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(54) Title: MODULATORS OF THE HISTAMINE H3 RECEPTOR AND THE TREATMENT OF DISORDERS RELATED THERETO

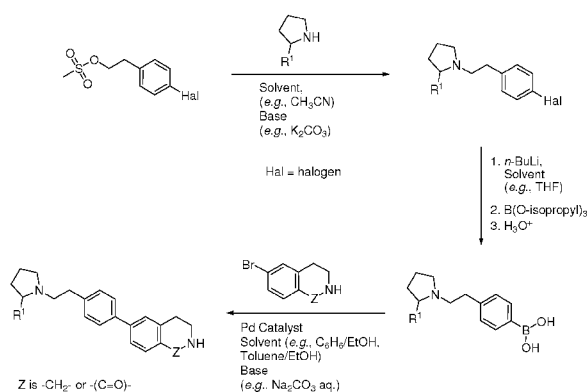
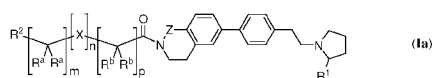


Figure 1

(57) Abstract: The present invention relates to compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof, that modulate the activity of the histamine H3 receptor. Compounds of the present invention and pharmaceutical compositions thereof are directed to methods useful in the treatment of histamine H3-associated disorders.



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MODULATORS OF THE HISTAMINE H3 RECEPTOR AND THE TREATMENT OF DISORDERS RELATED THERETO

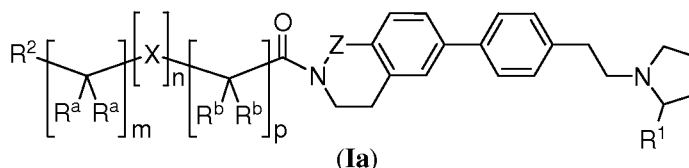
FIELD OF THE INVENTION

5 The present invention relates to compounds of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the histamine H3 receptor (H3R) and are useful in methods for the treatment of histamine H3 receptor-associated disorders, such as, cognitive disorders, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness such as excessive daytime sleepiness, narcolepsy, shift-work sleep disorder, drowsiness as a side effect from a medication, maintenance of vigilance to aid in the completion of tasks and the like, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea and the like, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, pruritus, and the like.

15

SUMMARY OF THE INVENTION

One aspect of the present invention encompasses, *inter alia*, certain isoquinoline (*i.e.*, Z is $-\text{CH}_2-$) and isoquinolinone (*i.e.*, Z is $-(\text{C}=\text{O})-$) derivatives selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



20

wherein:

m, n, and p are each independently 0 or 1;

X is selected from the group: $-\text{S}-$, $-\text{O}-$, C_3 - C_6 cycloalkylene, and CR^cR^c ;

Z is $-\text{CH}_2-$ or $-(\text{C}=\text{O})-$;

25 R^1 is H or C_1 - C_4 alkyl;

R^2 is selected from the group: C_1 - C_4 alkoxycarbonyl, carboxyl, and 1H-tetrazol-5-yl;

and

each R^a , R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, amino, halogen, and hydroxyl.

30

Another aspect of the present invention relates to the unexpected discovery that inhibition of the H3R in an individual, such as by administration of a H3R antagonist, can reduce itching or pruritus. The present invention further relates to compounds of the present invention that are useful in the treatment of a condition characterized by itching, for example, in an individual. In certain embodiments, the individual is a human. The inventors have discovered that the G-protein coupled

histamine 3 receptor is a key effector of the itch sensation. Accordingly, in one embodiment, the present invention provides a method of treating pruritus in a subject in need thereof by administering a therapeutically effective amount of a compound of the present invention that modulates the H3R. In addition, the inventors have discovered that peripherally restricted
5 antagonists of H3R are capable of mediating the inhibition of itch. Peripherally restricted compounds may be advantageous to the extent that the peripheral restriction reduces the CNS effects of H3R inhibition. Such effects may include, for example, wakefulness.

One aspect of the present invention pertains to compositions comprising a compound of the present invention.

10 One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods of inducing wakefulness in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 One aspect of the present invention pertains to methods for treating a histamine H3 receptor-associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20 One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for inducing wakefulness.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of a histamine H3 receptor-associated disorder.

25 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of inducing wakefulness.

30 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method for the treatment of a histamine H3 receptor-associated disorder.

A process for preparing a composition comprising formulating a compound of the present invention and a pharmaceutically acceptable carrier.

35 A process for preparing a composition comprising admixing a compound of the present invention and a pharmaceutically acceptable carrier.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

5 **Figure 1** shows a general synthesis of biaryl derivatives useful as intermediates in the preparation of compounds of the present invention. First, a mesylate derivative is coupled with an R¹ substituted pyrrolidine and subsequently converted to an aryl boronic acid by treatment of an aryl lithium intermediate with triisopropylborate followed by hydrolysis. Next the aryl boronic acid is coupled with an aryl bromide in the presence of a palladium catalyst to prepare the biaryl derivatives.

Figure 2 shows general methods for preparing compounds of the present invention. A variety of methods can be used to acylate a secondary amine (Z = CH₂). For example, **Method A** shows the use of carboxylic acids in the presence of a coupling agent to prepare compounds of the invention; and **Method B** shows the use of acid chlorides to prepare compounds of the invention, optionally in the presence of a base, such as an amine base.

Figure 3 shows a general method for preparing compounds of the present invention. A variety of methods can be used to acylate a secondary amine (Z = CH₂) and the nitrogen of an amide group (Z = carbonyl, *i.e.*, -(C=O)-). For example, **Method C** shows the use of acid anhydrides in the presence of a base to prepare compounds of the invention. When Z = CH₂ the base is optional.

Figure 4 shows the data from the administration of **Compound 1** in the chronic DNFB-mediated allergic pruritus mouse model. The data shows that **Compound 1** effectively inhibits chronic DNFB-mediated allergic pruritus in mice.

Figure 5 shows the data from the administration of **Compound 1** in the histamine-induced pruritus mouse model. The data shows that **Compound 1** effectively inhibits histamine-induced pruritus in mice.

Figure 6 shows the data from the administration of **Compound 3** in the histamine-induced pruritus mouse model. The data shows that **Compound 3** effectively inhibits histamine-induced pruritus in mice.

30 **Figure 7** shows that central administration of a H3R antagonist, **Compound A**, does not inhibit histamine-induced pruritus. **Figure 7A** shows ICV administration of **Compound A** increases cognitive function in mice. **Figure 7B** shows that ICV administration of **Compound A** is unable to inhibit histamine-induced pruritus. Suggesting that brain exposure of a H3R antagonist is not sufficient and that histamine induced pruritus is peripherally mediated.

35

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term “**agonists**” refers to moieties that interact and activate the receptor, such as the histamine H3 receptor and initiate a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term “**antagonists**” refers to moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

The term “**contact or contacting**” refers to bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, “contacting” a histamine H3 receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a histamine H3 receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a histamine H3 receptor.

The term “**in need of treatment**” and the term “**in need thereof**” when referring to treatment are used interchangeably to mean a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, *etc.* in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver’s expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term “**individual**” refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates and most preferably humans.

The term “**inverse agonists**” refers to moieties that bind to the endogenous form of the receptor or to the constitutively activated form of the receptor and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50% and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

The term “**modulate or modulating**” refers to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term “**pharmaceutical composition**” refers to a composition comprising at least one active ingredient; including but not limited to, salts, solvates and hydrates of compounds of the present invention; whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term “**therapeutically effective amount**” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver; or by an individual, which includes one or more of the following:

(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

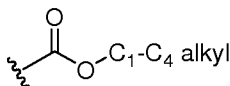
(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology) and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

CHEMICAL GROUP, MOIETY OR RADICAL

The term “**C₁-C₄ alkoxy**” is intended to mean a radical comprising a C₁-C₄ alkyl group attached directly to an oxygen atom, wherein C₁-C₄ alkyl has the same definition as found herein. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples include, but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, isobutoxy, *s*-butoxy, and the like.

The term “**C₁-C₄ alkoxycarbonyl**” refers to a radical comprising a single C₁-C₄ alkoxy group attached to the carbon of a carbonyl group, wherein C₁-C₄ alkoxy has the same definition as found herein. The alkoxycarbonyl group may be represented by the following:



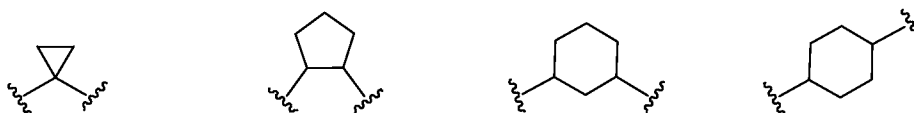
The term “**C₁-C₄ alkyl**” refers to a straight or branched carbon radical containing 1 to 4 carbons. Some embodiments are 1 to 3 carbons. Some embodiments are 1 to 2 carbons. Some

embodiments are 1 carbon. Examples of an alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, and *s*-butyl, isobutyl.

The term “**amino**” refers to the group -NH₂.

The term “**carboxy**” refers to the group -CO₂H.

- 5 The term “**C₃-C₆ cycloalkylene**” refers to a saturated ring di-radical containing 3 to 6 carbons. Some embodiments contain 3 to 5 carbons. Some embodiments contain 5 to 6 carbons. Some embodiments contain 3 to 4 carbons. Examples include cyclopropanediyl, cyclobutanediyl, cyclopentanedyl, cyclohexanedyl, and the like. In some embodiments, C₃-C₆ cycloalkylene is selected from cyclopropane-1,1-diyl, cyclobutane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cyclopropane-1,2-diyl, cyclobutane-1,2-diyl, cyclopentane-1,2-diyl, cyclohexane-1,2-diyl, cyclopentane-1,3-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, and the like. For further clarity, several representative chemical structures for are shown below:

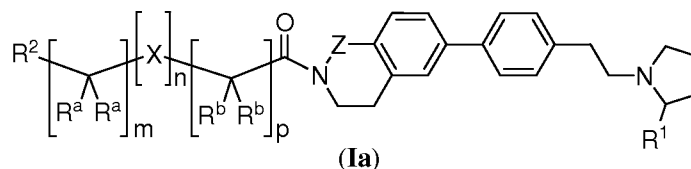


cyclopropane-1,1-diyl cyclopentane-1,2-diyl cyclohexane-1,3-diyl cyclohexane-1,4-diyl

- 15 The term “**halogen**” or “**halo**” refers to a fluoro, chloro, bromo or iodo group.
The term “**hydroxyl**” refers to the group -OH.

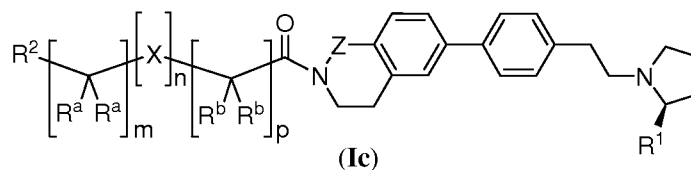
COMPOUNDS OF THE INVENTION:

- 20 One aspect of the present invention pertains to certain compounds as shown in Formula (Ia):



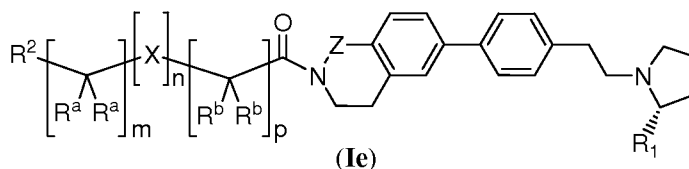
and pharmaceutically acceptable salts, solvates and hydrates thereof; wherein: R¹, R², R^a, R^b, X, Z, m, n, and p have the same definitions as described herein, *supra* and *infra*.

- 25 One aspect of the present invention pertains to certain compounds as shown in Formula (Ic):



and pharmaceutically acceptable salts, solvates and hydrates thereof; wherein: R¹, R², R^a, R^b, X, Z, m, n, and p have the same definitions as described herein, *supra* and *infra*.

One aspect of the present invention pertains to certain compounds as shown in Formula (Ie):



and pharmaceutically acceptable salts, solvates and hydrates thereof; wherein: R^1 , R^2 , R^a , R^b , X, Z, m, n, and p have the same definitions as described herein, *supra* and *infra*.

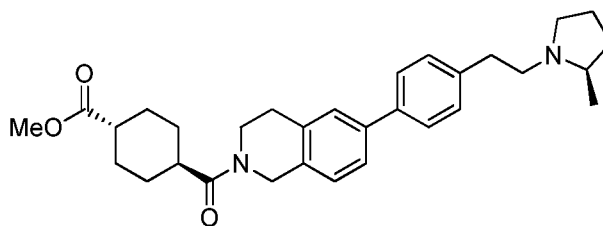
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (*e.g.*, R^1 , R^2 , R^a , R^b , X, Z, m, n, and p) contained within the generic chemical formulae described herein, for example, (Ia), (Ic), (Ie), (Ig), (Ii), (IIc), (Ile), (IIg), (Ili), (IIk), (IIm), (IIo), (IIq), (IIs), (IIu), (IIw), and (IIy), are specifically embraced by the present invention just as if each and every combination was individually explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (*i.e.*, compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein.

As used herein, “substituted” indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is “substituted” it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, “substituted with one or more substituents” refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

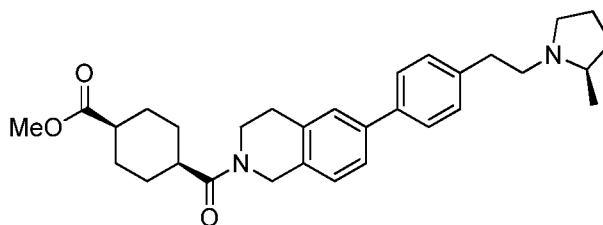
Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

5 It is understood and appreciated that compounds of Formula (Ia) and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereoisomers. The invention is understood to extend to and embrace all such enantiomers, diastereoisomers and mixtures thereof, including but not limited to racemates. It is understood that compounds of Formula (Ia) and formulae used throughout this disclosure are intended to
10 represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

It is understood and appreciated that certain compounds of Formula (Ia) and formulae related thereto exist as meso isomers. Such meso isomers may be referred to as *cis* and *trans*. The *trans* meso isomers of compounds of Formula (Ia) are named herein using the prefix (1*r*,4*r*) and the *cis* meso isomers of compounds of Formula (Ia) are named herein using the prefix
15 (1*s*,4*s*), as illustrated with **Compound 25** shown below:



(1*r*,4*r*)- or *trans*- mesoisomer
(1*r*,4*r*)-methyl 4-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate

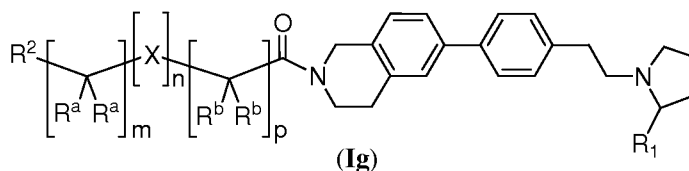


(1*s*,4*s*)- or *cis*- mesoisomer
(1*s*,4*s*)-methyl 4-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate

The Group Z:

In some embodiments, Z is $-\text{CH}_2-$.

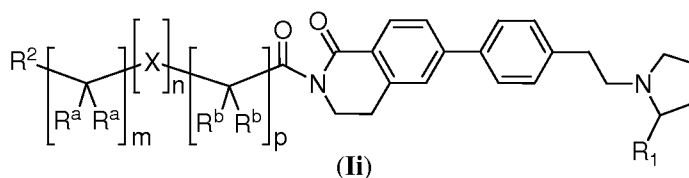
20 One aspect of the present invention pertains to certain compounds as shown in Formula (Ig):



and pharmaceutically acceptable salts, solvates and hydrates thereof; wherein: R^1 , R^2 , R^a , R^b , X , m , n , and p have the same definitions as described herein, *supra* and *infra*.

In some embodiments, Z is $-(C=O)-$.

5 One aspect of the present invention pertains to certain compounds as shown in Formula (Ii):



and pharmaceutically acceptable salts, solvates and hydrates thereof; wherein: R^1 , R^2 , R^a , R^b , X , m , n , and p have the same definitions as described herein, *supra* and *infra*.

10

The Variables m , n , and p :

In some embodiments, m is 0.

In some embodiments, m is 1.

In some embodiments, n is 0.

15 In some embodiments, n is 1.

In some embodiments, p is 0.

In some embodiments, p is 1.

In some embodiments, m , n , and p are each 0.

In some embodiments, m is 0, n is 0, and p is 1.

20 In some embodiments, m is 0, n is 1, and p is 0.

In some embodiments, m is 0, n is 1, and p is 1.

In some embodiments, m , n , and p are each 1.

In some embodiments, m , n , and p are each independently 0 or 1; provided that when m is 1, then n and p are both 1.

25

The Group R^1 :

In some embodiments, R^1 is H or C_1 - C_4 alkyl.

In some embodiments, R^1 is H.

In some embodiments, R^1 is C_1 - C_4 alkyl.

30 In some embodiments, R^1 is methyl.

The Group R²:

In some embodiments, R² is selected from the group: C₁-C₄ alkoxy carbonyl, carboxyl, and 1*H*-tetrazol-5-yl.

5 In some embodiments, R² is C₁-C₄ alkoxy carbonyl.

In some embodiments, R² is selected from the group: methoxy carbonyl and ethoxy carbonyl.

In some embodiments, R² is carboxyl.

In some embodiments, R² is 1*H*-tetrazol-5-yl.

10

The Group R^a:

In some embodiments, each R^a is selected independently from the group: H, C₁-C₃ alkyl, amino, halogen, and hydroxyl.

In some embodiments, R^a is H.

15 In some embodiments, R^a is halogen.

In some embodiments, R^a is hydroxyl.

In some embodiments, each R^a is selected independently from the group: H, C₁-C₃ alkyl, and amino.

In some embodiments, R^a is C₁-C₃ alkyl.

20 In some embodiments, each R^a is selected independently from the group: H, methyl, and amino.

In some embodiments, R^a is methyl.

In some embodiments, R^a is amino.

25 **The Group R^b:**

In some embodiments, each R^b is selected independently from the group: H, C₁-C₃ alkyl, amino, halogen, and hydroxyl.

In some embodiments, R^b is H.

In some embodiments, R^b is halogen.

