3.35 (m, 0.5H), 3.34-3.28 (m, 0.5H), 2.45-2.36 (m, 3H), 2.31-2.13 (m, 1H), 2.05-1.94 (m, 0.5H), 1.92-1.80 (m, 0.5H).

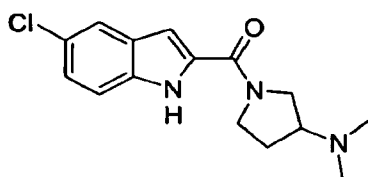
Example 24: (3-Amino-pyrrolidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone hydrochloride salt.



MS (ESI): mass calcd. for $C_{13}H_{14}ClN_3O$, 263.08; m/z found, 264.3 $[M+H]^+$.

1H NMR (MeOD): 7.68-7.63 (m, 1H), 7.47-7.41 (m, 1H), 7.25-7.18 (m, 1H), 7.06-6.91 (m, 1H), 4.36-3.75 (m, 5H), 2.62-2.37 (m, 1H), 2.33-2.07 (m, 1H).

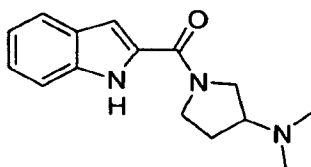
5 Example 25: (5-Chloro-1H-indol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone.



MS (ESI): mass calcd. for $C_{15}H_{18}ClN_3O$, 291.11; m/z found, 292.3 $[M+H]^+$.

10 1H NMR (DMSO): 7.70-7.65 (m, 1H), 7.46 (s, 1H), 7.44-7.43 (m, 1H), 7.22-7.17 (m, 1H), 7.01 (s, 1H), 6.94 (s, 1H), 4.07-3.94 (m, 2H), 3.86-3.69 (m, 1H), 3.59-3.44 (m, 1H), 3.36-3.24 (m, 2H), 3.19-3.14 (m, 1H), 2.22-2.18 (m, 6H).

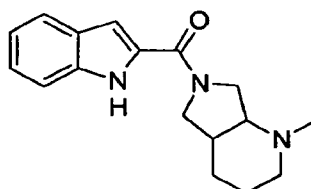
Example 26: (3-Dimethylamino-pyrrolidin-1-yl)-(1H-indol-2-yl)-methanone.



MS (ESI): mass calcd. for $C_{16}H_{19}N_3O$, 257.15; m/z found, 258.4 $[M+H]^+$.

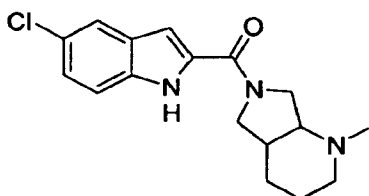
15 1H NMR ($CDCl_3$): 9.62 (br s, 1H), 7.65 (d, $J = 8.5$, 1H), 7.43 (d, $J = 9.0$, 1H), 7.28 (d, $J = 8.2$, 1H), 7.12 (t, $J = 8.0$, 1H), 6.84 (br s, 1H), 5.5-5.35 (m, 1H), 3.33 (br s, 3H), 2.92 (m, 1H), 2.86-2.77 (m, 1H), 2.65-2.55 (m, 1H), 2.37 (s, 3H), 2.35-2.26 (m, 2H), 1.94 (br s, 1H).

20 Example 27: cis-(1H-Indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone.



MS (ESI): mass calcd. for $C_{17}H_{21}N_3O$, 283.17; m/z found, 284.4 $[M+H]^+$. 1H NMR (mixture of rotamers; $CDCl_3$): 9.49-9.38 (m, 1H), 7.71-7.63 (m, 1H), 7.47-7.41 (m, 1H), 7.32-7.27 (m, 1H), 7.17-7.10 (m, 1H), 6.93-6.89 (m, 0.6H), 6.88-6.85 (m, 0.4H), 4.15-4.10 (m, 0.4H), 4.08-4.02 (m, 0.6H), 4.00-3.89 (m, 1.3H), 3.86-3.73 (m, 1H), 3.67-3.59 (m, 0.7H), 2.92-2.87 (m, 0.4H), 2.85-2.72 (m, 1H), 2.72-2.66 (m, 0.6H), 2.56-2.46 (m, 0.7H), 2.45-2.37 (m, 0.3H), 2.35-2.27 (m, 3H), 2.25-2.12 (m, 1H), 1.92-1.54 (m, 5H).

