receptor drugs" Nature Reviews Drug Discovery (2005) v. 4, p107-120; Arrang, et al. Nature, 327:117-123 (1987); Leurs and Timmerman, ed. "The History of H_3 Receptor: a Target for New Drugs," Elsevier (1998)).

The activity of histamine H_3 receptors can be modified or regulated by the administration of histamine H_3 receptor ligands. The ligands can demonstrate antagonist, inverse agonist, or partial agonist activity. For example, histamine H_3 receptors have been linked to conditions and disorders related to the central nervous system involving memory, cognitive and other neurological processes, obesity, and also peripheral and systemic activities, such those involved in asthma and allergic rhinitis. Although various classes of compounds demonstrating H_3 receptor-modulating activity exist, it would be beneficial to provide additional compounds demonstrating activity at the H_3 receptors that can be incorporated into pharmaceutical compositions useful for therapeutic methods.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a powder X-ray diffraction pattern of a L-tartrate monohydrate Form A polymorph of 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one.

FIGURE 2 is a powder X-ray diffraction pattern of a L-tartrate monohydrate Form B polymorph of 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one.

FIGURE 3 is a powder X-ray diffraction pattern of a hydrochloride trihemihydrate polymorph of 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one.

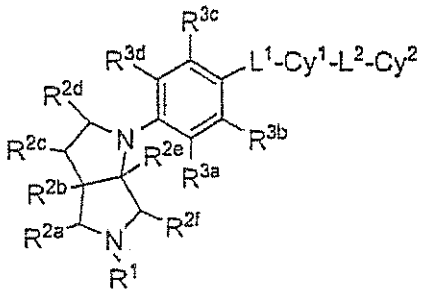
FIGURE 4 is a powder X-ray diffraction pattern of an anhydrous tartrate polymorph of 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one.

FIGURE 5 is a powder X-ray diffraction pattern of an anhydrous hydrochloride polymorph of 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one.

SUMMARY OF THE DISCLOSURE~~INVENTION~~

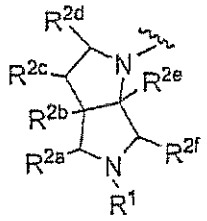
The disclosure~~invention~~ is directed to octahydro-pyrrolo[3,4-b]pyrrole derivatives and,

more particularly, octahydro-pyrrolo[3,4-b]pyrrole derivatives having a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, ester, amide, prodrug, or radioactive isotopic form thereof, wherein R^1 is alkyl, C_3-C_5 cycloalkyl, or (C_3-C_5 cycloalkyl)methyl; R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, and R^{2f} each is independently hydrogen, methyl, or fluoromethyl; R^{3a}, R^{3b}, R^{3c}, and R^{3d} are each independently hydrogen, alkyl, fluoroalkyl, fluoroalkoxy, alkoxy, thioalkoxy, halogen, or nitrile, with the proviso that when one or more of R^{3a}, R^{3b}, R^{3c}, and R^{3d} are alkyl, then at least one of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is fluoroalkyl, fluoroalkoxy, alkoxy, thioalkoxy, halogen, or nitrile; L^1 is a bond, oxygen, sulfur, carbonyl, alkylene, alkylcarbonyl, alkylamino, -C(=N-Oalkyl)-, NR^4, -C(=O) NR^4-, or –NR^4C(=O)-; L^2 is a bond, oxygen, sulfur, carbonyl, alkylene, alkylcarbonyl, alkylamino, -C(=N-Oalkyl)-, NR^5, -C(=O) NR^5-, or –NR^5C(=O)-; Cy^1 is aryl, cycloalkyl, cycloalkenyl, heteroaryl, or heterocycle; Cy^2 is aryl, cycloalkyl, cycloalkenyl, heteroaryl or heterocycle; R^4 and R^5 at each occurrence is hydrogen or alkyl; and provided that Cy^2 is not



In a first aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1 (2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form A demonstrating at least one characteristic peak in the powder X-ray diffraction pattern at values of two theta of 3.90±0.2, 16.72±0.2, 16.99±0.2, 17.17±0.2, 18.12±0.2, 19.72±0.2, 19.98±0.2, 20.25±0.2, 23.96±0.2, 27.65±0.2, and 28.93±0.2.

In a second aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form B demonstrating at least one characteristic peak in the powder X-ray diffraction pattern at values of two theta of 4.39±0.2, 10.45±0.2, 11.92±0.2, 12.52±0.2, 13.45±0.2, 16.71±0.2, 16.92±0.2, 17.62±0.2, 17.90±0.2, 19.10±0.2, 20.46±0.2, and 20.63±0.2.

In a third aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1 (2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one hydrochloride trihemihydrate demonstrating at least one characteristic peak in the powder X-ray diffraction pattern at values of two theta of 4.03±0.2, 13.92±0.2, 15.55±0.2, 15.61±0.2, 15.93±0.2, 16.15±0.2, 24.37±0.2, 24.66±0.2, 25.12±0.2, 25.68±0.2, and 27.90±0.2.

In a fourth aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-bJpyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl} pyridazin-3(2H)-one L-tartrate anhydrate demonstrating at least one characteristic peak in the powder X-ray diffraction pattern at values of two theta of 4.34±0.2, 8.69±0.2, 13.04±0.2, 15.82±0.2, 17.11±0.2, 18.35±0.2, 18.93±0.2, 20.74±0.2, 22.40±0.2, 23.04±0.2, and 26.45±0.2.