30 In some embodiments, R^b is hydroxyl.

In some embodiments, each R^b is selected independently from the group: H, C₁-C₃ alkyl, and halogen.

In some embodiments, each R^b is selected independently from the group: H, methyl, and fluoro.

35 In some embodiments, R^b is C₁-C₃ alkyl.

In some embodiments, R^b is methyl.

In some embodiments, R^b is fluoro.

The Group R^c:

In some embodiments, each R^c is selected independently from the group: H, C₁-C₃ alkyl, amino, halogen, and hydroxyl.

5 In some embodiments, each R^c is selected independently from the group: H, C₁-C₃ alkyl, halogen, and hydroxyl.

In some embodiments, R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.

In some embodiments, R^c is H.

10 In some embodiments, R^c is C₁-C₃ alkyl.

In some embodiments, R^c is methyl.

In some embodiments, R^c is amino.

In some embodiments, R^c is halogen.

In some embodiments, R^c is fluoro.

15 In some embodiments, R^c is hydroxyl.

The Variable X:

In some embodiments, X is -S-.

In some embodiments, X is -O-.

20 In some embodiments, X is C₃-C₆ cycloalkylene.

In some embodiments, X is selected from the group: cyclopropane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, and cyclohexane-1,4-diyl.

In some embodiments, X is cyclopropane-1,1-diyl.

25 In some embodiments, X is cyclopentane-1,1-diyl.

In some embodiments, X is cyclohexane-1,1-diyl.

In some embodiments, X is cyclohexane-1,2-diyl.

In some embodiments, X is cyclohexane-1,3-diyl.

In some embodiments, X is cyclohexane-1,4-diyl.

30 In some embodiments, X is CR^cR^c.

In some embodiments, X is CR^cR^c, and each R^c is selected independently from the group: H, C₁-C₃ alkyl, halogen, and hydroxyl.

In some embodiments, X is CR^cR^c, and each R^c is selected independently from the group: H, methyl, fluoro, and hydroxyl.

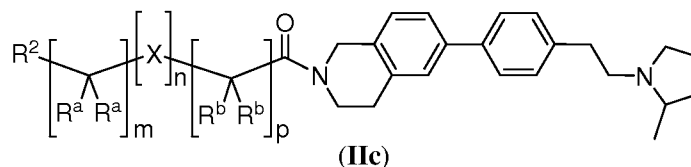
35

Certain Combinations of the Present Invention:

In some embodiments, each R^a, R^b, and R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.

In some embodiments, each R^a, R^b, and R^c is independently selected from the group: H, methyl, and hydroxyl.

5 Some embodiments of the present invention pertain to compounds of Formula (IIc) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

10 m, n, and p are each independently 0 or 1, provided that when m is 1 then both n and p are both 1;

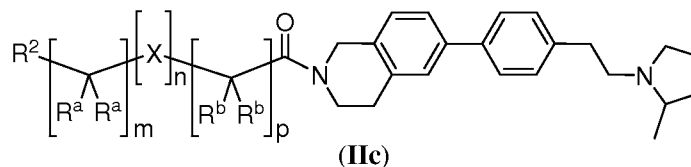
X is selected from the group: -S-, -O-, C₃-C₆ cycloalkylene, and CR^cR^c;

R² is selected from the group: C₁-C₄ alkoxy carbonyl, carboxyl, and 1*H*-tetrazol-5-yl;

and

each R^a, R^b, and R^c is independently selected from the group: H, C₁-C₃ alkyl, amino,
15 halogen, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIc) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

20 m, n, and p are each independently 0 or 1, provided that when m is 1 then n and p are
 both 1;

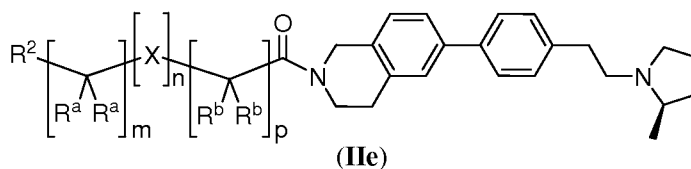
X is selected from the group: -S-, -O-, cyclopropane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, and CR^cR^c ;

25 R² is selected from the group: methoxycarbonyl, ethoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and

each R^a, R^b, and R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIe) and
30 pharmaceutically acceptable salts, solvates and hydrates thereof:

13



wherein:

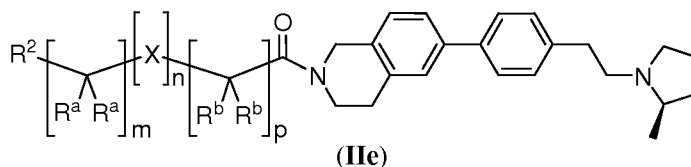
m, n, and p are each independently 0 or 1, provided that when m is 1 then both n and p are both 1;

5 X is selected from the group: -S-, -O-, C₃-C₆ cycloalkylene, and CR^cR^c;

R² is selected from the group: C₁-C₄ alkoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl;
and

each R^a, R^b, and R^c is independently selected from the group: H, C₁-C₃ alkyl, amino, halogen, and hydroxyl.

10 Some embodiments of the present invention pertain to compounds of Formula (IIe) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

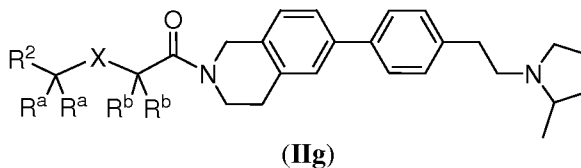
m, n, and p are each independently 0 or 1, provided that when m is 1 then n and p are both 1;

15 X is selected from the group: -S-, -O-, cyclopropane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, and CR^cR^c;

R² is selected from the group: methoxycarbonyl, ethoxycarbonyl, carboxyl, and 1*H*-
20 tetrazol-5-yl; and

each R^a, R^b, and R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIg) and pharmaceutically acceptable salts, solvates and hydrates thereof:



25

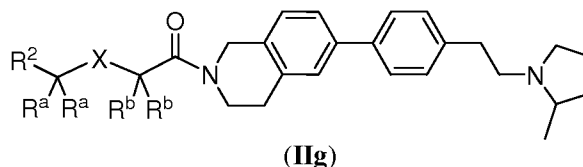
wherein:

X is selected from the group: -S-, -O-, C₃-C₆ cycloalkylene, and CR^cR^c;

R² is selected from the group: C₁-C₄ alkoxycarbonyl and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, amino, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIg) and pharmaceutically acceptable salts, solvates and hydrates thereof:



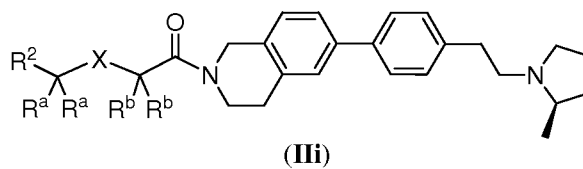
wherein:

X is selected from the group: $-S-$, $-O-$, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, and CR^cR^c ;

R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, methyl, amino, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (III) and pharmaceutically acceptable salts, solvates and hydrates thereof:



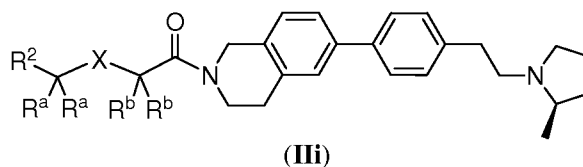
wherein:

X is selected from the group: $-S-$, $-O-$, C_3 - C_6 cycloalkylene, and CR^cR^c ;

R^2 is selected from the group: C_1 - C_4 alkoxy carbonyl and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, amino, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (III) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

X is selected from the group: $-S-$, $-O-$, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, and CR^cR^c ;

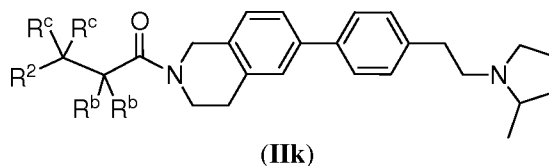
R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, methyl, amino, and hydroxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIIi) and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein X is CR^aR^c; and each R^a, R^b, and R^c is independently selected from the group: H, methyl, and hydroxyl.

In some embodiments, X is CR^aR^c; and each R^a, R^b, and R^c is independently selected from the group: H, methyl, and hydroxyl.

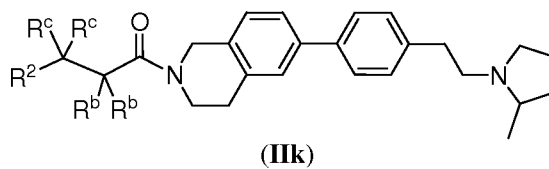
Some embodiments of the present invention pertain to compounds of Formula (IIIk) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

R² is selected from the group: C₁-C₄ alkoxy carbonyl and carboxyl; and each R^b, and R^c is independently selected from the group: H, C₁-C₃ alkyl, and halogen.

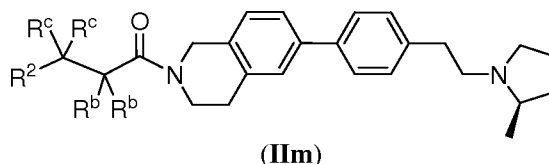
Some embodiments of the present invention pertain to compounds of Formula (IIIk) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

R² is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and each R^b, and R^c is independently selected from the group: H, methyl, and fluoro.

Some embodiments of the present invention pertain to compounds of Formula (IIIm) and pharmaceutically acceptable salts, solvates and hydrates thereof:

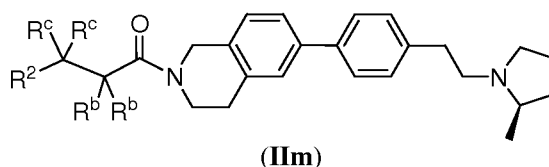


wherein:

R² is selected from the group: C₁-C₄ alkoxy carbonyl and carboxyl; and each R^b, and R^c is independently selected from the group: H, C₁-C₃ alkyl, and halogen.

Some embodiments of the present invention pertain to compounds of Formula (IIIm) and pharmaceutically acceptable salts, solvates and hydrates thereof:

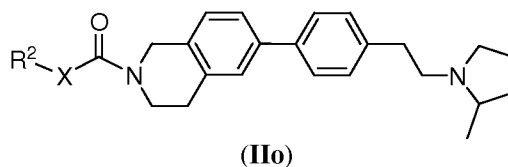
16



wherein:

R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and each R^b , and R^c is independently selected from the group: H, methyl, and fluoro.

5 Some embodiments of the present invention pertain to compounds of Formula (IIo) and pharmaceutically acceptable salts, solvates and hydrates thereof:

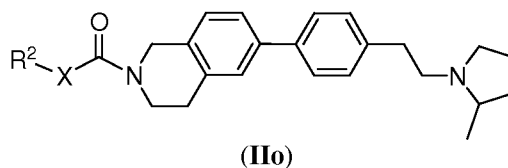


wherein:

X is C_3 - C_6 cycloalkylene; and

10 R^2 is selected from the group: C_1 - C_4 alkoxy carbonyl, and carboxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIo) and pharmaceutically acceptable salts, solvates and hydrates thereof:

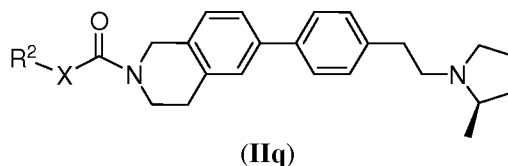


wherein:

15 X is selected from the group: cyclopropane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, and cyclohexane-1,4-diyl; and

R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIq) and pharmaceutically acceptable salts, solvates and hydrates thereof:



20

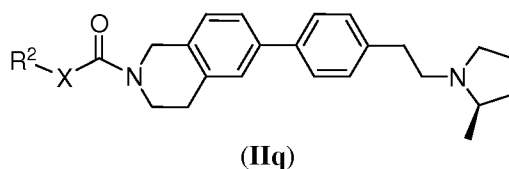
wherein:

X is C_3 - C_6 cycloalkylene; and

R^2 is selected from the group: C_1 - C_4 alkoxy carbonyl, and carboxyl.

Some embodiments of the present invention pertain to compounds of Formula (IIq) and
25 pharmaceutically acceptable salts, solvates and hydrates thereof:

17

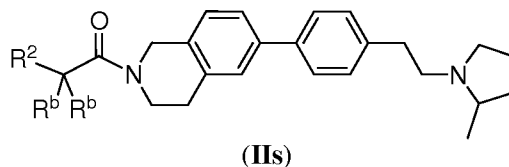


wherein:

X is selected from the group: cyclopropane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, and cyclohexane-1,4-diyl; and

5 R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl.

Some embodiments of the present invention pertain to compounds of Formula **(II_s)** and pharmaceutically acceptable salts, solvates and hydrates thereof:



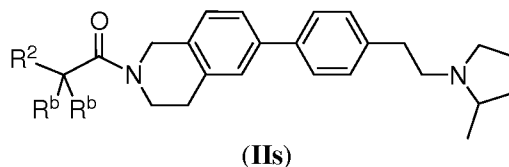
wherein:

10 R^2 is selected from the group: C₁-C₄ alkoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl;

and

each R^b is independently selected from the group: H, and C₁-C₃ alkyl.

Some embodiments of the present invention pertain to compounds of Formula **(II_s)** and pharmaceutically acceptable salts, solvates and hydrates thereof:



15

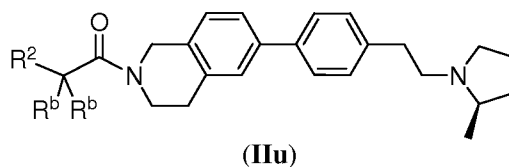
wherein:

R^2 is selected from the group: methoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and

each R^b is independently selected from the group: H, and methyl.

Some embodiments of the present invention pertain to compounds of Formula **(II_u)** and pharmaceutically acceptable salts, solvates and hydrates thereof:

20



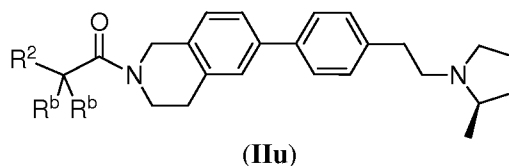
wherein:

R^2 is selected from the group: C₁-C₄ alkoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl;

and

25 each R^b is independently selected from the group: H, and C₁-C₃ alkyl.

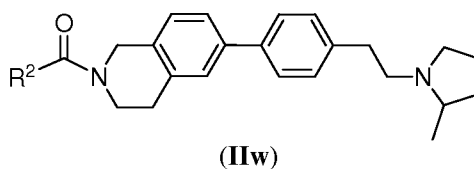
Some embodiments of the present invention pertain to compounds of Formula (IIu) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

- 5 R² is selected from the group: methoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and each R^b is independently selected from the group: H, and methyl.

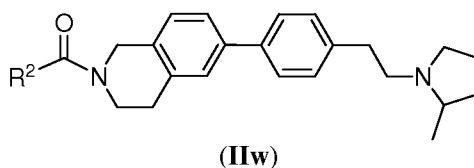
Some embodiments of the present invention pertain to compounds of Formula (IIw) and pharmaceutically acceptable salts, solvates and hydrates thereof:



- 10 wherein:

R² is selected from the group: C₁-C₄ alkoxy carbonyl, carboxyl, and 1*H*-tetrazol-5-yl.

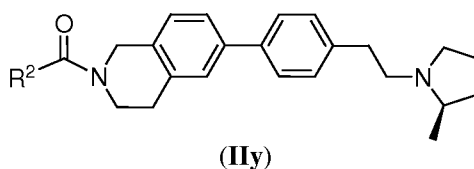
Some embodiments of the present invention pertain to compounds of Formula (IIw) and pharmaceutically acceptable salts, solvates and hydrates thereof:



- 15 wherein:

R² is selected from the group: methoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl.

Some embodiments of the present invention pertain to compounds of Formula (IIy) and pharmaceutically acceptable salts, solvates and hydrates thereof:

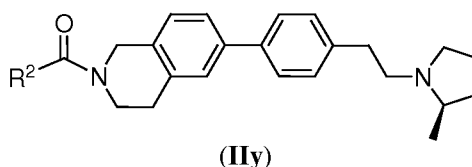


- 20 wherein:

R² is selected from the group: C₁-C₄ alkoxy carbonyl, carboxyl, and 1*H*-tetrazol-5-yl.

Some embodiments of the present invention pertain to compounds of Formula (IIy) and pharmaceutically acceptable salts, solvates and hydrates thereof:

19



wherein:

R² is selected from the group: methoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl.