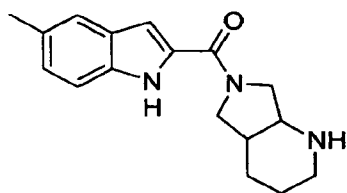
Example 28: cis-(5-Chloro-1H-indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone.



MS (ESI): mass calcd. for $C_{17}H_{20}ClN_3O$, 317.13; m/z found, 318.4 $[M+H]^+$.

1H NMR (mixture of rotamers; $CDCl_3$): 9.95-9.79 (m, 1H), 7.66-7.58 (m, 1H), 7.42-7.34 (m, 1H), 7.25-7.19 (m, 1H), 6.86-6.81 (m, 0.6H), 6.81-6.77 (m, 0.4H), 4.14-4.07 (m, 0.7H), 4.07-4.04 (m, 0.3H), 4.00-3.86 (m, 1.4H), 3.85-3.72 (m, 1H), 3.67-3.59 (m, 0.6H), 2.91-2.86 (m, 0.4H), 2.85-2.73 (m, 1H), 2.71-2.65 (m, 0.6H), 2.56-2.38 (m, 1H), 2.35-2.27 (m, 3H), 2.25-2.11 (m, 1H), 1.92-1.53 (m, 5H).

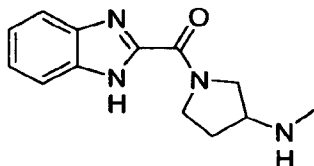
Example 29: cis-(5-Methyl-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone hydrochloride salt.



MS (ESI): mass calcd. for $C_{17}H_{21}N_3O$, 283.17; m/z found, 284.4 $[M+H]^+$. 1H

NMR (DMSO): 7.54 (s, 1H), 7.46-7.42 (m, 1H), 7.21-7.13 (m, 1H), 6.91 (s, 1H), 4.19-4.09 (m, 0.4H), 4.03-3.91 (m, 1H), 3.86-3.75 (m, 1.6H), 3.73-3.67 (m, 2H), 3.29-3.11 (m, 1H), 2.91-2.79 (m, 1H), 2.74-2.64 (m, 0.7H), 2.52-2.42 (m, 0.3H), 1.84-1.51 (m, 4H).

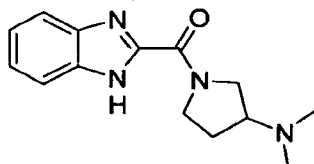
Example 30: (1H-Benzoimidazol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone hydrochloride salt.



MS (ESI): mass calcd. for C₁₃H₁₆N₄O, 244.13; m/z found, 245.3 [M+H]⁺.

5 ¹H NMR (MeOD): 5-8.15 (m, 1H), 7.92-7.78 (m, 1H), 7.70-7.52 (m, 1H), 4.53-4.25 (m, 1H), 4.24-3.38 (m, 4H), 2.91-2.69 (m, 3H), 2.67-2.49 (m, 0.7H), 2.48-2.21 (m, 1H), 2.19-2.07 (m, 0.3H).

Example 31: (1H-Benzoimidazol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone.



10

¹H NMR (mixture of rotamers; CDCl₃): 7.92-7.35 (m, 2H), 7.25 (m, 2H), 6.70-6.55 (m, 0.5H), 5.45-5.30 (m, 0.5H), 3.69 (s, 1H), 3.16 (s, 2H), 2.90-2.75 (m, 2H), 2.70-2.52 (m, 1H), 2.40-2.20 (m, 6H), 1.95-1.80 (m, 1H).

15 Biological Testing:

Binding Assay on Recombinant Human Histamine H₄ Receptor

SK-N-MC cells or COS7 cells were transiently transfected with pH4R and grown in 150 cm² tissue culture dishes. Cells were washed with saline solution, scraped with a cell scraper and collected by centrifugation (1000 rpm, 5 min).

20 Cell membranes were prepared by homogenization of the cell pellet in 20 mM Tris-HCl with a polytron tissue homogenizer for 10 sec at high speed.