In a fifth aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one hydrochloride anhydrate demonstrating at least one characteristic peak in the powder X-ray diffraction pattern at values of two theta of 6.27±0.2, 12.59±0.2, 15.15±0.2, 16.71±0.2, 18.49±0.2, 18.95±0.2, 20.31±0.2, 20.97±0.2, 22.44±0.2, 23.82±0.2, 24.03±0.2, 24.67±0.2, 31.90±0.2, and 32.75±0.2.

In a sixth aspect, there is provided a substantially pure crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form A.

In a seventh aspect, there is provided a substantially pure crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1 (2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form B.

In an eighth aspect, there is provided a substantially pure crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl} pyridazin-3(2H)-one hydrochloride trihemihydrate.

In a ninth aspect, there is provided a substantially pure crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-L-tartrate anhydrate.

In a tenth aspect, there is provided a substantially pure crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one hydrochloride anhydrate.

In an eleventh aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form A having the unit cell parameters wherein a is 7.6 Å, b is 7.4 Å, c is 22.7 Å and ß is 94.1°.

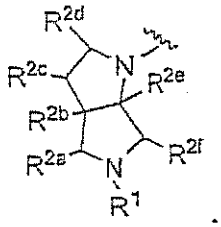
In a twelfth aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate monohydrate Form B having the unit cell parameters wherein a is 7.6 Å, b is 8.7 Å, c is 40.3 Å.

In a thirteenth aspect, there is provided a crystalline 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one hydrochloride trihemihydrate having the unit cell parameters wherein a is 7.3 Å, b is 7.4 Å, c is 22.2 Å and α, ß, γ are each respectively 86.3°, 81.0°, and 77.3°.

In a fourteenth aspect, there is provided a process for preparing 2-{4'-[(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one comprising recrystallizing 2-{4'- [(3aR,6aR)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl]-1,1'-biphenyl-4-yl}pyridazin-3(2H)-one L-tartrate salt in water and dimethyl acetamide or ethanol.

Another aspect of the disclosure~~invention~~ relates to pharmaceutical compositions comprising compounds of the disclosure~~invention~~. Such compositions can be administered in accordance with a method of the disclosure~~invention~~, typically as part of a therapeutic regimen for treatment or prevention of conditions and disorders related to H_3 receptor activity.

In addition, compounds of the disclosure~~invention~~ can have the formula (II) and also



Yet another aspect of the disclosure~~invention~~ relates to a method of selectively modulating H_3 receptor activity. The method is useful for treating, or preventing conditions and disorders related to H_3 receptor modulation in mammals. Such conditions and disorders include Alzheimer's disease, asthma, allergic rhinitis, attention-deficit hyperactivity disorder, bipolar disorder, cognitive dysfunction, cognitive deficits in psychiatric disorders, deficits of memory, deficits of learning, dementia, cutaneous carcinoma, drug abuse, diabetes, type II diabetes, depression, epilepsy, gastrointestinal disorders, inflammation, insulin resistance syndrome, jet lag, medullary thyroid carcinoma, melanoma, Meniere's disease, metabolic syndrome, mild cognitive impairment, migraine, mood and attention alteration, motion sickness, narcolepsy, neurogenic inflammation, obesity, obsessive compulsive disorder, pain, Parkinson's disease, polycystic ovary syndrome, schizophrenia, cognitive deficits of schizophrenia, seizures, septic shock, Syndrome X, Tourette's syndrome, vertigo, and sleep disorders. More particularly, the method is useful for treating or preventing conditions and disorders related conditions and disorders related to the central nervous system involving memory, cognitive and other neurological processes, obesity, and also peripheral and systemic activities, such those involved in asthma, allergic rhinitis and obesity. Accordingly, the compounds and the compositions of the disclosure~~invention~~ are useful as a medicament for treating or preventing H_3 receptor modulated disease.

Yet another aspect of the disclosure~~invention~~ relates to radiolabelled pharmaceutical compositions. Radiolabelled forms of compounds of formula (I) can be provided as compositions of the disclosure~~invention~~ and administered in accordance with a method of the disclosure~~invention~~, typically for assessing or diagnosing conditions and disorders related to H_3 receptor activity, for example in medical imaging. More particularly, positron-emitting isotopes of compounds of the disclosure~~invention~~ may be used for medical imaging in PET (positron emitting tomography), wherein the localization of histamine H_3 receptors, and the extent to which these receptors are occupied by

ligands, can be determined. In this use, the compounds of the disclosureinvention possess at least one atom of a positron-emitting radioisotope selected from ^{11}C, ^{18}F, ^{15}O, and ^{13}N. Compounds of the disclosure~~invention~~ may also incorporate isotopes that useful for sPECT imaging, for example ^{123}I. The disclosure~~invention~~ also relates to particular salts and polymorphs of certain compounds of the disclosure~~invention~~ as well as compositions comprising and processes for preparing such compounds, salts, and polymorphs. The disclosure~~invention~~ also relates to compounds that are intermediates in processes for preparing the compounds, salts, and polymorphs described herein.

The compounds, compositions comprising the compounds, processes for making the compounds, methods for treating or preventing conditions and disorders by administering the compounds, radiolabelled forms of the compounds, particular salts of certain compounds, particularly polymorphs of certain compounds, and compositions containing such salts, polymorphs, and radiolabelled forms of the compounds are further described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definition of Terms

Certain terms as used in the specification are intended to refer to the following definitions, as detailed below.

The term "acyl" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of acyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term "acyloxy" as used herein means an acyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of acyloxy include, but are not limited to, acetyloxy, propionyloxy, and isobutyryloxy.

The term "alkenyl" as used herein means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, and preferably 2, 3, 4, 5, or 6 carbons, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and