One aspect of the present invention encompasses every combination of one or more
 5 compounds selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:

1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)ethanone;

4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-
 10 oxobutanoic acid;

3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;

2,2-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;

3-methyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;

3-hydroxy-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;

2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethylthio)acetic acid;

2,2,3,3-tetrafluoro-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;

2,2-dimethyl-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;

2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethoxy)acetic acid;

5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;

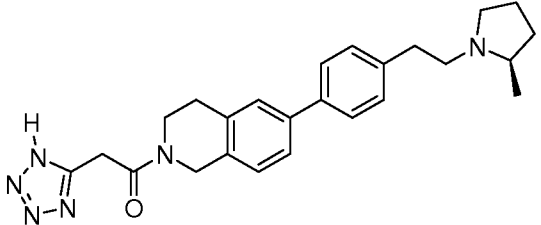
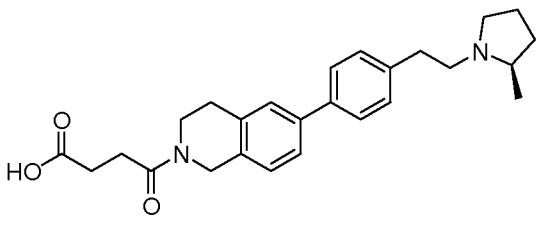
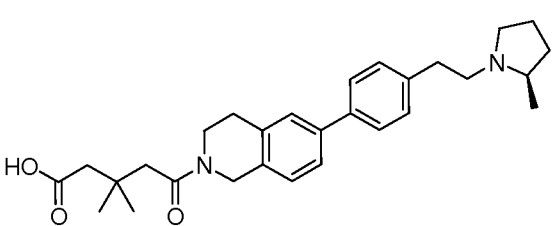
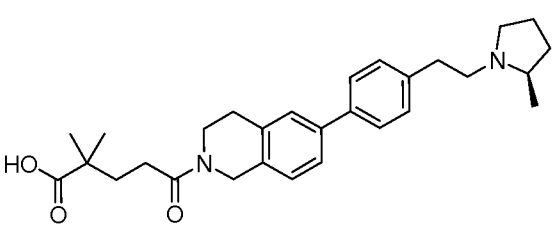
methyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate;

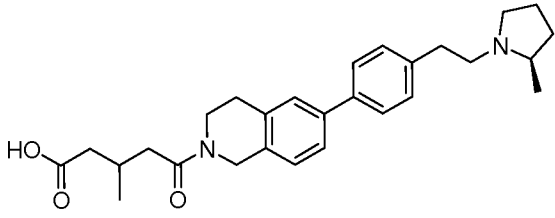
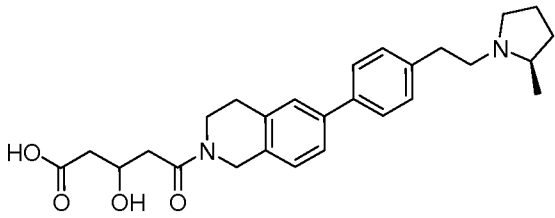
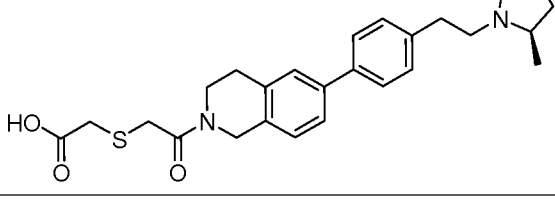
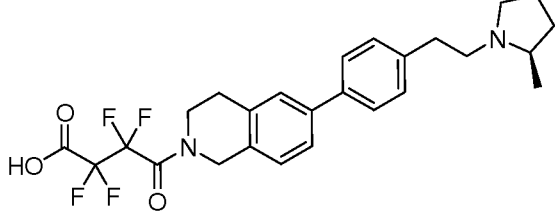
ethyl 2-amino-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate;

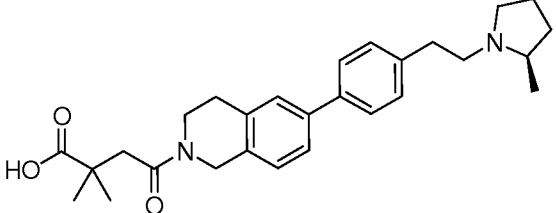
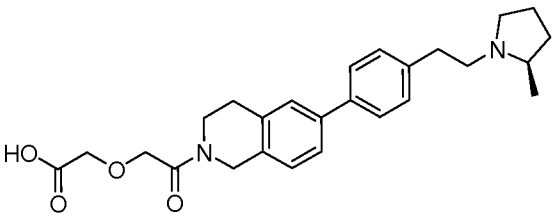
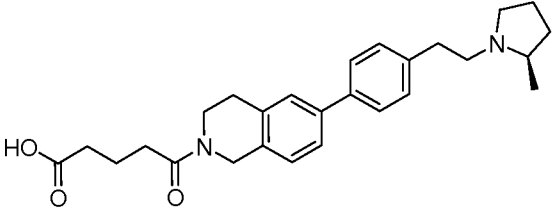
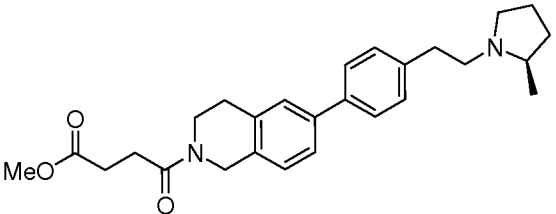
(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)(1*H*-tetrazol-5-yl)methanone;

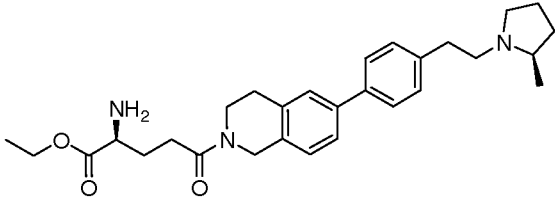
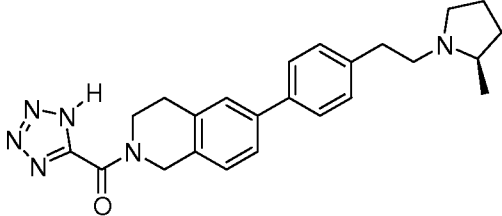
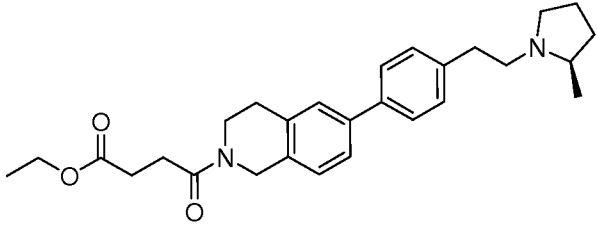
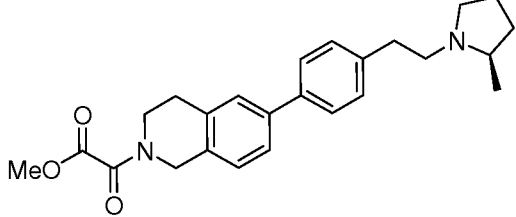
- ethyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate;
- methyl 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetate;
- 5 2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclopentyl)acetic acid;
- 2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetic acid;
- 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
- 10 methyl 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-oxopropanoate;
- methyl 1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylate;
- 15 2-methyl-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)propan-1-one;
- methyl 3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate;
- methyl 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate;
- 20 methyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate;
- 1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylic acid;
- 25 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
- 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
- 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;
- 30 ethyl 2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetate; and
- methyl 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate.
- 35 One aspect of the present invention encompasses every combination of one or more compounds selected from the compounds in **Table A** and pharmaceutically acceptable salts, solvates, and hydrates thereof.

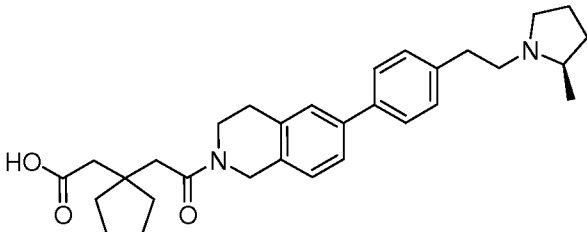
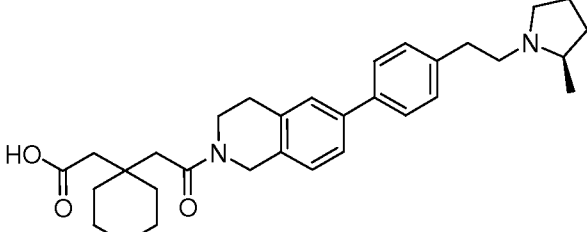
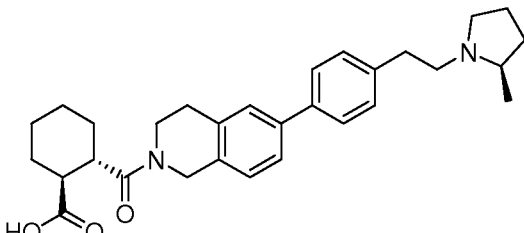
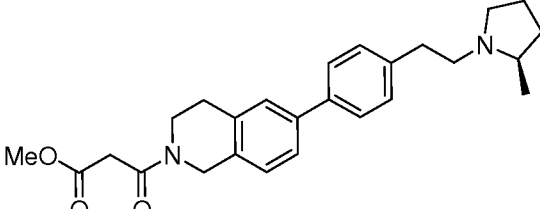
Table A

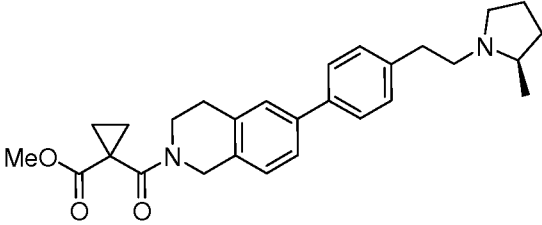
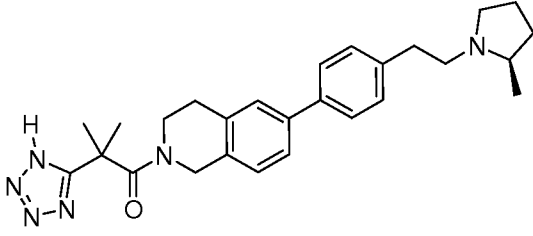
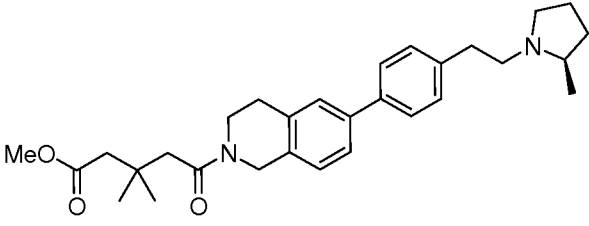
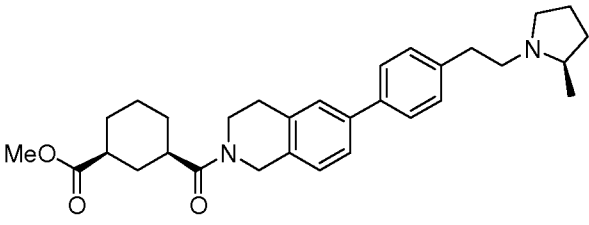
Cmpd No.	Chemical Structure/Chemical Name
1	 <i>(R)</i>-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-2-(1<i>H</i>-tetrazol-5-yl)ethanone
2	 <i>(R)</i>-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-4-oxobutanoic acid
3	 <i>(R)</i>-3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-5-oxopentanoic acid
4	 <i>(R)</i>-2,2-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-5-oxopentanoic acid

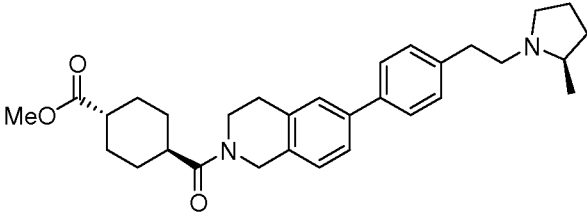
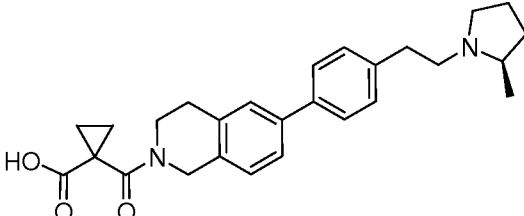
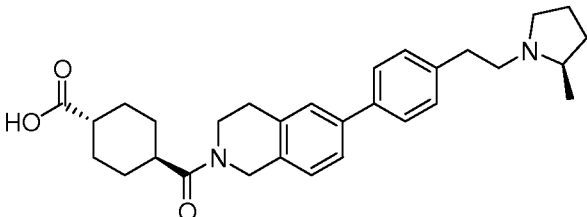
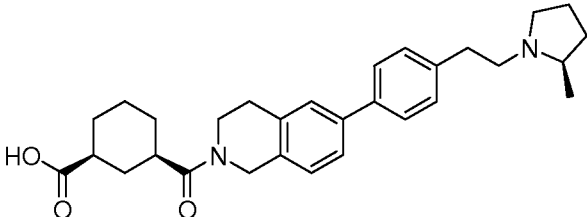
Cmpd No.	Chemical Structure/Chemical Name
5	
	3-methyl-5-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-5-oxopentanoic acid
6	
	3-hydroxy-5-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-5-oxopentanoic acid
7	
	<i>(R)</i> -2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2-oxoethylthio)acetic acid
8	
	<i>(R)</i> -2,2,3,3-tetrafluoro-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-4-oxobutanoic acid

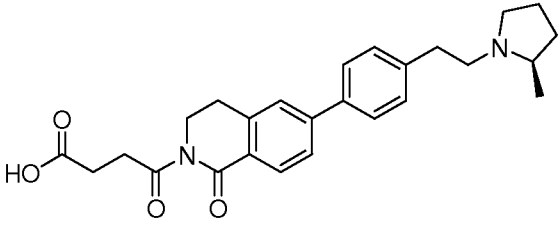
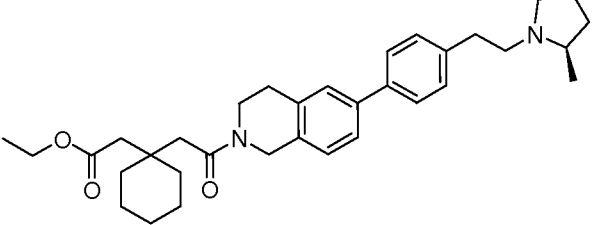
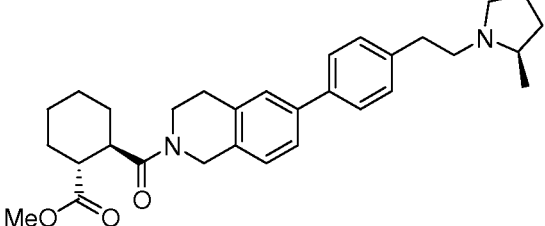
Cmpd No.	Chemical Structure/Chemical Name
9	 <i>(R)</i>-2,2-dimethyl-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-4-oxobutanoic acid
10	 <i>(R)</i>-2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-2-oxoethoxy)acetic acid
11	 <i>(R)</i>-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-5-oxopentanoic acid
12	 <i>(R)</i>-methyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-4-oxobutanoate

Cmpd No.	Chemical Structure/Chemical Name
13	
	(S)-ethyl 2-amino-5-(6-(4-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)-5-oxopentanoate
14	
	(R)-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)(1H-tetrazol-5-yl)methanone
15	
	(R)-ethyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)-4-oxobutanoate
16	
	(R)-methyl 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoacetate

Cmpd No.	Chemical Structure/Chemical Name
17	
	<i>(R)</i>-2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-2-oxoethyl)cyclopentyl)acetic acid
18	
	<i>(R)</i>-2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-2-oxoethyl)cyclohexyl)acetic acid
19	
	<i>(1S,2S)</i>-2-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid
20	
	<i>(R)</i>-methyl 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1<i>H</i>)-yl)-3-oxopropanoate

Cmpd No.	Chemical Structure/Chemical Name
21	
	(R)-methyl 1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylate
22	
	(R)-2-methyl-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-(1H-tetrazol-5-yl)propan-1-one
23	
	(R)-methyl 3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)-5-oxopentanoate
24	
	(1S,3R)-methyl 3-(6-(4-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate

Cmpd No.	Chemical Structure/Chemical Name
25	
	(1 <i>r</i> ,4 <i>r</i>)-methyl 4-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate
26	
	(R)-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylic acid
27	
	(1 <i>r</i> ,4 <i>r</i>)-4-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid
28	
	(1 <i>S</i> ,3 <i>R</i>)-3-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid

Cmpd No.	Chemical Structure/Chemical Name
29	 <chem>CC1(CCN(C1)CCc2ccc(cc2)C3=Cc4ccccc4N3C(=O)CC(=O)O)C(=O)CC(=O)O</chem> <i>(R)</i> -4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1-oxo-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-4-oxobutanoic acid
30	 <chem>CCOC(=O)CC1(CCN(C1)CCc2ccc(cc2)C3=Cc4ccccc4N3C(=O)CC(=O)O)C(=O)CC(=O)O</chem> <i>(R)</i> -ethyl 2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2-oxoethyl)cyclohexyl)acetate
31	 <chem>COC(=O)C1(CCN(C1)CCc2ccc(cc2)C3=Cc4ccccc4N3C(=O)CC(=O)O)C(=O)CC(=O)O</chem> <i>(1R,2R)</i> -methyl 2-(6-(4-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in **Table A** including diastereoisomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates and particularly hydrates, thereof.

The compounds of the Formula (**Ia**) of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3rd Edition, 1999 [Wiley]).

It is understood that the present invention embraces each diastereoisomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers (such as, by chiral HPLC, recrystallization of
5 diastereoisomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

INDICATIONS AND METHODS OF PROPHYLAXIS AND/OR TREATMENT

10 Histamine [2-(imidazol-4-yl)ethylamine] exerts its physiological effects through four distinct G-protein coupled receptors (GPCRs), termed H1, H2, H3 and H4. The histamine H3 receptor was first identified in 1983, when it was determined that the H3 receptor acted as an autoreceptor controlling both the synthesis and release of histamine (see: Arrang *et al. Nature* 1983, 302, 832-7). At least four human and three rat splice variants have proven functional
15 activity in pharmacological assays (Passani *et al., Trends in Pharmacol. Sci.* 2004, **25**, 618-625). Rat and human histamine H3 receptors also show constitutive activity which means that they can transduce a signal even in the absence of a ligand. Histamine H3 receptors also function as heteroreceptors, modulating the release of a number of other transmitter substances including serotonin, acetylcholine, dopamine and noradrenaline (see: Brown *et al. Prog. Neurobiol.* 2001,
20 **63**, 637-672). Thus, there are a number of therapeutic applications for ligands which target the histamine H3 receptor, where the ligand functions as either an antagonist or inverse agonist (for reviews see: Leurs *et al. Nat. Rev. Drug. Discov.* 2005, 4, 107-120; Passani *et al. Trends Pharmacol. Sci.* 2004, 25, 618-625).

Accordingly, preclinical studies have identified a number of indications which are
25 amenable to treatment with histamine H3 receptor antagonists and inverse agonists, such as compounds of the present invention. The compounds disclosed herein are believed to be useful in the treatment and/or prevention of several diseases and disorders, and in the amelioration of symptoms thereof. These compounds can be used alone or in combination with other compounds for the treatment and/or prevention of diseases and disorders. Without limitation, these diseases and
30 disorders include the following.