Homogenate was centrifuged at 1000 rpm for 5 min at 4 °C. The supernatant was then collected and centrifuged at 20,000 x g for 25 min at 4 °C. The final

25 pellet was resuspended in 50 mM Tris-HCl. Cell membranes were incubated with ³H-histamine (5–70 nM) in the presence or absence of excess histamine (10,000 nM). Incubation occurred at room temperature for 45 min. Membranes were harvested by rapid filtration over Whatman GF/C filters and washed 4 times with ice-cold 50 mM Tris HCl. Filters were then dried, mixed with scintillant and

counted for radioactivity. SK-N-MC or COS7 cells expressing human histamine H₄ receptor were used to measure the affinity of binding of other compounds and their ability to displace ³H-ligand binding by incubating the above-described reaction in the presence of various concentrations of inhibitor or compound to be tested. For competition binding studies using ³H-histamine, K_i values were calculated, based on an experimentally determined K_D value of 5 nM and a ligand concentration of 5 nM, according to Y.-C. Cheng and W.H. Prusoff (*Biochem. Pharmacol.* 1973, 22(23):3099–3108): $K_i = (IC_{50}) / (1 + ([L] / (K_D)))$. Results for the compounds tested in this assay are presented in Table 1 as an average (mean) of results obtained. Where activity is shown as greater than (>) a particular value, the value is the solubility limit of the compound in the assay medium or the highest concentration tested in the assay.

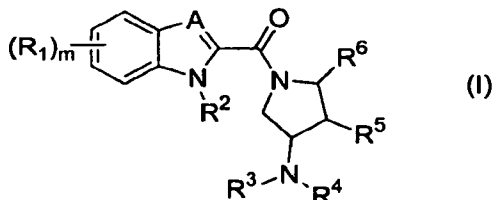
Table 1.

EX	K _i (nM)		EX	K _i (nM)
1	1110		16	680
2	3200		17	38
3	430		18	>10000
4	160		19	150
5	40		20	>10000
6	>10000		21	280
7	20		22	>5000
8	53		23	680
9	540		24	190
10	8		25	1160
11	27		26	9000
12	>10000		27	560
12A	180		28	240
13	28		29	41
14	>10000		30	2000
15	220		31	8200

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 that is a compound of Formula (I):



wherein:

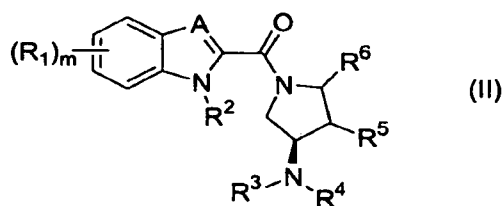
- 5 A is CH or N;
 each R¹ is independently Cl, Br, methyl, ethyl, NO₂, or CF₃;
 m is 0, 1, or 2;
 R² is H;
 R³ is H, methyl, or ethyl; and
- 10 1) R⁴ is H, methyl, or ethyl; one of R⁵ and R⁶ is H, methyl, or ethyl and the other is H; or
 2) R⁴ and R⁵ together form -(CH₂)₃-; and R⁶ is H; or
 3) R⁴ and R⁶ together form -CH₂-; and R⁵ is H;
 a pharmaceutically acceptable salt of compound of Formula (I), a
- 15 pharmaceutically acceptable prodrug of compound of Formula (I), or a
 pharmaceutically active metabolite of compound of Formula (I).
2. A chemical entity as defined in claim 1, wherein A is CH.
- 20 3. A chemical entity as defined in claim 1, wherein A is N.
4. A chemical entity as defined in claim 1, wherein R¹ is Cl.
5. A chemical entity as defined in claim 1, wherein m is 0 or 1.
- 25 6. A chemical entity as defined in claim 1, wherein R³ is H or methyl.
7. A chemical entity as defined in claim 1, wherein R⁴ is methyl, R⁵ is H, and R⁶ is H.

30

8. A chemical entity as defined in claim 1, wherein R⁴ and R⁵ together form -(CH₂)₃-, and R⁶ is H.

9. A chemical entity as defined in claim 1, wherein R⁴ and R⁶ together form -CH₂-, and R⁵ is H.

10. A chemical entity as defined in claim 1, wherein said Formula (I) is Formula (II):



10

11. A chemical entity selected from:

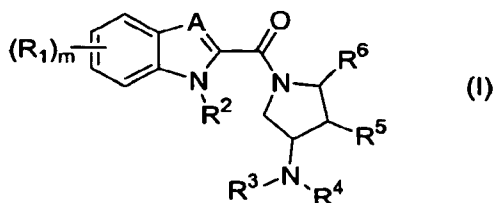
- (S,S)-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-methanone;
- (S,S)-(1H-Indol-2-yl)-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-methanone;
- (1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
- (R)-(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
- cis-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- (S,S)-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- cis-(5-Chloro-1H-benzoimidazol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- (R)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
- (S)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
- cis-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- (R,R)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- (S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- cis-(5-Fluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- cis-(7-Nitro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- cis-(4,6-Difluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
- (S)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
- (R)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

(S)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(S)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(3-Amino-pyrrolidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone;
(5-Chloro-1H-indol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone;
(3-Dimethylamino-pyrrolidin-1-yl)-(1H-indol-2-yl)-methanone;
cis-(1H-Indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Chloro-1H-indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-
methanone;
cis-(5-Methyl-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone; and
pharmaceutically acceptable salts thereof.

12. A chemical entity as defined in claim 1, wherein said chemical entity is a
compound of Formula (I) or a pharmaceutically acceptable salt of said compound
5 of Formula (I).

13. A chemical entity as defined in claim 10, wherein said chemical entity is a
compound of Formula (II) or a pharmaceutically acceptable salt of said compound
10 of Formula (II).

14. 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 of an agent selected from compounds of
15 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);



wherein:

A is CH or N;

each R¹ is independently Cl, Br, methyl, ethyl, NO₂, or CF₃;

5 m is 0, 1, or 2;

R² is H;

R³ is H, methyl, or ethyl; and

1) R⁴ is H, methyl, or ethyl; one of R⁵ and R⁶ is H, methyl, or ethyl and the other is H; or

10 2) R⁴ and R⁵ together form $-(CH_2)_3-$; and R⁶ is H; or

3) R⁴ and R⁶ together form $-CH_2-$; and R⁵ is H.

15. A pharmaceutical composition as recited in claim 14, wherein said Formula (I) is Formula (II).

15

16. A pharmaceutical composition according to claim 14, wherein said agent is selected from:

(S,S)-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-methanone;

(S,S)-(1H-Indol-2-yl)-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-methanone;

(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

(R)-(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

cis-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(S,S)-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

cis-(5-Chloro-1H-benzoimidazol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(R)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

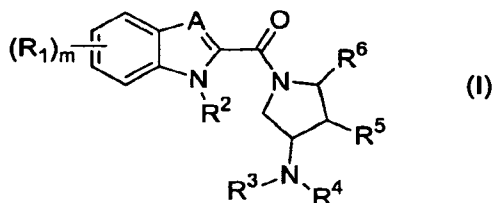
(S)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

cis-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(R,R)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Fluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(7-Nitro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(4,6-Difluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(S)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(S)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(3-Amino-pyrrolidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone;
(5-Chloro-1H-indol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone;
(3-Dimethylamino-pyrrolidin-1-yl)-(1H-indol-2-yl)-methanone;
cis-(1H-Indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Chloro-1H-indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-
methanone;
cis-(5-Methyl-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone; and
pharmaceutically acceptable salts thereof.

17. A method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by histamine H₄ receptor activity,
- 5 comprising administering to a subject in need of such treatment an effective amount of at least one agent 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):



wherein:

A is CH or N;

each R¹ is independently Cl, Br, methyl, ethyl, NO₂, or CF₃;

5 m is 0, 1, or 2;

R² is H;

R³ is H, methyl, or ethyl; and

1) R⁴ is H, methyl, or ethyl; one of R⁵ and R⁶ is H, methyl, or ethyl and the other is H; or

10 2) R⁴ and R⁵ together form $-(CH_2)_3-$; and R⁶ is H; or

3) R⁴ and R⁶ together form $-CH_2-$; and R⁵ is H.