Histamine H3 receptor antagonists have been shown to increase wakefulness (*e.g.* Lin J. S. *et al. Brain Research* 1990, 523, 325-330). This effect demonstrates that H3 receptor antagonists can be useful for disorders of sleep and wakefulness (Parmentier *et al. J. Neurosci.* 2002, **22**, 7695-7711; Ligneau *et al. J. Pharmacol. Exp. Ther.* 1998, 287, 658-666). For
35 example, histamine H3 receptor antagonists and inverse agonists can be used to treat the somnolence syndrome associated with different pathological conditions, for example, sleep apnea and Parkinson's disease or circumstances associated with lifestyle, for example, daytime

somnolence from sleep deprivation as a result of nocturnal jobs, overwork, or jet-lag (see Passani *et al.*, *Trends Pharmacol. Sci.* 2004, 25, 618-625). Somnolence is one of the major problems of public health because of its high prevalence (19-37% of the general population) and risk for causing work and traffic accidents.

5 Sleep apnea (alternatively sleep apnoea) is a common sleep disorder characterized by brief interruptions of breathing during sleep. These episodes, called apneas, last 10 seconds or more and occur repeatedly throughout the night. People with sleep apnea partially awaken as they struggle to breathe, but in the morning they may not be aware of the disturbances in their sleep. The most common type of sleep apnea is obstructive sleep apnea (OSA), caused by
10 relaxation of soft tissue in the back of the throat that blocks the passage of air. Central sleep apnea (CSA) is caused by irregularities in the brain's normal signals to breathe. The hallmark symptom of the disorder is excessive daytime sleepiness. Additional symptoms of sleep apnea include restless sleep, loud snoring (with periods of silence followed by gasps), falling asleep during the day, morning headaches, trouble concentrating, irritability, forgetfulness, mood or
15 behaviour changes, weight gain, increased heart rate, anxiety, and depression.

Few drug-based treatments of obstructive sleep apnea are known despite over two decades of research and tests. Oral administration of the methylxanthine theophylline (chemically similar to caffeine) can reduce the number of episodes of apnea, but can also produce side effects such as palpitations and insomnia. Theophylline is generally ineffective in
20 adults with OSA, but is sometimes used to treat CSA, and infants and children with apnea. In 2003 and 2004, some neuroactive drugs, particularly modern-generation antidepressants including mirtazapine, have been reported to reduce incidences of obstructive sleep apnea. When other treatments do not completely treat the OSA, drugs are sometimes prescribed to treat a patient's daytime sleepiness or somnolence. These range from stimulants such as
25 amphetamines to modern anti-narcoleptic medicines. The drug modafinil is seeing increased use in this role as of 2004.

In addition, for example, histamine H3 receptor antagonists and inverse agonists can be used to treat narcolepsy (Tedford *et al. Soc. Neurosci. Abstr.* 1999, **25**, 460.3). Narcolepsy is a neurological condition most often characterized by Excessive Daytime Sleepiness (EDS),
30 episodes of sleep and disorder of REM or rapid eye movement sleep. The main characteristic of narcolepsy is overwhelming Excessive Daytime Sleepiness (EDS), even after adequate nighttime sleep. A person with narcolepsy is likely to become drowsy or to fall asleep, often at inappropriate times and places. In addition, nighttime sleep may be fragmented with frequent awakenings. Classic symptoms of narcolepsy include, for example, cataplexy which is sudden
35 episodes of loss of muscle function, ranging from slight weakness (such as limpness at the neck or knees, sagging facial muscles, or inability to speak clearly) to complete body collapse. Episodes may be triggered by sudden emotional reactions such as laughter, anger, surprise, or

fear, and may last from a few seconds to several minutes. Another symptom of narcolepsy is sleep paralysis, which is the temporary inability to talk or move when waking up. Other symptoms include, for example, hypnagogic hallucinations which are vivid, often frightening, dream-like experiences that occur while dozing, falling asleep and/or while awakening, and automatic behaviour which occurs when a person continues to function (talking, putting things away, etc.) during sleep episodes, but awakens with no memory of performing such activities. Daytime sleepiness, sleep paralysis, and hypnagogic hallucinations also occur in people who do not have narcolepsy, such as in people who are suffering from extreme lack of sleep. Cataplexy is generally considered unique to narcolepsy.

Currently the treatments available for narcolepsy treat the symptoms, but not the underlying cause. For cataplexy and REM-sleep symptoms, antidepressant medications and other drugs that suppress REM sleep are prescribed. The drowsiness is normally treated using stimulants such as methylphenidate (Ritalin), amphetamines (Adderall), dextroamphetamine (Dexedrine), methamphetamine (Desoxyn), modafinil (Provigil), etc. Other medications used are codeine and selegiline. The cataplexy is treated using clomipramine, imipramine, or protriptyline but this need only be done in severe cases. The drug gamma-hydroxybutyrate (GHB) (Xyrem) is approved in the USA by the Food and Drug Administration to treat both the cataplexy and excessive daytime sleepiness associated with narcolepsy.

Interestingly, modafinil (Provigil) has recently been shown to increase hypothalamic histamine release (Ishizuka *et al. Neurosci. Lett.* 2003, 339, 143-146).

In addition, recent studies using the classic Doberman model of narcolepsy with a non-imidazole histamine H3 receptor antagonist showed that a histamine H3 receptor antagonist can reduce the number of cataplectic attacks and the duration of the attacks (Carruthers *Ann. Meet. Eur. Histamine Res. Soc.* 2004, Abs. p31).

In summary, histamine H3 receptor antagonists and inverse agonists can be used for the treatment and/or prevention of conditions associated with excessive daytime sleepiness such as hypersomnia, narcolepsy, sleep apnea, time zone change disorder, and other disorders which are associated with excessive daytime sleepiness such as fibromyalgia, and multiple sclerosis (Parmentier *et al., J. Neurosci.* 2002, **22**, 7695-7711; Ligneau *et al. J. Pharmacol. Exp. Ther.* 1998, 287, 658-666). Other conditions include excessive sleepiness due to shift-work, medical disorders, psychiatric disorders, narcolepsy, primary hypersomnia, and the like. Histamine H3 receptor antagonists and inverse agonists can also be used occasionally to promote wakefulness or vigilance in shift workers, sleep deprivation, post anesthesia grogginess, drowsiness as a side effect from a medication, military use and the like.

In addition, wakefulness is a prerequisite for several brain functions including attention, learning, and memory and is required for appropriate behaviours in response to environmental challenges. Histamine H3 receptor antagonists and inverse agonists have been shown to improve

cognitive performance in various animal models (Hancock and Fox in *Milestones in Drug Therapy*, ed. Buccafusco, 2003). These compounds can be used as pro-cognitive agents and can increase vigilance. Therefore, histamine H3 receptor antagonists and inverse agonists can be used in aging or degenerative disorders in which vigilance, attention and memory are impaired, for example, as in Alzheimer's disease or other dementias.

Alzheimer's disease (AD), a neurodegenerative disorder, is the most common cause of dementia. It is characterized clinically by progressive cognitive deterioration together with neuropsychiatric symptoms and behavioural changes. The most striking early symptom is memory loss, which usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories. As the disorder progresses, cognitive (intellectual) impairment extends to the domains of language, skilled movements, recognition and functions closely related to the frontal and temporal lobes of the brain such as decision-making and planning. There is currently no cure for AD, although there are drugs which offer symptomatic benefit, specifically with respect to short-term memory impairment. These drugs include acetylcholinesterase inhibitors such as donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon) and NMDA antagonists such as memantine.

Histamine H3 receptor antagonists and inverse agonists can be used to treat or prevent cognitive disorders (Passani *et al. Trends Pharmacol. Sci.* 2004, **25**, 618-625), epilepsy (Vohora *et al. Pharmacol. Biochem. Behav.* 2001, **68**, 735-741), depression (Perez-Garcia *et al. Psychopharmacol.* 1999, **142**, 215-220), attention deficit hyperactivity disorder (ADHD), (Fox *et al. Behav. Brain Res.* 2002, **131**, 151-61), and schizophrenia (Fox *et al. J. Pharmacol. Exp. Ther.* 2005, 313, 176-190). These indications are described briefly below. For additional information, see reviews by Leurs *et al.*, *Nat. Rev. Drug. Discov.* 2005, 4, 107-120, and Vohora *Investigational Drugs* 2004, 7, 667-673). Histamine H3 receptor antagonists or inverse agonists can also be used as a novel therapeutic approach to restore cortical activation in comatose or brain-traumatized patients (Passani *et al.*, *Trends in Pharmacol. Sci.* 2004, **25**, 618-625).

As stated above, histamine H3 receptor antagonists and inverse agonists can be used to treat or prevent epilepsy. Epilepsy (often referred to as a seizure disorder) is a chronic neurological condition characterized by recurrent unprovoked seizures. In terms of their pattern of activity, seizures may be described as either partial (focal) or generalized. Partial seizures only involve a localized part of the brain, whereas generalized seizures involve the entire cortex. There are many different epilepsy syndromes, each presenting with its own unique combination of seizure type, typical age of onset, EEG findings, treatment, and prognosis. Some common seizure syndromes include, for example, infantile spasms (West syndrome), childhood absence epilepsy, and benign focal epilepsy of childhood (Benign Rolandic epilepsy), juvenile myoclonic epilepsy, temporal lobe epilepsy, frontal lobe epilepsy and Lennox-Gastaut syndrome.

Compounds of the present invention can be used in combination with various known drugs. For example, compounds of the present invention can be used with one or more drugs that prevent seizures or reduce seizure frequency: these include carbamazepine (common brand name Tegretol), clobazam (Frisium), clonazepam (Klonopin), ethosuximide (Zarontin),
5 felbamate (Felbatol), fosphenytoin (Cerebyx), flurazepam (Dalmane), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), mephenytoin (Mesantoin), phenobarbital (Luminal), phenytoin (Dilantin), pregabalin (Lyrica), primidone (Mysoline), sodium valproate (Epilim), tiagabine (Gabitril), topiramate (Topamax), valproate semisodium (Depakote), valproic acid (Depakene, Convulex), and vigabatrin (Sabril). Other
10 drugs are commonly used to abort an active seizure or interrupt a seizure flurry; these include diazepam (Valium) and lorazepam (Ativan). Drugs used only in the treatment of refractory status epilepticus include paraldehyde (Paral) and pentobarbital (Nembutal).

As stated above, a histamine H3 receptor antagonist or inverse agonist can be used as the sole agent of treatment or can be used in combination with other agents. For example,
15 Vohora *et al.* show that a histamine H3 receptor antagonist can work as an anti-epilepsy, anti-seizure drug and also showed effect with sub-effective doses of the H3 receptor antagonist in combination with sub-effective doses of known anti-epileptic drugs (Vohora *et al. Pharmacol. Biochem. Behav.* 2001, **68**, 735-741).

Perez-Garcia *et al. (Psychopharmacol.* 1999, **142**, 215-220) tested the ability of a
20 histamine H3 receptor agonist and antagonist on experimental mouse models of anxiety (elevated plus-maze) and depression (forced swimming test). They found that while the compounds did not have a significant effect on the model of anxiety, an H3 receptor antagonist did have a significant dose-dependent effect in the model of depression. Thus, histamine H3 receptor antagonists or inverse agonists can have antidepressant effects.

25 Clinical depression is a state of sadness or melancholia that has advanced to the point of being disruptive to an individual's social functioning and/or activities of daily living. Clinical depression affects about 16% of the population on at least one occasion in their lives. Clinical depression is currently the leading cause of disability in the U.S. as well as other countries, and is expected to become the second leading cause of disability worldwide (after heart disease) by
30 the year 2020, according to the World Health Organization.

Compounds of the present invention can be used in combination with various known drugs. For example, compounds of the present invention can be used with one or more of the drugs currently available that can relieve the symptoms of depression. They include, for example, monoamine oxidase inhibitors (MAOIs) such as Nardil or Moclobemide (Manerix),
35 tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), escitalopram (Lexapro), and sertraline (Zoloft), norepinephrine

reuptake inhibitors such as reboxetine (Edronax), and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Effexor) and duloxetine (Cymbalta).

As stated above, histamine H3 receptor antagonists and inverse agonists can be used to treat or prevent attention deficit hyperactivity disorder (ADHD). According to the Diagnostic and Statistical Manual of Mental Disorders-IV-TR, ADHD is a developmental disorder that arises in childhood, in most cases before the age of 7 years, is characterized by developmentally inappropriate levels of inattention and/or hyperactive-impulsive behavior, and results in impairment in one or more major life activities, such as family, peer, educational, occupational, social, or adaptive functioning. ADHD can also be diagnosed in adulthood.

The first-line medications used to treat ADHD are mostly stimulants, which work by stimulating the areas of the brain responsible for focus, attention, and impulse control. The use of stimulants to treat a syndrome often characterized by hyperactivity is sometimes referred to as a paradoxical effect, but there is no real paradox in that stimulants activate brain inhibitory and self-organizing mechanisms permitting the individual to have greater self-regulation. The stimulants used include, for example, methylphenidate (sold as Ritalin, Ritalin SR and Ritalin LA), Metadate, Metadate ER, Metadate CD, Concerta, Focalin, Focalin XR or Methylin. The stimulants also include, for example, amphetamines such dextroamphetamine, sold as Dexedrine, Dexedrine Spansules, Adderall, and Adderall XR, a trade name for a mixture of dextroamphetamine and laevoamphetamine salts, methamphetamine sold as Desoxyn, bupropion, a dopamine and norepinephrine reuptake inhibitor, marketed under the brand name Wellbutrin. A non-stimulant medication to treat ADHD is Atomoxetine (sold as Strattera) a norepinephrine reuptake inhibitor. Other drugs sometimes used for ADHD include, for example, benzphetamine, Provigil/Alertec/modafinil and clonidine. Recently it has been reported that in a rat pup model for ADHD, a histamine H3 receptor antagonist was at least as effective as methylphenidate (Ritalin) (Hancock and Fox in *Milestones in Drug Therapy*, ed. Buccafusco, 2003). Compounds of the present invention can be used in combination with various known drugs. For example, compounds of the present invention can be used with one or more of the drugs used to treat ADHD and related disorders.

As stated above, histamine H3 receptor antagonists and inverse agonists can be used to treat or prevent schizophrenia. Schizophrenia is a psychiatric diagnosis that describes a mental disorder characterized by impairments in the perception or expression of reality and by significant social or occupational dysfunction. A person experiencing untreated schizophrenia is typically characterized as demonstrating disorganized thinking, and as experiencing delusions or auditory hallucinations. Although the disorder is primarily thought to affect cognition, it can also contribute to chronic problems with behavior and emotion. Schizophrenia is often described in terms of "positive" and "negative" symptoms. Positive symptoms include delusions, auditory hallucinations and thought disorder, and are typically regarded as manifestations of psychosis.

Negative symptoms are so named because they are considered to be the loss or absence of normal traits or abilities, and include features such as flat, blunted or constricted affect and emotion, poverty of speech and lack of motivation. Some models of schizophrenia include formal thought disorder and planning difficulties in a third group, a "disorganization syndrome."

5 The first line pharmacological therapy for schizophrenia is usually the use of antipsychotic medication. Antipsychotic drugs are only thought to provide symptomatic relief from the positive symptoms of psychosis. The newer atypical antipsychotic medications (such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole) are usually preferred over older typical antipsychotic medications (such as chlorpromazine and haloperidol) due to their favorable side-effect profile. While the atypical antipsychotics are associated with less extra pyramidal side-effects and tardive dyskinesia than the conventional antipsychotics, some of the agents in this class (especially olanzapine and clozapine) appear to be associated with metabolic side effects such as weight gain, hyperglycemia and hypertriglyceridemia that must be considered when choosing appropriate pharmacotherapy.

15 Histamine H3 receptor antagonists or inverse agonists can be used to treat obesity (Hancock, *Curr. Opin. Investig. Drugs* 2003, 4, 1190-1197). The role of neuronal histamine in food intake has been established for many years and neuronal histamine release and/or signalling has been implicated in the anorectic actions of known mediators in the feeding cycle such as leptin, amylin and bombesin. In the brain, the H3 receptor is implicated in the regulation of histamine release in the hypothalamus. Moreover, *in situ* hybridization studies have revealed histamine H3 receptor mRNA expression in rat brown adipose tissue, indicating a role in the regulation of thermogenesis (Karlstedt *et al.*, *Mol. Cell. Neurosci.* 2003, **24**, 614-622). Furthermore, histamine H3 receptor antagonists have been investigated in various preclinical models of obesity and have shown to be effective in reducing food intake, reducing weight, and decreasing total body fat in mice (Hancock, *et al.* *Eur. J. Pharmacol.* 2004, **487**, 183-197). The most common drugs used for the treatment of obesity are sibutramine (Meridia) and orlistat (Xenical), both of which have limited effectiveness and significant side effects. Therefore, novel anti-obesity agents, such as histamine H3 receptor antagonists or inverse agonists, are needed.

25 Histamine H3 receptor antagonists or inverse agonists can also be used to treat upper airway allergic responses (U.S. Pat. Nos. 5,217,986; 5,352,707 and 5,869,479) including allergic rhinitis and nasal congestion. Allergic rhinitis is a frequently occurring chronic disease that affects a large number of people. Recent analysis of histamine H3 receptor expression in the periphery by quantitative PCR revealed that H3 receptor mRNA is abundantly expressed in human nasal mucosa (Varty *et al.* *Eur. J. Pharmacol.* 2004, **484**, 83-89). In addition, in a cat model of nasal decongestion, a combination of histamine H3 receptor antagonists with the H1 receptor antagonist chlorpheniramine resulted in significant nasal decongestion without the hypertensive effect seen with adrenergic agonists. (McLeod *et al.* *Am. J. Rhinol.* 1999, **13**, 391-

399). Thus, histamine H3 receptor antagonists or inverse agonists can be used alone or in combination with H1 receptor blockage for the treatment of allergic rhinitis and nasal congestion.

Histamine H3 receptor antagonists or inverse agonists have therapeutic potential for the treatment of pain (Medhurst *et al. Biochemical Pharmacology* (2007), 73(8), 1182-1194).

Itch, or pruritus, is the unpleasant sensation that leads to a desire to scratch (for reviews, see *Journal of Investigative Dermatology* (2006) 126: 1705-1718; and *Lancet* (2003) 361: 690-94). It is a common and distressing symptom in a variety of conditions and diseases. Itch typically occurs in peripheral diseases such as allergic conjunctivitis, allergic rhinitis, hemorrhoids, atopic dermatitis, allergic dermatitis, acute and chronic urticaria (hives), psoriasis and dermatoses of fungal, allergic and non-allergic origin. Itching can also be a major symptom of many systemic diseases such as, Hodgkin's disease, chronic renal failure, polycythemia vera, hyperthyroidism, malignancy, infection, chronic cholestatic liver disease and end-stage renal disease, and cholestasis. In addition, senile itch without an obvious cause, except perhaps xerosis, occurs in more than half of the population aged 70 years. In all cases chronic severe generalized itch can be disabling.

While not intending to be complete, diseases or conditions associated with itch further include primary biliary cirrhosis (PBC), primary sclerosis cholangitis (PSC), chronic renal disease, epidural morphine, pregnancy, diabetes mellitus, thyroid illness, hyperparathyroidism, iron deficiency anemia, viral infection, aquagenic pruritus, and psychogenic itch. Itch causes sufferers to scratch, leading to skin damage, increased risk of skin infection, and worsening of inflammation. However, despite the prevalence of this clinically important symptom, the pathogenesis of itch is not well understood, and treatment options are limited (Paus, R., et al., *J. Clin. Invest.* 2006, 116:1174-1185).

Itching can be elicited by chemical, electrical, mechanical and thermal stimulation. So far no morphological structure has been identified as a specific receptor for the itch sensation, but it is assumed that itch receptors are linked to the free nerve endings of C-fibers close to the dermo-epidermal junction. The impulses set up in the thin, non-myelinated, slowly conducting C-fibers enter the spinal cord via the dorsal horn, then ascend in the contralateral spinothalamic tract, pass via the thalamus and end in the somatosensory cortex of the post-central gyrus. Itching and pain are related phenomena, and it was previously believed that itching was equal to sub-threshold pain, i.e. with increased activity in the C-fibers the perceived sensation changed from itching to pain. Although itch was once thought to be a subliminal form of pain (intensity theory), current evidence points to separate sensory neuronal systems mediating the two modalities. First, pain and itch are dissociable. Pain and itch evoke different motor responses, scratching for itch and withdrawal for pain. Second, based on clinical observations, systemically-administered opioids have a dichotomous effect on these two sensory modalities.

μ -Opioid receptor agonists reduce pain but can cause itch. Furthermore, antagonizing the central μ -opioid receptors, for example with naloxone or naltrexone, suppresses pruritus and at the same time may lower the pain threshold.

Itch due to skin inflammation is thought to be mediated at least partly by activation of skin mast cells, which release pruritogenic mediators to activate receptors on peripheral nerve endings to transmit itch signals. Among the substances released from mast cells, histamine is a particularly potent pruritogen. When injected into the skin, histamine causes strong itch sensations in humans and animals. Therefore, antagonists of histamine receptors have been explored as itch treatments. There are several topical and systemic agents that suppress itching in selected clinical settings. Unfortunately, no universally effective anti-pruritic drug exists. Therefore, there is an urgent need for new approaches for managing itch.

Compounds of the present invention are useful in the treatment of itch or pruritus. Accordingly, one aspect of the present invention relates to the inhibition of the histamine 3 receptor (H3R) in an individual, such as by administration of a compound of the present invention, can reduce itching or pruritus. In **Example 5** the G-protein coupled H3R is shown as a key effector of the itch sensation. Accordingly, in one embodiment, the present invention provides a method of preventing and/or treating itch in an individual in need thereof by administering a therapeutically effective amount of a compound or agent that modulates the H3R.

In addition, peripherally restricted inhibitors of H3R are capable of mediating the inhibition of itch. Accordingly, screening for peripherally restricted inhibitors (*i.e.* antagonists), and the application of peripherally restricted inhibitors in the various embodiments of the invention is contemplated. Peripherally restricted compounds may be advantageous to the extent that the peripheral restriction reduces the CNS effects of H3R inhibition. Such effects may include, for example, wakefulness. In one embodiment of this invention, H3R inhibitors, for example antagonists and inverse agonists, are peripherally restricted and may be assayed or screened based on their inability or reduced ability to inhibit H3R in the CNS (for example, in the brain).

In a particular therapeutic setting, peripherally restricted compounds of the present invention can be advantageous in the treatment of pruritus to the extent that the peripheral restriction reduces the CNS effects associated with H3R inhibition. For example, an individual suffering from pruritus can benefit from a treatment with a peripherally restricted compound of the present invention and yet not experience or experience to a less extent the CNS effects associated with H3R inhibition, such as, wakefulness.

In one embodiment, the compound of the present invention is restricted in some manner from crossing the blood brain barrier. In another embodiment, the compound of the present invention is less than 100% restricted to the periphery. In one embodiment, the compound of the present invention has a brain:plasma ratio (B/P) which is less than 1 in at least one species. In

some embodiments, the species is a mouse. In some embodiments, the species is a C57BL/6 mouse.

In one embodiment, the H3R antagonist has a brain to plasma ratio of about 0.5 or less. In another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.4 or less. In
5 another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.3 or less. In another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.2 or less. In another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.15 or less. In another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.1 or less. In
10 another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.01 or less. In another embodiment, the H3R antagonist has a brain to plasma ratio of about 0.1 to about 0.001.

In one embodiment, the invention comprises a method for treating or preventing itching or the symptoms thereof in an individual wherein an inhibitor of H3R is administered to the individual.

In one embodiment, the invention disclosed herein is suitable for the prevention and/or
15 treatment of itch that is associated with a disease or disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to
20 medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito
25 sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.

Itching can be associated with various types of cancers such as Hodgkin's disease, Lymphoma, Leukemia, Kaposi's sarcoma, AIDs, liver metastases, and renal failure, and may be
30 associated with some antibiotics. Acute itching, during the infusion of chemotherapy could be an early sign of a hypersensitivity reaction. Chemotherapy medications commonly associated with risk of allergic reactions include: L-asparaginase, paclitaxel, docetaxel, teniposide, procarbazine, and cytarabine. Itching can occur as chronic side effect of anti-cancer treatments including Proleukin® (Interleukin-2), Interferon (Intron® & Roferon®), radiation therapy, acute
35 and chronic graft-versus-host disease (GVHD), and occasionally supportive growth factors including Neupogen® (G-CSF) and Leukine® (GM-CSF).

Certain Embodiments of the Present Invention

One aspect of the present invention pertains to methods of inducing wakefulness in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5 One aspect of the present invention pertains to methods for treating a histamine H3 receptor-associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10 One aspect of the present invention pertains to methods for treating a histamine H3 receptor-associated disorder selected from the group: a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease,
15 pain, and pruritus in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20 One aspect of the present invention pertains to methods for treating a cognitive disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25 One aspect of the present invention pertains to methods for treating epilepsy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

 One aspect of the present invention pertains to methods for treating a disorder of sleep and wakefulness in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30 One aspect of the present invention pertains to methods for treating narcolepsy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35 One aspect of the present invention pertains to methods for treating shift-work sleep disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating cataplexy in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating jet lag in an
5 individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating sleep apnea in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10 One aspect of the present invention pertains to methods for treating excessive daytime sleepiness in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating attention deficit
15 hyperactivity disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating schizophrenia in an individual comprising administering to the individual in need thereof a therapeutically effective
20 amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating pain in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating pruritus in an
25 individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating pruritus in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof,
30 wherein pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch,
35 uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn,

wound healing, itch associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for inducing wakefulness.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of a histamine H3 receptor-associated disorder.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of a disorder selected from the group: a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, and pruritus.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of a cognitive disorder.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of epilepsy.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of a disorder of sleep and wakefulness.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of narcolepsy.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of shift-work sleep disorder.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of cataplexy.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of jet lag.

5 One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of sleep apnea.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of excessive daytime sleepiness.

10 One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of attention deficit hyperactivity disorder.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of schizophrenia.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of pain.

20 One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of pruritus.

One aspect of the present invention pertains to the use of a compound of the present invention or a pharmaceutical composition thereof in the manufacture of a medicament for the treatment of pruritus, wherein pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of the human or animal body by therapy.

5 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of inducing wakefulness.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of a histamine H3 receptor-associated disorder.

10 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of a histamine H3 receptor-associated disorder selected from the group: a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic
15 responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, and pruritus.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of a cognitive disorder.

20 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of epilepsy.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of a disorder of sleep and wakefulness.

25 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of narcolepsy.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of shift-work sleep disorder.

30 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of cataplexy.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of jet lag.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of sleep apnea.

35 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of excessive daytime sleepiness.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of attention deficit hyperactivity disorder.

5 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of schizophrenia.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of pain.

One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of pruritus.

10 One aspect of the present invention pertains to a compound of the present invention or a pharmaceutical composition thereof for use in a method of treatment of pruritus, wherein the pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic
15 infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch
20 associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.

25

PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a
30 compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising formulating at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a
35 pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, 5
tableting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles 10
(including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

15 A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*).

20 While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a 25
compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical 30
(including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single 35
pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as histamine H3 receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and refers to a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or

4 doses. Depending on the individual and as deemed appropriate from the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt, solvate or hydrate of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances

which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

5 In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

 The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, 10 magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or 15 without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets and lozenges can be used as solid forms suitable for oral administration.

 For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously 20 therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

25 Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile 30 injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed 35 including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (*e.g.* by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may
5 take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

10 Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins,
15 methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants,
20 thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with
25 an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and
30 acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of
35 a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable

propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, *e.g.*, gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic,

hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Sciences*, 66:1-19 (1977).

5 The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

10 Compounds of the present invention can be converted to “pro-drugs.” The term “pro-drugs” refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to
15 eliminate a property of the compound. In one general aspect, the “pro-drug” approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

20 Some embodiments of the present invention include a method of producing a pharmaceutical composition for “combination-therapy” comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

25 It is noted that when the histamine H3 receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as histamine H3 receptor modulators, for the treatment of an H3-associated disease or disorder in companionship animals
30 (e.g., cats, dogs, *etc.*) and in livestock animals (e.g., cows, chickens, fish, *etc.*) Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

HYDRATES AND SOLVATES

35 It is understood that when the phrase “pharmaceutically acceptable salts, solvates, and hydrates” or the phrase “pharmaceutically acceptable salt, solvate, or hydrate” is used when referring to compounds described herein, it embraces pharmaceutically acceptable solvates

and/or hydrates of the compounds, pharmaceutically acceptable salts of the compounds, as well as pharmaceutically acceptable solvates and/or hydrates of pharmaceutically acceptable salts of the compounds. It is also understood that when the phrase “pharmaceutically acceptable solvates and hydrates” or the phrase “pharmaceutically acceptable solvate or hydrate” is used when referring to compounds described herein that are salts, it embraces pharmaceutically acceptable solvates and/or hydrates of such salts.

It will be apparent to those skilled in the art that the dosage forms described herein may comprise, as the active component, either a compound described herein or a pharmaceutically acceptable salt or as a solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds described herein and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillery, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids,” in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999. Accordingly, one aspect of the present invention pertains to methods of administering hydrates and solvates of compounds described herein and/or their pharmaceutical acceptable salts, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

ISOTOPES

The present disclosure includes all isotopes of atoms occurring in the present compounds, intermediates, salts and crystalline forms thereof. Isotopes include those atoms having the same atomic number but different mass numbers. One aspect of the present invention includes every combination of one or more atoms in the present compounds, intermediates, salts, and crystalline forms thereof that is replaced with an atom having the same atomic number but a different mass number. One such example is the replacement of an atom that is the most naturally abundant isotope, such as ^1H or ^{12}C , found in one the present compounds, intermediates, salts, and crystalline forms thereof, with a different atom that is not the most naturally abundant isotope, such as ^2H or ^3H (replacing ^1H), or ^{11}C , ^{13}C , or ^{14}C (replacing ^{12}C). A compound wherein such a replacement has taken place is commonly referred to as being an isotopically-labeled compound. Isotopic-labeling of the present compounds, intermediates, salts, and crystalline forms thereof can be accomplished using any one of a variety of different

synthetic methods know to those of ordinary skill in the art and they are readily credited with understanding the synthetic methods and available reagents needed to conduct such isotopic-labeling. By way of general example, and without limitation, isotopes of hydrogen include ^2H (deuterium) and ^3H (tritium). Isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C . Isotopes of nitrogen include ^{13}N and ^{15}N . Isotopes of oxygen include ^{15}O , ^{17}O , and ^{18}O . An isotope of fluorine includes ^{18}F . An isotope of sulfur includes ^{35}S . An isotope of chlorine includes ^{36}Cl . Isotopes of bromine include ^{75}Br , ^{76}Br , ^{77}Br , and ^{82}Br . Isotopes of iodine include ^{123}I , ^{124}I , ^{125}I , and ^{131}I . Another aspect of the present invention includes compositions, such as, those prepared during synthesis, preformulation, and the like, and pharmaceutical compositions, such as, those prepared with the intent of using in a mammal for the treatment of one or more of the disorders described herein, comprising one or more of the present compounds, intermediates, salts, and crystalline forms thereof, wherein the naturally occurring distribution of the isotopes in the composition is perturbed. Another aspect of the present invention includes compositions and pharmaceutical compositions comprising compounds as described herein wherein the compound is enriched at one or more positions with an isotope other than the most naturally abundant isotope. Methods are readily available to measure such isotope perturbations or enrichments, such as, mass spectrometry, and for isotopes that are radio-isotopes additional methods are available, such as, radio-detectors used in connection with HPLC or GC.

OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds of the present invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the histamine H3 receptor in tissue samples, including human and for identifying histamine H3 receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel H3 receptor assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radio-labeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{75}Br , ^{76}Br , ^{77}Br , ^{82}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* histamine H3 receptor labeling and competition assays, compounds that

incorporate ^3H , ^{14}C , ^{82}Br , ^{125}I , ^{131}I or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C , ^{18}F , ^{125}I , ^{123}I , ^{124}I , ^{131}I , ^{75}Br , ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound of Formula (Ia), (Ic), (Ie), (Ig), (Ii), (Iic), (Ile), (Ilg), (Ili), (Ilk), (IIm), (Ilo), (IIq), (IIs), (IIu), (IIw), and (IIy) that has incorporated at least one radionuclide; in some embodiments the radionuclide is selected from the group consisting of ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br .

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^3H and/or ^{14}C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Drawings and Examples *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the scarcer radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas: This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^3H]: This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

C. Reduction with Lithium Aluminum Hydride [^3H]: This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. *N*-Methylation using Methyl Iodide [^3H]: This procedure is usually employed to prepare *O*-methyl or *N*-methyl (^3H) products by treating appropriate precursors with high specific activity methyl iodide (^3H). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

- A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as a diazonium tetrafluoroborate salt and subsequently to ^{125}I labeled compound using Na^{125}I . A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.
- 5 B. Ortho ^{125}I iodination of phenols: This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.
- C. Aryl and heteroaryl bromide exchange with ^{125}I : This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [*i.e.* $\text{Pd}(\text{Ph}_3\text{P})_4$] or through an
- 10 aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [*e.g.*, $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.
- A radiolabeled histamine H3 receptor compound of Formula (**Ia**) can be used in a
- 15 screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (*i.e.*, test compound) can be evaluated for its ability to reduce binding of the “radio-labeled compound of Formula (**Ia**)” to the H3 receptor. Accordingly, the ability of a test compound to compete with the “radio-labeled compound of Formula (**Ia**)” for the binding to the histamine H3 receptor directly correlates to its binding affinity.
- 20 The labeled compounds of the present invention bind to the histamine H3 receptor. In one embodiment the labeled compound has an IC_{50} less than about 500 μM , in another embodiment the labeled compound has an IC_{50} less than about 100 μM , in yet another embodiment the labeled compound has an IC_{50} less than about 10 μM , in yet another embodiment the labeled compound has an IC_{50} less than about 1 μM and in still yet another
- 25 embodiment the labeled inhibitor has an IC_{50} less than about 0.1 μM .

Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, *inter alia*, a review of this disclosure.

- As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects,
- 30 advantages and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

- 35 **Example 1: Syntheses of compounds of the present invention.**

Illustrated syntheses for compounds of the present invention are shown in Figures 1 through 3 where the symbols have the same definitions as used throughout this disclosure.

The compounds of the invention and their syntheses are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version 7.0.1, AutoNom version 2.2, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman) and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

LCMS spec: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2.

Example 1.1: Preparation of Intermediate (R)-6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline.

The intermediate (R)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline was prepared in a similar manner as described in WO2009/105206 which is incorporated herein by reference in its entirety.

Step A: Preparation of (R)-1-(4-Bromophenethyl)-2-methylpyrrolidine.

A 4 L jacketed reactor equipped with a mechanical stirrer, thermocouple, gas inlet, heating/cooling and condenser was charged with 4-bromophenethyl methanesulfonate (199.8 g, 716 mmol), followed by acetonitrile (2.2 L), and the resulting slurry was stirred. Water (270 mL) was then added, followed by gradual addition of potassium carbonate (297.2 g, 2.147 mol). (R)-2-methylpyrrolidine L-tartrate (168.8 g, 717 mmol) was then added, and the reaction

mixture was heated at 71 °C overnight. The reaction mixture was cooled and the solvent was removed. The residue was suspended in water (500 mL) and extracted with isopropyl acetate (2 × 400 mL). The organic extracts were combined, rinsed with water (150 mL), dried over sodium sulfate, filtered and concentrated to dryness to provide a golden yellow oil (191 g). This material was combined with 185 g of material which was prepared by the same method and dissolved in isopropyl acetate (2 × 500 mL). The mixture was extracted with 1 N HCl (2 × 300 mL and 200 mL). The acidic aqueous layer was separated and pH adjusted to 11-12 with 25% NaOH. This was then extracted with isopropyl acetate (2 × 350 mL, washed with water (150 mL) and dried over MgSO₄ (100 g). Upon filtration and solvent removal, a pale yellow oil was obtained to provide the title compound (337.5 g). LCMS m/z = 268.1 [M+H]⁺; ¹H NMR (CDCl₃, 400 MHz) δ ppm 1.16 (d, J = 6.2 Hz, 3H), 1.46-1.55 (m, 1H), 1.71-1.81 (m, 1H), 1.82-1.90 (m, 1H), 1.94-2.01 (m, 1H), 2.24-2.31 (m, 1H), 2.32-2.39 (m, 1H), 2.41-2.47 (m, 1H), 2.84 (t, J = 8.2 Hz, 2H), 3.01-3.08 (m, 1H), 3.26-3.31 (m, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H).