18. A method as recited in claim 17, wherein said Formula (I) is Formula (II).

15 19. A method according to claim 17, wherein said agent is selected from:

(S,S)-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-methanone;

(S,S)-(1H-Indol-2-yl)-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-methanone;

(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

(R)-(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

cis-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(S,S)-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

cis-(5-Chloro-1H-benzoimidazol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(R)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

(S)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;

cis-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(R,R)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

(S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

cis-(5-Fluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

cis-(7-Nitro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(4,6-Difluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(S)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(S)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(3-Amino-pyrrolidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone;
(5-Chloro-1H-indol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone;
(3-Dimethylamino-pyrrolidin-1-yl)-(1H-indol-2-yl)-methanone;
cis-(1H-Indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Chloro-1H-indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-
methanone;
cis-(5-Methyl-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone; and
pharmaceutically acceptable salts thereof.

20. A method according to claim 17, wherein the disease, disorder, or medical condition is inflammation.

5

21. A method according to claim 17, wherein the disease, disorder, or medical condition is selected from the group consisting of: inflammatory disorders, allergic disorders, dermatological disorders, autoimmune disease, lymphatic disorders, and immunodeficiency disorders.

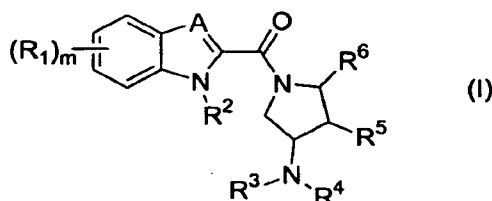
10

22. A method according to claim 17, wherein the disease, disorder, or medical condition is selected from: allergy, asthma, chronic obstructed pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, colitis, Crohn's disease, ulcerative colitis, psoriasis,

pruritis, itchy skin, atopic dermatitis, urticaria, hives, ocular inflammation, conjunctivitis, nasal polyps, allergic rhinitis, nasal itch, scleroderma, autoimmune thyroid diseases, immune-mediated diabetes mellitus, lupus, Myasthenia gravis, autoimmune neuropathies, Guillain-Barré, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, autoimmune oophoritis, autoimmune orchitis, autoimmune disease of the adrenal gland, polymyositis, dermatomyositis, spondyloarthropathies, ankylosing spondylitis, and Sjogren's syndrome.

23. A method according to claim 17, wherein the disease, disorder, or medical condition is selected from: allergy, asthma, autoimmune diseases, and pruritis.

24. A method for modulating histamine H₄ receptor activity, comprising exposing histamine H₄ receptor to an effective amount of at least one agent selected from a compound of Formula (I) and a salt of a compound of Formula (I):



wherein:

A is CH or N;

each R¹ is independently Cl, Br, methyl, ethyl, NO₂, or CF₃;

m is 0, 1, or 2;

R² is H;

R³ is H, methyl, or ethyl; and

1) R⁴ is H, methyl, or ethyl; one of R⁵ and R⁶ is H, methyl, or ethyl and the other is H; or

2) R⁴ and R⁵ together form $-(CH_2)_3-$; and R⁶ is H; or

3) R⁴ and R⁶ together form $-CH_2-$; and R⁵ is H.

25. A method as recited in claim 24, wherein said Formula (I) is Formula (II).

26. A method according to claim 24, wherein said at least one agent is at least one of:

(S,S)-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-2-yl)-methanone;
(S,S)-(1H-Indol-2-yl)-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-methanone;
(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(1H-Indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
cis-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(S,S)-(1H-Indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Chloro-1H-benzoimidazol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(R)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(S)-(5-Chloro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
cis-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(R,R)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(S,S)-(5-Chloro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Fluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(7-Nitro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(4,6-Difluoro-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(S)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(5-Fluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(7-methyl-1H-indol-2-yl)-methanone;
(S)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(R)-(3-Methylamino-pyrrolidin-1-yl)-(5-methyl-1H-indol-2-yl)-methanone;
(S)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(R)-(4,6-Difluoro-1H-indol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(3-Amino-pyrrolidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone;
(5-Chloro-1H-indol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone;
(3-Dimethylamino-pyrrolidin-1-yl)-(1H-indol-2-yl)-methanone;
cis-(1H-Indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
cis-(5-Chloro-1H-indol-2-yl)-(1-methyl-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;

cis-(5-Methyl-1H-indol-2-yl)-(octahydro-pyrrolo[3,4-b]pyridin-6-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-methylamino-pyrrolidin-1-yl)-methanone;
(1H-Benzoimidazol-2-yl)-(3-dimethylamino-pyrrolidin-1-yl)-methanone; and
salts thereof.