Step B: Preparation of (*R*)-4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenylboronic Acid.

A 1 L 3-neck flask equipped with mechanical stirrer, thermometer, and addition funnel under N₂ was charged with a solution of (*R*)-1-(4-bromophenethyl)-2-methylpyrrolidine (26.8 g, 100 mmol) in anhydrous THF (250 mL). The reaction mixture was then cooled to an internal temperature of -78 °C. A solution of butyllithium (2.5 M in hexane, 52 mL, 130 mmol) was added dropwise, maintaining an internal temperature < -70 °C. Once addition was complete, stirring was continued an additional 15 min prior to the addition of triisopropyl borate (75 g, 400 mmol), followed by a rinse with 50 mL anhydrous THF while maintaining an internal temperature < -65 °C during addition. The reaction mixture was then allowed to warm to ambient temperature over 1.5 h, and was then quenched by dropwise addition of 2 N HCl (100 mL). The resulting mixture was stirred overnight, and the solvent volume was reduced to about 150 mL. The resulting suspension was cooled in an ice bath and filtered, rinsing sparingly with cold isopropanol. The filtrate volume was again reduced to 50 mL and the process was repeated. The filter cakes were combined, taken up in boiling isopropanol (250 mL), dissolving most, but not all of the solids. The mixture was then cooled in an ice bath and filtered, then the filtrate was concentrated to half volume and the process was repeated to provide two additional crops. A white solid was obtained as the title compound (23 g). LCMS m/z = 234.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.41 (d, J = 6.6 Hz, 3H), 1.59-1.68 (m, 1H), 1.89-2.00 (m, 2H), 2.15-2.22 (m, 1H), 3.00-3.07 (m, 2H), 3.11-3.19 (m, 2H), 3.37-3.50 (m, 2H), 3.57-3.65 (m, 1H), 4.80-6.75 (bs, 3 H), 7.27 (d, J = 7.6 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H).

Step C: Preparation of Intermediate (*R*)-6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline.

To a round-bottom flask was added 6-bromo-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.00 g, 8.05 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (2.063 g, 8.85 mmol), tetrakis(triphenylphosphine)palladium (0) (0.279 g, 0.241 mmol), benzene (30.00 mL), ethanol (10.00 mL), and 2.0 M aqueous solution of sodium bicarbonate (8.05 mL, 16.09 mmol). The reaction mixture was refluxed for 6 h. Upon completion, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was taken up in 1 M HCl solution and washed with ethyl acetate. The aqueous layer was basified with 10% aqueous NaOH to pH~11, extracted with ethyl acetate, and concentrated. The residue was purified by silica gel column, eluting with 5-10% 2.0 M ammonia in methanol/DCM to give a yellow solid (1.20 g). LCMS *m/z* = 321.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.99-1.04 (m, 3H), 1.22-1.33 (m, 1H), 1.59-1.69 (m, 2H), 1.81-1.92 (m, 1H), 2.13 (q, *J* = 8.67 Hz, 1H), 2.20-2.34 (m, 2H), 2.65-2.83 (m, 5H), 2.94-3.04 (m, 3H), 3.10-3.18 (m, 1H), 3.91 (s, 2H), 7.09 (d, *J* = 8.08 Hz, 1H), 7.29 (d, *J* = 8.08 Hz, 2H), 7.33-7.40 (m, 2H), 7.53 (d, *J* = 8.08 Hz, 2H).

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Example 1.2: Preparation of (*R*)-1-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)ethanone (Compound 1).

(*R*)-6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (20.0 mg, 0.062 mmol), 2-(1*H*-tetrazol-5-yl)acetic acid (8.8 mg, 0.069 mmol), DIEA (32.7 μL, 0.187 mmol), and HATU (28.5 mg, 0.075 mmol) were added to a vial with DMF (0.4 mL). The reaction was briefly heated with a heat gun to dissolve all the starting material. Then the reaction was stirred overnight at room temperature. The reaction was diluted with DMSO (0.4 mL) and purified by preparative LC/MS to give the TFA salt of the title compound (24.6 mg). LCMS *m/z* = 431.2.

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Example 1.3: Preparation of (*R*)-4-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic Acid (Compound 2).

To a mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (260 mg, 0.661 mmol) and dihydrofuran-2,5-dione (79 mg, 0.793 mmol) in THF (15 mL) was added TEA (0.332 mL, 2.379 mmol). The reaction was stirred at 60 °C overnight. The mixture was filtered. The filtrate was concentrated to give a solid. The solid was triturated in ACN, filtered, and collected to give the neutral form of the title compound. LCMS *m/z* = 421.6 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.01 (d, *J* = 6.00 Hz, 3H), 1.23-1.34 (m, 1H), 1.59-1.70 (m, 2H), 2.81-2.91 (m, 1H), 2.15 (t, *J* = 8.72, 1H), 2.22-2.35 (m, 2H), 2.46 (t, *J* = 6.22, 2H), 2.60-2.66 (m, 2H), 2.66-2.85 (m, 3H), 2.90-3.03 (m, 2H), 3.10-3.17 (m, 1H), 3.66-3.74 (m, 2H), 4.62 (s, 1H), 4.69 (s, 1H), 7.26 (t, *J* = 8.80 Hz, 1H), 7.30 (d, *J* = 8.13 Hz, 2H), 7.45 (d, *J* = 6.01 Hz, 2H), 7.55 (d, *J* = 8.03 Hz, 2H).

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Example 1.4: Preparation of (*R*)-2,2,3,3-tetrafluoro-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid (Compound 8).

In a reaction vial was placed (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (30 mg, 0.076 mmol), 3,3,4,4-tetrafluorodihydrofuran-2,5-dione (39.4 mg, 0.229 mmol) and sodium bicarbonate (32.0 mg, 0.381 mmol) in THF (1.5 mL). The reaction was stirred at room temperature for 1 h and heated at 60 °C for 30 min. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in 2 M HCl and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 493.4 [M+H]⁺.

Example 1.5: Preparation of (*R*)-3,3-Dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic Acid (Compound 3).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.4** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 4,4-dimethyldihydro-2*H*-pyran-2,6(3*H*)-dione. LCMS m/z = 463.6 [M+H]⁺; ¹H NMR (400 MHz, CD₃CN) δ ppm 0.97 (s, 3H), 1.02 (s, 3H), 1.15 (d, *J* = 6.74, 0.3H), 1.35 (d, *J* = 6.52, 2.7H), 1.58-1.71 (m, 1H), 1.90-2.00 (m, 2H), 2.10-2.20 (m, 1H), 2.25 (s, 1H), 2.28 (s, 1H), 2.53 (s, 1H), 2.55 (s, 1H), 2.81-2.93 (m, 2H), 2.95-3.07 (m, 4H), 3.25-3.35 (m, 1H), 3.39-3.40 (m, 1H), 3.61-3.71 (m, 1H), 3.77-3.82 (m, 2H), 4.72 (s, 1H), 4.74 (s, 1H), 7.18 (t, *J* = 8.37 Hz, 1H), 7.28 (d, *J* = 8.17 Hz, 2H), 7.39 (d, *J* = 8.04 Hz, 2H), 7.52 (d, *J* = 8.16 Hz, 2H).

Example 1.6: Preparation of (*R*)-2,2-Dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic Acid (Compound 4).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.4** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 3,3-dimethyldihydro-2*H*-pyran-2,6(3*H*)-dione. LCMS m/z = 463.5 [M+H]⁺.

Example 1.7: Preparation of 3-Methyl-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic Acid (Compound 5).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.4** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 4-methyldihydro-2*H*-pyran-2,6(3*H*)-dione. LCMS m/z = 449.3 [M+H]⁺.

Example 1.8: Preparation of 3-hydroxy-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid (Compound 6).

In a reaction vial was placed (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (48 mg, 0.122 mmol), 4-(*tert*-butyldimethylsilyloxy)dihydro-2*H*-pyran-2,6(3*H*)-dione (89 mg, 0.366 mmol), and sodium bicarbonate (51.3 mg, 0.610 mmol) in DMF (2 mL). The reaction was stirred at 60 °C overnight. The mixture was filtered and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 451.4 [M+H]⁺.

Example 1.9: Preparation of (*R*)-2-(2-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethylthio)acetic Acid (Compound 7).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.4** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 1,4-oxathiane-2,6-dione. LCMS m/z = 453.5 [M+H]⁺.

Example 1.10: Preparation of (*R*)-2,2-Dimethyl-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic Acid (Compound 9).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.4** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 3,3-dimethyldihydrofuran-2,5-dione. LCMS m/z = 449.6 [M+H]⁺.

Example 1.11: Preparation of (*R*)-2-(2-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethoxy)acetic Acid (Compound 10).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (30 mg, 0.076 mmol), 1,4-dioxane-2,6-dione (10.62 mg, 0.092 mmol), and sodium carbonate (28.3 mg, 0.267 mmol) in THF (2 mL) was heated at 60 °C for 30 min. The mixture was then stirred at room temperature overnight. The precipitate was filtered, dissolved in 2 M HCl and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 437.4 [M+H]⁺.

Example 1.12: Preparation of (*R*)-5-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic Acid (Compound 11).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (30 mg, 0.076 mmol), dihydro-2*H*-pyran-2,6(3*H*)-dione (10.44 mg, 0.092 mmol), and TEA (0.038 mL, 0.275 mmol) in THF (2 mL) was heated at 60 °C

for 1 h. The mixture was purified by HPLC to give the TFA salt of the title compound. LCMS $m/z = 435.6$ $[M+H]^+$.

Example 1.13: Preparation of (*R*)-Methyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate (Compound 12).

To (*R*)-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid (15 mg, 0.036 mmol) was added HCl (1.25 M in MeOH, 2 mL, 2.500 mmol). The mixture was stirred at 60 °C for 30 min and room temperature for 1 h. The solvent was removed and residue was triturated in acetonitrile three times and dried to give the title compound. LCMS $m/z = 435.4$ $[M+H]^+$.

Example 1.14: Preparation of (*S*)-Ethyl 2-amino-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate (Compound 13).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (30 mg, 0.076 mmol), (*S*)-*tert*-butyl 2,6-dioxotetrahydro-2*H*-pyran-3-ylcarbamate (22.73 mg, 0.099 mmol), and TEA (0.038 mL, 0.275 mmol) in THF (1.5 mL) was heated at 60 °C for 3 h. The resulting mixture was concentrated. The residue was treated with 2 M HCl in EtOH and purified by HPLC to give the TFA salt of the title compound. LCMS $m/z = 478.4$ $[M+H]^+$.

Example 1.15: Preparation of (*R*)-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)(1*H*-tetrazol-5-yl)methanone (Compound 14).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline bis(2,2,2-trifluoroacetate) (30 mg, 0.055 mmol), disodium salt of 1*H*-tetrazole-5-carboxylic acid (8.64 mg, 0.055 mmol), HATU (22.88 mg, 0.060 mmol), and TEA (0.023 mL, 0.164 mmol) in DMF (1.5 mL) was stirred at 60 °C for 1 h. The mixture was filtered. The filtrate was purified by HPLC to give the TFA salt of the title compound. LCMS $m/z = 417.4$ $[M+H]^+$.

Example 1.16: Preparation of (*R*)-Ethyl 4-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate (Compound 15).

To (*R*)-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid (15 mg, 0.036 mmol) was added HCl (2 M in ethanol, 1.783 mL, 3.57 mmol). The solution was stirred for 24 h at room temperature and concentrated. The residue was triturated with ACN to give the title compound. LCMS $m/z = 449.6$ $[M+H]^+$.

Example 1.17: Preparation of (*R*)-Methyl 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetate (Compound 16).

To (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (50 mg, 0.156 mmol) in THF (1.5 mL) was added methyl 2-chloro-2-oxoacetate (28.7 mg, 0.234 mmol). The reaction was stirred at room temperature for 1 h. The mixture was concentrated and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 407.5 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.27 (d, J = 6.87 Hz, 0.3H), 1.46 (d, J = 6.52 Hz, 2.7H), 1.71-1.85 (m, 1H), 2.02-2.12 (m, 2H), 2.24-2.31 (m, 1H), 2.94-3.02 (m, 2H), 3.05-3.19 (m, 4H), 3.37-3.48 (m, 1H), 3.50-3.60 (m, 1H), 3.69 (t, J = 5.97, 1H), 3.73-3.81 (m, 1H), 3.83 (t, J = 6.12, 1H), 3.91 (s, 3H), 4.64 (s, 1H), 4.74 (s, 1H), 7.22-7.32 (m, 1H), 7.39 (d, J = 8.19 Hz, 2H), 7.45-7.53 (m, 2H), 7.63 (d, J = 8.19 Hz, 2H).

Example 1.18: Preparation of (*R*)-2-(1-(2-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclopentyl)acetic Acid (Compound 17).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (40 mg, 0.125 mmol) and 8-oxaspiro[4.5]decane-7,9-dione (20.99 mg, 0.125 mmol) in THF (1 mL) was heated at 60 °C overnight. The mixture was added 1 M HCl and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 489.4 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.27 (d, J = 6.83 Hz, 0.3H), 1.46 (d, J = 6.53 Hz, 2.7H), 1.49-1.69 (m, 4H), 1.70-1.80 (m, 5H), 2.02-2.12 (m, 2H), 2.23-2.33 (m, 1H), 2.46 (d, J = 12.2 Hz, 2H), 2.71 (d, J = 5.53 Hz, 2H), 2.96 (t, J = 6.04 Hz, 1H), 3.01 (t, J = 5.84 Hz, 1H), 3.06-3.20 (m, 4H), 3.38-3.48 (m, 1H), 3.53-3.61 (m, 1H), 3.74-3.84 (m, 1H), 3.85-3.92 (m, 2H), 4.81 (s, 1H), 4.83 (s, 1H), 7.29 (t, J = 7.89, 1H), 7.40 (d, J = 8.17 Hz, 2H), 7.48-7.53 (m, 2H), 7.64 (d, J = 8.18 Hz, 2H).

Example 1.19: Preparation of (*R*)-2-(1-(2-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetic Acid (Compound 18).

A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (20 mg, 0.062 mmol) and 3-oxaspiro[5.5]undecane-2,4-dione (11.37 mg, 0.062 mmol) in DMF (1 mL) was stirred at room temperature for 3 h. The mixture was purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 503.2 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.28 (d, J = 6.87 Hz, 0.3H), 1.29-1.30 (m, 1H), 1.48 (d, J = 6.52 Hz, 2.7H), 1.49-1.65 (m, 9H), 1.70-1.85 (m, 1H), 2.01-2.12 (m, 2H), 2.24-2.32 (m, 1H), 2.53 (d, J = 11.6 Hz, 2H), 2.65 (d, J = 5.28 Hz, 2H), 2.97 (t, J = 6.01 Hz, 1H), 3.02 (t, J = 5.79 Hz, 1H), 3.07-3.18 (m, 4H), 3.37-3.46 (m, 1H), 3.50-3.61 (m, 1H), 3.75-3.84 (m, 1H), 3.90-3.95 (m, 2H), 4.83 (s, 1H), 4.88 (s, 1H), 7.27-7.33 (m, 1H), 7.40 (d, J = 8.18 Hz, 2H), 7.48-7.54 (m, 2H), 7.64 (d, J = 8.20 Hz, 2H).

Example 1.20: Preparation of (1*S*,2*S*)-2-(6-(4-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic Acid (Compound 19).

5 A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (20 mg, 0.062 mmol) and (3*aR*,7*aR*)-hexahydroisobenzofuran-1,3-dione (9.62 mg, 0.062 mmol) in DMF (0.7 mL) was stirred at room temperature for 3 h. The mixture was purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 475.3 [M+H]⁺.

10 **Example 1.21: Preparation of (*R*)-Methyl 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-oxopropanoate (Compound 20).**

 A mixture of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (30 mg, 0.076 mmol), methyl 3-chloro-3-oxopropanoate (11.45 mg, 0.084 mmol), and TEA (0.034 mL, 0.244 mmol) was stirred at room temperature for
15 3 h. The mixture was added 1 M HCl (1 mL) and purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 421.5 [M+H]⁺.

Example 1.22: Preparation of (*R*)-Methyl 1-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylate (Compound 21).

 To a solution of (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (44 mg, 0.112 mmol) and 1-(methoxycarbonyl)cyclopropanecarboxylic acid (17.73 mg, 0.123 mmol) in DMF (1 mL) were added HATU (46.8 mg, 0.123 mmol) and TEA (0.047 mL, 0.336 mmol). The reaction was
25 stirred at room temperature for 4 h. The mixture was purified by HPLC to give the TFA salt of the title compound. LCMS m/z = 447.4 [M+H]⁺; ¹H NMR (400 MHz, CD₃CN) δ ppm 1.15 (d, J = 6.88 Hz, 0.3H), 1.17-1.22 (m, 1H), 1.22-1.27 (m, 1H), 1.34 (d, J = 6.44 Hz, 2.7H), 1.34-1.38 (m, 2H), 1.59-1.71 (m, 1H), 1.90-1.99 (m, 2H), 2.11-2.21 (m, 1H), 2.77-2.87 (m, 2H), 2.94-3.23 (m, 5H), 3.25-3.34 (m, 1H), 3.59 (s, 3H), 3.63-3.73 (m, 3H), 4.60 (s, 2H), 7.09-7.19 (m, 1H),
30 7.27 (d, J = 8.21 Hz, 2H), 7.34-7.40 (m, 2H), 7.52 (d, J = 8.16 Hz, 2H).

Example 1.23: Preparation of (*R*)-2-Methyl-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)propan-1-one (Compound 22).

35 The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.22** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride and 2-methyl-2-(1*H*-tetrazol-5-yl)propanoic acid. LCMS

$m/z = 459.4$ $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.15 (d, $J = 6.37$ Hz, 0.3H), 1.34 (d, $J = 6.50$ Hz, 2.7H), 1.58 (s, 6H), 1.60-1.70 (m, 1H), 1.90-1.99 (m, 2H), 2.11-2.21 (m, 1H), 2.93-3.08 (m, 4H), 3.24-3.37 (m, 2H), 3.40-3.49 (m, 2H), 3.60-3.71 (m, 2H), 4.25-4.49 (m, 2H), 6.96 (bs, 1H), 7.21-7.27 (m, 2H), 7.27-7.33 (m, 1H), 7.47 (d, $J = 8.11$ Hz, 2H).

5

Example 1.24: Preparation of (*R*)-Methyl 3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate (Compound 23).

The HCl salt of the title compound was prepared in a similar manner to the one described in **Example 1.13** using (*R*)-3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid. LCMS $m/z = 477.4$ $[M+H]^+$.

Example 1.25: Preparation of (1*S*,3*R*)-Methyl 3-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate (Compound 24).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.22** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline bis(2,2,2-trifluoroacetate) and (1*R*,3*S*)-3-(methoxycarbonyl)cyclohexanecarboxylic acid. LCMS $m/z = 489.5$ $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.15 (d, $J = 6.86$ Hz, 0.3H), 1.17-1.37 (m, 3H), 1.35 (d, $J = 6.51$ Hz, 2.7H), 1.38-1.52 (m, 1H), 1.59-1.71 (m, 2H), 1.71-1.79 (m, 1H), 1.90-1.99 (m, 2H), 2.10-2.20 (m, 1H), 2.30-2.39 (m, 1H), 2.50-2.72 (m, 1H), 2.73-2.79 (m, 1H), 2.82-2.88 (m, 1H), 2.94-3.06 (m, 4H), 3.24-3.35 (m, 1H), 3.37-3.48 (m, 1H), 3.52 (s, 3H), 3.64-3.74 (m, 3H), 4.58 (s, 1H), 4.63 (s, 1H), 7.15 (d, $J = 7.79$ Hz, 1H), 7.27 (d, $J = 8.16$ Hz, 2H), 7.33-7.40 (m, 2H), 7.51 (d, $J = 8.16$ Hz, 2H).

Example 1.26: Preparation of (1*r*,4*r*)-Methyl 4-(6-(4-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate (Compound 25).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.22** using (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline bis(2,2,2-trifluoroacetate) and (1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarboxylic acid. LCMS $m/z = 489.5$ $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.28 (d, $J = 6.87$ Hz, 0.3H), 1.46 (d, $J = 6.52$ Hz, 2.7H), 1.48-1.59 (m, 4H), 1.70-1.90 (m, 3H), 1.99-2.12 (m, 4H), 2.24-2.41 (m, 2H), 2.66-2.77 (m, 1H), 2.84-2.91 (m, 1H), 2.96-3.00 (m, 1H), 3.05-3.21 (m, 4H), 3.40-3.49 (m, 1H), 3.54-3.62 (m, 1H), 3.65 (s, 3H),

3.73-3.83 (m, 3H), 4.70 (s, 1H), 4.76 (s, 1H), 7.24-7.30 (m, 1H), 7.39 (d, $J = 8.18$ Hz, 2H), 7.45-7.51 (m, 2H), 7.64 (d, $J = 8.18$ Hz, 2H).

Example 1.27: Preparation of (*R*)-1-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylic Acid (Compound 26).

To a solution of (*R*)-methyl 1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylate 2,2,2-trifluoroacetate (7 mg, 0.012 mmol) in MeOH (1 mL) was added 5 M NaOH (0.062 mL, 0.312 mmol). The reaction was stirred at 60 °C for 4 h. The mixture was concentrated and the residue was dissolved in H₂O (2 mL). The mixture was added 1 M HCl (1 mL) and purified by HPLC. LCMS $m/z = 433.2$ $[M+H]^+$; ¹H NMR (400 MHz, CD₃CN) δ ppm 1.15 (d, $J = 6.87$ Hz, 0.3H), 1.17-1.24 (m, 2H), 1.34 (d, $J = 6.29$ Hz, 2.7H), 1.33-1.38 (m, 2H), 1.60-1.71 (m, 1H), 1.90-1.99 (m, 2H), 2.11-2.21 (m, 2H), 2.80-2.87 (m, 1H), 2.95-3.07 (m, 4H), 3.25-3.35 (m, 1H), 3.40-3.49 (m, 1H), 3.58-3.72 (m, 3H), 4.62 (s, 2H), 7.14-7.19 (m, 1H), 7.28 (d, $J = 8.14$ Hz, 2H), 7.34-7.39 (m, 2H), 7.52 (d, $J = 8.16$ Hz, 2H).

Example 1.28: Preparation of (1*r*,4*r*)-4-(6-(4-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic Acid (Compound 27).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.27** using (1*r*,4*r*)-methyl 4-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate 2,2,2-trifluoroacetate. LCMS $m/z = 475.5$ $[M+H]^+$; ¹H NMR (400 MHz, CD₃CN) δ ppm 1.16 (d, $J = 6.85$ Hz, 0.3H), 1.34 (d, $J = 6.52$ Hz, 2.7H), 1.36-1.47 (m, 4H), 1.59-1.76 (m, 3H), 1.88-1.99 (m, 3H), 2.11-2.21 (m, 2H), 2.55-2.65 (m, 1H), 2.72-2.79 (m, 1H), 2.82-2.89 (m, 1H), 2.94-3.10 (m, 4H), 3.25-3.36 (m, 1H), 3.39-3.50 (m, 1H), 3.61-3.71 (m, 3H), 4.58 (s, 2H), 4.64 (s, 1H), 7.16 (d, $J = 7.76$ Hz, 1H), 7.28 (d, $J = 8.15$ Hz, 2H), 7.33-7.40 (m, 2H), 7.52 (d, $J = 8.13$ Hz, 2H).

Example 1.29: Preparation of (1*S*,3*R*)-3-(6-(4-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic Acid (Compound 28).

The TFA salt of the title compound was prepared in a similar manner to the one described in **Example 1.27** using (1*S*,3*R*)-methyl 3-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate 2,2,2-trifluoroacetate. LCMS $m/z = 475.6$ $[M+H]^+$.

Example 1.30: Preparation of (*R*)-4-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic Acid (Compound 29).

Step A: Preparation of (*R*)-6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one.

5 In a microwave reaction vial was placed (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (500 mg, 1.855 mmol), 6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (419 mg, 1.855 mmol), dichlorobis(phenyldi-*tert*-butylphosphine)palladium (11.54 mg, 0.019 mmol), and sodium carbonate (393 mg, 3.71 mmol) in a mixture of toluene (10 mL), EtOH (3 mL), and water (2 mL). The reaction was heated under
10 microwave irradiation at 125 °C for 2 h. The mixture was extracted with toluene and 1 M HCl. The aqueous layer was separated and purified by HPLC to give the title compound. LCMS m/z = 335.3 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.15 (d, J = 6.86 Hz, 0.3H), 1.34 (d, J = 6.53 Hz, 2.7H), 1.59-1.70 (m, 1H), 1.90-1.99 (m, 2H), 2.11-2.21 (m, 1H), 2.42-2.48 (m, 2H), 2.87-2.93 (m, 2H), 2.93-3.06 (m, 4H), 3.39-3.49 (m, 1H), 3.62-3.72 (m, 1H), 6.81 (d, J = 8.16
15 Hz, 1H), 7.26 (d, J = 8.22 Hz, 2H), 7.31-7.39 (m, 2H), 7.49 (d, J = 8.25 Hz, 2H), 8.19 (s, 1H).

Step B: Preparation of (*R*)-4-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic Acid (Compound 29).

To a suspension of NaH (8.03 mg, 0.334 mmol) in THF (1 mL) was added (*R*)-6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one 2,2,2-trifluoroacetate
20 (15 mg, 0.033 mmol). The mixture was stirred at room temperature for 30 min. Dihydrofuran-2,5-dione (16.74 mg, 0.167 mmol) was then added to the mixture. The reaction was stirred at room temperature for 3 h. The mixture was quenched with 1 M HCl and purified by HPLC. LCMS m/z = 435.2 $[M+H]^+$; 1H NMR (400 MHz, CD_3CN) δ ppm 1.15 (d, J = 6.85 Hz, 0.3H), 1.35 (d, J = 6.53 Hz, 2.7H), 1.59-1.71 (m, 1H), 1.91-2.00 (m, 2H), 2.11-2.21 (m, 1H), 2.42-2.47
25 (m, 2H), 2.59-2.65 (m, 2H), 2.85-2.91 (m, 2H), 2.95-3.07 (m, 4H), 3.14-3.19 (m, 2H), 3.25-3.35 (m, 1H), 3.39-3.50 (m, 1H), 3.62-3.72 (m, 1H), 7.25-7.32 (m, 3H), 7.38-7.47 (m, 2H), 7.54 (d, J = 8.25 Hz, 2H).

Example 1.31: Preparation of (*R*)-Ethyl 2-(1-(2-(6-(4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetate (Compound 30).

The HCl salt of the title compound was prepared in a similar manner to the one described in **Example 1.13** using (*R*)-2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetic acid. LCMS m/z = 431.7
35 $[M+H]^+$.

Example 1.32: Preparation of (1*R*,2*R*)-Methyl 2-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate (Compound 31).

To (2*R*)-1-(4-(2-((1*R*,2*R*)-2-carboxycyclohexanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)phenethyl)-2-methylpyrrolidinium 2,2,2-trifluoroacetate (2.0 mg, 3.40 μ mol) was added HCl (1.25 M in methanol, 1.006 mL, 1.257 mmol). The reaction was stirred at 60 °C overnight. The mixture was concentrated and triturated with ACN to give the title compound. LCMS m/z = 489.4 $[M+H]^+$.

Example 2: [3 H] *N*-Alpha-Methyl-Histamine Competitive Histamine H3 Receptor Binding Assay.

The histamine receptor binding assay is conducted using standard laboratory procedures as described below. A crude membrane fraction is prepared from whole rat brain cortex using a polytron to homogenize the tissue followed by differential centrifugation in a HEPES-based buffer containing protease inhibitors. Membranes are frozen at -80 °C until needed. Frozen membranes are thawed and resuspended in ice-cold assay buffer consisting of 50 mM TRIS containing 5 mM EDTA (pH = 7.4). 50 μ g of membrane protein is added to each well of a 96-well assay plate along with the test compound and [3 H]-*N*- α -methyl-histamine (1 nM final assay concentration). Imetit is used as an assay positive control at varying concentrations. The plate is incubated for 30 min at room temperature. The assay is terminated by rapid filtration through a 96-well glass fiber filtration plate (GF/C) using a cell harvester (Perkin-Elmer). Captured membranes are washed three times with cold assay buffer and the plates are dried at 50 °C. 35 μ L of scintillation cocktail is added to each well and membrane-bound radioactivity is recorded using a TopCount 96-well plate scintillation counter (Perkin-Elmer).

Example 3: Receptor Binding Assays

Compounds that bind to GPCRs can be identified by their ability to displace a radiolabeled or fluorescently labeled tracer ligand from the receptor. The tracer ligand can be a receptor agonist, inverse agonist or a neutral antagonist. Receptor binding assays can be performed using either whole cells or membrane fractions prepared from such cells.

In a typical radioligand binding assay, cell membranes prepared from cells either endogenously or recombinantly expressing the desired receptor, are prepared and allowed to equilibrate with a mixture of a test ligand and tracer radioligand. Following equilibration, the cell membranes are captured by rapid filtration and washed with cold assay buffer to remove any unbound compounds. A liquid scintillant is typically added to the captured membranes and the samples are then counted on a scintillation counter. Compounds that bind to the receptor and

displace the radioligand result in lower counts. For some receptors, the radiolabeled tracer ligand can be replaced by a fluorescently labeled ligand.

Homogeneous binding assays have also been developed for some receptors. These can involve the use of either radioactive tracer ligands (e.g., scintillation proximity assays) or
5 fluorescent tracer ligands (fluorescence polarization binding assays).

Example 3.1: Human Histamine H3 Receptor Binding Assay – MDS Pharma Services (Taiwan).

Compounds of the invention can be tested for their ability to bind to the human
10 histamine H3 receptor using the MDS Pharma Services (Taiwan) assay, Catalogue No. 239810.

Example 3.2: Rat Cortex H3 Receptor Radioligand Binding Assay.

Cell membranes prepared from isolated, Sprague-Dawley rat cortex, which are known to abundantly express the rat H3 receptor, are plated into 96-well microtiter plates at a
15 concentration of 50 µg total membrane protein per well. Test compounds, prepared in assay buffer (50 mM Tris-HCl, pH7.4, with 5 mM EDTA) containing the selective H3 receptor agonist radioligand [³H] *N*-methylhistamine (final assay concentration 1.25 nM), are added to each well on the plate. Test compound concentrations typically begin at 2 or 10 µM (final assay concentration) and 1:5 serial dilutions are prepared in order to generate 10-point dose-response
20 curves for IC₅₀ and K_i determinations. After a 1 hour, room temperature incubation, membranes are harvested into a PEI-washed filter plate (Whatman GF/C Unifilter) by rapid filtration (Perkin Elmer harvester) and washed three times with ice cold assay buffer (3 x 150 µL). Filter plates are then partially dried in a 50°C oven for 1-2 hours. Finally, the plate bottoms are sealed and BetaScint (Perkin Elmer 1205-440; 25 µL per well) is added to each well. Plates are then read
25 on a TopCount (Packard Instruments). Raw counts are then used to plot dose-response curves for serially diluted test compounds. The resulting IC₅₀ values can be converted to K_i values using the Cheng-Prusoff equation and the K_d value for [³H] *N*-methylhistamine at the rat H3 receptor (0.4 nM).

30 **Example 3.3: Assays for Determination of GPCR Activation or Inhibition.**

A variety of assays are available for assessment of activation or inhibition of GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane [³⁵S]GTPγS Binding Assays.

35 When a G protein-coupled receptor is in its active state, either as a result of agonist ligand binding or constitutive activation, the receptor couples to G proteins, stimulating the release of GDP and subsequent binding of GTP to the G protein alpha subunit. The activated G

protein alpha subunit acts as a GTPase and slowly hydrolyzes the GTP back to GDP. The non-hydrolyzable GTP analog, [³⁵S]GTPγS, can be utilized to monitor binding of GTP to membrane-associated G proteins. Typically, test compounds are incubated with receptor-expressing cell membranes in the presence of [³⁵S]GTPγS for 30 to 60 minutes. If the test compound is an agonist or an inverse agonist at the receptor of interest, enhanced or diminished uptake of [³⁵S]GTPγS into the membrane-associated G-proteins will be detected. A neutral antagonist, with no intrinsic efficacy at the receptor, can be detected by its ability to prevent agonist-stimulated [³⁵S]GTPγS exchange. The advantage of using [³⁵S]GTPγS binding to measure activation is that: (a) under appropriate assay conditions, it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the rest of the G protein mediated intracellular signaling cascade.

Human H3 Receptor GTPγS Assay.

In a typical [³⁵S]GTPγS assay, recombinant human H3 receptor-expressing CHO-K1 cell membranes (90 μg membrane protein per well) are equilibrated in assay buffer (20 mM HEPES (pH 7.4), 10 mM MgCl₂, 100 mM NaCl, 1 mM DTT, 1 mM EDTA) containing test compounds and 10 μM GDP for 20 minutes. SPA beads (scintillation microsphere beads) are then added and incubated for 60 minutes at 30°C. The reaction is then initiated by the addition of 0.3 nM [³⁵S]GTPγS for 30 minutes. Plates are then sealed, centrifuged and counted in a scintillation counter (Packard TopCount).

The recombinantly-expressed histamine H3 receptor is known to be constitutively active. In the above example, test compounds that have either positive (agonist) or negative (inverse agonist) efficacy at the H3 receptor would be detected by their ability to increase or decrease basal levels of [³⁵S]GTPγS binding, respectively. In an alternate configuration, the assay may be modified to include a low dose (typically an EC₈₀₋₉₀ concentration) of a selective H3 receptor agonist such as N-methylhistamine. In this approach, the ability to detect agonists is diminished and the ability to detect inverse agonists is increased. Additionally, antagonists (ligands with no intrinsic receptor efficacy) that block binding of the agonist to the receptor will be detected.

2. cAMP Assays.

GPCRs coupled to either Gs or Gi G-proteins modulate levels of intracellular cAMP and cAMP levels can be determined using a variety of commercially available assay kits. Examples of commonly used cAMP detection assays include FlashPlate® (New England Nuclear), HTRF® (Cisbio), cAMP-Screen® (Applied Biosystems), HitHunter® (Applied Biosystems/DiscoverX), CatchPoint® (Molecular Devices), AlphaScreen® (Perkin Elmer), GloSensor® (Promega) and numerous ELISA products. Most of these assays rely on the use of an anti-cAMP antibody to detect cAMP.

Homogeneous time-resolved fluorescence assays (HTRF®, Cisbio) detect levels of cAMP in lysed cell preparations using a europium or terbium cryptate-labeled anti-cAMP antibody and fluorophore-labeled cAMP (cAMP-d2). In the absence of exogenous cAMP, the anti-cAMP antibody binds to cAMP-d2. Photoexcitation of the cryptate donor results in a combination of cryptate emission at 620 nm and fluorescence resonance energy transfer (FRET) from the cryptate to the acceptor d2 fluorophore, which then fluoresces at 665 nm. The 620/665 nm emission ratio is monitored. In the presence of exogenous cAMP, which competes with cAMP-d2 for binding to the anti-cAMP antibody, FRET is decreased and the 620/665 nm emission ratio therefore increases, providing a sensitive and accurate means to measure cAMP levels in biological assays.

Human H3 Receptor HTRF cAMP Assay.

Compounds of the present invention were evaluated using the human H3 receptor (H3R) HTRF cAMP assay. In this assay, HEK293 cells expressing the human H3 receptor were suspended in PBS containing 100 μ M IBMX and plated into 384-well assay plates (Perkin Elmer Proxiplate 384-Plus; 15,000 cells per well; 5 μ L plating volume) and allowed to equilibrate for an hour. Test compounds were serially diluted in 100% DMSO and then further diluted in PBS containing forskolin (2 μ M). Test compounds (5 μ L) were then added to the assay plate and the mixture was incubated for 1 hour. HTRF assay reagents (Cisbio, Dynamic 2 cAMP Kit), cAMP-d2 and cryptate-labeled anti-cAMP antibody, are mixed with cell lysis buffer and added to the assay plate. After 1-hour incubation with these reagents, the assay plate was read on an HTRF-compatible microplate reader (Perkin Elmer EnVision or BMG Pherastar). A cAMP standard curve was included on each assay plate and HTRF emission ratios for test compounds were fit to this curve to generate accurate measures of cAMP levels in each test well. The observed H3R IC₅₀ values in the HTRF cAMP assay for several compounds of the present invention are shown in **Table B**.

Table B

Compound No.	IC₅₀ H3R
1	1.42 nM
2	0.52 nM
3	0.82 nM
7	0.59 nM
8	1.06 nM
10	0.44 nM
13	0.92 nM
22	1.88 nM
25	0.45 nM
31	1.99 nM

In addition to the compounds and their corresponding H3R IC₅₀ values disclosed in **Table B**, all other compounds in **Table A** had observed H3R IC₅₀ values in the HTRF cAMP assay ranging from about 430 pM to about 7 nM. Compound 23 was not tested in the HTRF cAMP assay.

5 In an alternate configuration, designed to detect antagonists (ligands with no intrinsic receptor efficacy) that block binding of the agonist to the receptor the assay is modified to include a low dose of histamine (typically 20 nM) in the test compound buffer. The recombinantly-expressed histamine H3 receptor is known to be constitutively active. In the above example, test compounds that have either positive (agonist) or negative (inverse agonist) 10 efficacies are detected by their ability to decrease or increase forskolin stimulated levels of cAMP, respectively. In this configuration, both inverse agonists and antagonists are efficiently detected.

3. *Xenopus* Melanophore Assays.

15 Melanophores are skin cells found in lower vertebrates. They contain pigmented organelles termed melanosomes. Melanophores are able to redistribute these melanosomes along a microtubule network upon G-protein coupled receptor (GPCR) activation. The result of this pigment movement is an apparent lightening or darkening of the cells. In melanophores, the decreased levels of intracellular cAMP that result from activation of a Gi-coupled receptor such as the H3 receptor cause melanosomes to migrate to the center of the cell, resulting in a dramatic 20 lightening in color. If cAMP levels are then raised, following activation of a Gs-coupled receptor or addition of an H3 receptor inverse agonist, the melanosomes are re-dispersed and the cells appear dark again. The response of the melanophores takes place within minutes of receptor activation and results in a simple, robust color change. The response can be easily detected using a conventional absorbance microplate reader or a modest video imaging system.

25 Since the H3 receptor is a constitutively active Gi-coupled receptor, melanophores expressing the H3 receptor will exhibit partial pigment aggregation in the resting state. Stimulation with an H3 receptor agonist or inverse agonist will cause either further pigment aggregation or dispersion, respectively. A neutral antagonist at the H3 receptor would be detected by its ability to inhibit pigment aggregation stimulated by a selective H3 receptor 30 agonist

4. Intracellular Calcium and Inositol Phosphate Assays.

GPCRs coupled to Gq G-proteins regulate the activity of phospholipase C, resulting in the modulation of intracellular inositol phosphates (IP) and diacylglycerol levels. Increased IP levels result in activation of the IP receptor with consequent release of calcium ions into the 35 cytosol. Levels of intracellular IP can be determined in cells loaded with [³H]-myo-inositol, resulting in the production of tritiated IP, which can be detected using standard radiometric

techniques. IP levels can also be determined using an HTRF IP-One assay (Cisbio) which relies on an antibody to inositol monophosphate to detect IP.

Cytosolic calcium can be monitored using membrane-permeable dyes that become fluorescent when bound to calcium. The most widely used instrument for conducting
5 intracellular calcium release assays is the Fluorometric Imaging Plate Reader (FLIPR®, Molecular Devices). The FLIPR instrument is able to simultaneously add test compounds to all wells on appropriate microplates and take real-time measurements of the fluorescence of calcium bound dye, allowing accurate measurement of intracellular calcium levels. Similar experiments can be performed with a number of alternate, commercially available instruments
10 or by the imaging of single cells or small numbers of cells with a fluorescence microscope.

Intracellular calcium levels can also be measured in cells engineered to express calcium sensitive proteins such as aequorin. Aequorin is a photoprotein isolated from jellyfish. While the calcium sensitive dyes used in FLIPR experiments require an excitation source in order to fluoresce, aequorin emits light in the presence of calcium without the need for an excitation
15 source.

Receptors that do not normally couple to Gq G-proteins, such as the H3 receptor, can be artificially coupled to the IP/calcium signaling pathway through the use of promiscuous G-proteins (G₁₅ and G₁₆). These G-proteins signal through the Gq pathway and therefore regulate intracellular calcium release, but are promiscuous in the sense that they can couple to receptors
20 that do not normally interact with Gq proteins. Alternatively, chimeric G-proteins may be used. These chimeric proteins typically utilize a Gq alpha protein in which approximately 5 amino acids at the carboxy-terminus are replaced with the corresponding amino acids from Gi alpha subunits. The resulting chimeric alpha subunit will recognize and be activated by Gi-coupled receptors but will signal through the Gq pathway to release intracellular calcium

25 In a typical FLIPR assay, cells expressing the H3 receptor and either a promiscuous G-protein (G₁₅ or G₁₆) or a chimeric G-protein (G_{qi}) are suspended in assay buffer and plated into black 384-well assay plates. Calcium dye is then added to the wells and allowed to incubate with the cells for one hour prior to test compound addition on an instrument such as a FLIPR. H3 receptor agonists will stimulate and H3 receptor inverse agonists will inhibit, respectively,
30 calcium release. Antagonists and inverse agonists are typically detected by their ability to block the action of a selective H3 receptor agonist.

5. β -Arrestin Assays.

Activation of a GPCR typically results in receptor phosphorylation via a variety of kinases and then recruitment of β -arrestin from the cytosol. By monitoring the translocation of
35 β -arrestin proteins from the cytosol to GPCRs in the cell membrane or quantitating the amount of receptor-arrestin complex formed in the cell, one can determine the extent of receptor activation. The recruitment of arrestin and the formation of arrestin-GPCR complexes can result

from both constitutive receptor activity and the influence of test compounds, with agonists promoting arrestin-receptor complexation.

a.) Arrestin translocation assays. In a typical arrestin translocation assay, cells expressing the receptor of interest are plated in transparent assay plates and allowed to fully
5 adhere to the bottom of the wells. Test compounds are then added and incubated with the cells for up to an hour. The intracellular location of arrestin may be monitored by the use of cells recombinantly expressing a modified arrestin protein fused to a fluorescent protein such as green fluorescent protein (GFP). Alternatively, cells can be fixed and permeabilized, then treated with a fluorescently labeled anti- β -arrestin antibody.

10 b.) Arrestin-receptor interaction assays. The association of β -arrestin with a GPCR can be monitored by tagging both β -arrestin and the receptor of interest with peptides or proteins that can interact to produce a biological readout when the receptor and arrestin are brought into close proximity upon receptor activation. Commercially available examples include Path
15 Hunter® (DiscoverX), in which the receptor and arrestin are tagged with complementary fragments of β -galactosidase that can combine via enzyme complementation upon receptor activation to produce active luciferase enzyme; and Tango® (Invitrogen), which utilizes an arrestin protein tagged with a protease and the receptor of interest tagged with a transcription factor at the cytoplasmic carboxyl terminus. The transcription factor is linked to the receptor via a protease-sensitive amino acid sequence and upon recruitment of protease-tagged arrestin, the
20 transcription factor is cleaved from the receptor and translocates to the cell nucleus to initiate a transcriptional readout. Another commonly used technique for the measurement of arrestin-GPCR protein-protein interactions is bioluminescence resonance energy transfer (BRET). In this example, both arrestin and the receptor of interest are tagged with fluorescent proteins. One of the proteins is considered a donor while the other is an acceptor. Under conditions of low
25 receptor activation, where arrestin is located primarily in the cytosol and the receptor is located primarily at the cell membrane, photoexcitation of the donor fluorescent protein, tagged to either the receptor or arrestin, results primarily in fluorescence emission from the donor. Upon receptor activation, resulting in close association of the receptor and arrestin, excitation of the donor protein is followed by BRET energy transfer to the acceptor protein and fluorescence
30 emission from the acceptor protein at a longer wavelength that would be expected from the donor protein.

6. Reporter Gene Assays.

Activation of a GPCR typically results in changes in the activities of numerous protein signaling pathways within the cell. Some of these signaling pathways also lead to the
35 modulations of intracellular concentrations of second messenger molecules such as cAMP, inositol phosphates, diacylglycerol and calcium. Many of these signaling pathways can ultimately result in a transcriptional response in the cell nucleus. Reporter gene assays take

advantage of this response. Typically, cells are engineered to express a reporter gene product such as β -galactosidase or luciferase with gene expression regulated by a promoter that is sensitive to the type of signaling expected from the receptor of interest. In a typical example, cells expressing a receptor capable of modulating cAMP levels within the cell (Gi or Gs coupled) and a luciferase reporter gene under the control of a cAMP response element (CRE) can be used to determine intracellular cAMP levels. Activation of a Gs-coupled receptor or treatment with forskolin, leading to the production of cAMP, will increase reporter gene expression. Activation of a Gi coupled receptor such as the H3 receptor, leading to reductions in cAMP production, will reduce levels of reporter gene expression. For the constitutively active H3 receptor, agonists or inverse agonists would be detected by their ability to either decrease or increase forskolin-stimulated reporter gene expression, respectively. A neutral antagonist would be detected by its ability to block the actions of a selective H3 agonist.

Example 4: Blockade of RAMH-Induced Drinking Assay.

When administered to rodents, histamine H3 receptor agonists, such as (*R*)- α -methyl-histamine (RAMH), induce a drinking response that is sensitive to reversal with a histamine H3 receptor inhibitor. Blockade of RAMH-induced drinking can therefore be utilized as an *in vivo* assay for functional histamine H3 receptor inhibition activity. In this assay, male Sprague Dawley rats (250-350 g) are housed three per cage and maintained under a reverse 12 h light cycle (lights off at 1130 h). At 1030 h on the day of test, rats are individually housed in new cages and food is removed. 120 min later, rats are administered test article (vehicle or histamine H3 receptor inhibitor, 0.3 mg/kg PO). 30 min later, water is removed, and RAMH (vehicle or RAMH 3 mg/kg salt SC) is administered. 10 min after administration of RAMH, weighed water bottles are placed in the cages, and drinking is allowed for 20 min. Water consumption is determined for each animal by weighing each bottle to the nearest 0.1 g. Data is expressed as percentage reduction in water intake according to the following formula:

$$(((\text{VEH}/\text{RAMH}) - (\text{ANTAGONIST}/\text{RAMH})) / ((\text{VEH}/\text{RAMH}) - (\text{VEH}/\text{VEH}))) * 100$$

Example 5: H3R Antagonists Inhibit Itch in Allergic Models for Pruritus.

To perform the DNFB allergic pruritus model, female C57BL/6 mice (5/group) were sensitized two times/week via epicutaneous administration of the allergen DNFB (0.3% in 4:1 acetone:olive oil) on the rostral back skin. On the 14th day after initial DNFB administration, mice were challenged again with epicutaneous DNFB; at 5h post-DNFB challenge, mice were dosed with **Compound 1** at 1, 3, 10, and 30 mg/kg, IP. Scratching bouts were counted from 30-50 minutes post-compound dosing (See **Figure 4**). **Compound 1** inhibited pruritus in a dose

dependent fashion. These data demonstrate that H3R antagonists can inhibit pruritus mediated by endogenous pruritogens released from an immune response.

Example 6A: Pharmacology Study of Compound 2 in male C57BL6 Mouse, Brain to Plasma Ratio Determination.

The analyte plasma concentrations were determined by LC/MS/MS. Male C57BL6 Mice were dosed (IP) with **Compound 2** at 3.00 and 30.0 mg/kg (as a free base). Mouse plasma and brain samples were taken at 0.5 hr (30 mg/kg group only) and 1.0 hr post dose. For **Compound 2** the LLQ was observed to be the following: Plasma = 10.0 ng/mL; and Brain = 3.00 ng/mL.

Compound 2 (3 mg/kg dose)

The plasma concentration was 402 ± 202 ng/mL at 1 hr; the brain concentration was 5.37 ± 2.72 ng/g at 1 hr.; and the brain to plasma ratio was 0.0112 at 1 hr.

Compound 2 (30 mg/kg dose)

The plasma concentrations were 259 ± 78.0 ng/mL and 407 ± 65.0 ng/mL at 0.5 hr and 1 hr, respectively; the brain concentration was 4.13 ± 1.56 ng/g 1 hr (**Compound 2** was not detected in the brain sample at 0.5 hr); and the brain to plasma ratio was 0.0099 at 1 hr.

Example 6B: Pharmacology Study of Compound 3 in male C57BL6 Mouse, Brain to Plasma Ratio Determination.

The analyte plasma concentrations were determined by LC/MS/MS. Male C57BL6 Mice were dosed (IP) with **Compound 3** at 3.00 mg/kg (as a free acid). Mouse plasma and brain samples were taken at 0.5 hr and 1.0 hr post dose. For **Compound 3** the LLQ was observed to be the following: Plasma = 10.0 ng/mL; and Brain = 7.50 ng/mL.

Compound 3 (3 mg/kg dose)

The plasma concentrations (mean $\pm$ SD, n=3/timepoint) were 1700 ± 419 and 776 ± 124 ng/mL at 0.5 and 1 h; respectively; the brain concentrations were 33.4 ± 4.1 and 20.0 ± 8.2 ng/g at 0.5 and 1 h; respectively; and the brain to plasma ratios were 0.0200 at 0.5 h and 0.0252 at 1 h.

Example 7: Histamine-Induced Model for Pruritus.

H3R inhibitors, **Compound 1** and **Compound 3**, were dissolved in saline at the appropriate concentration and 100 μ L was administered orally (**Compound 3**) or intraperitoneally (**Compound 1**) into 8-week-old C57BL/6 female mice. Thirty minutes post-dosing, 25 μ L of 40 mg/mL histamine (HA) solution was injected subcutaneously at the rostral part of the back. Mice were video recorded and the number of scratching bouts that occurred between 5 and 25 minutes after histamine injection was counted. Both compounds were found to

inhibit histamine-induced scratching behavior in mice, see **Figure 5 (Compound 1)** and **Figure 6 (Compound 3)**.

Example 8: Central Administration of a H3R Antagonist Does not Inhibit Histamine-induced Pruritus.

When administered peripherally, centrally penetrant H3R antagonists have many effects in the rodent. These include increasing cognition, and inhibiting histamine (HA)-induced pruritus. In order to assess whether there was a brain-mediated component to blockade of HA-induced pruritus, a known H3R antagonist was administered directly into the brain, and effects on both HA-induced pruritus and performance in a cognitive task were measured. The known H3R antagonist used was (*R*)-2-hydroxy-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (referred herein as **Compound A**), see Compound 10 in PCT publication WO2009/105206.

Male C57BL/6 mice were implanted with chronically indwelling cannulae aimed at the lateral ventricle. Cannulated mice (6-7/group) were dosed with either vehicle (PO) and vehicle (ICV), **Compound A** (10 mg/kg PO) and vehicle (ICV), or vehicle (PO) and **Compound A** (10 µg ICV). Scratching bouts were counted from 5-25 minutes post-histamine challenge. In the Object Recognition task, cannulated mice were allowed to explore an open-field (50 X 37 X 24 cm) for five minute habituation sessions on two consecutive days. On day three (training day), two identical objects were presented near opposite corners of the open-field (10 cm from walls), and mice allowed to explore the objects for 10 min. Immediately after training, mice were removed from the arena and injected ICV with either vehicle or **Compound A** (10 µg). 24 h later, subjects were placed back in the open field in which one of the previously presented objects was replaced by a novel object. Subjects were allowed to explore the two objects for a five-minute session during which their behavior was video recorded for subsequent analysis. The difference between exploration times of the novel and familiar objects as a factor of total object exploration time ((N-F)/(N+F)) was taken as a measure of performance (cognitive index).

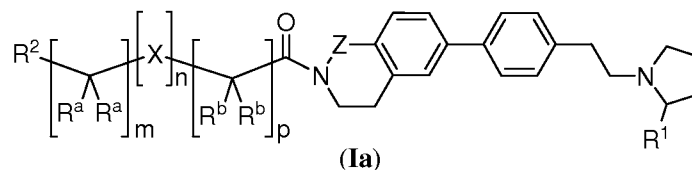
These data demonstrated that an intracerebroventricular (ICV) dose of **Compound A** increased cognitive function (**Figure 7A**) but was unable to inhibit HA-induced pruritus (**Figure 7B**). **Compound A** was able to inhibit HA-induced pruritus when administered orally (**Figure 7B**, *p.o.*) suggesting that brain exposure is not sufficient for activity in the HA-induced pruritus test, and therefore that HA-induced pruritus is peripherally mediated.

Those skilled in the art will recognize that various modifications, additions, substitutions and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention.

CLAIMS

What is claimed is:

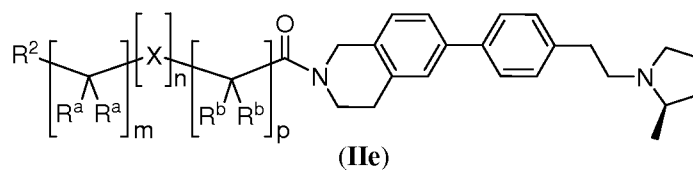
- 5 1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

- 10 m, n, and p are each independently 0 or 1;
 X is selected from the group: $-S-$, $-O-$, C_3-C_6 cycloalkylene, and CR^cR^c ;
 Z is $-CH_2-$ or $-(C=O)-$;
 R^1 is H or C_1-C_4 alkyl;
 R^2 is selected from the group: C_1-C_4 alkoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and
 15 each R^a , R^b , and R^c is independently selected from the group: H, C_1-C_3 alkyl, amino, halogen, and hydroxyl.
2. A compound according to claim 1, wherein Z is $-CH_2-$.
- 20 3. A compound according to claim 1 or 2, wherein m, n, and p are each 0.
4. A compound according to claim 1 or 2, wherein m is 0, n is 0, and p is 1.
5. A compound according to claim 1 or 2, wherein m is 0, n is 1, and p is 0.
- 25 6. A compound according to claim 1 or 2, wherein m is 0, n is 1, and p is 1.
7. A compound according to claim 1 or 2, wherein m, n, and p are each 1.
- 30 8. A compound according to claim 1 or 2, wherein m, n, and p are each independently 0 or 1; provided that when m is 1, then n and p are both 1.
9. A compound according to any one of claims 1 to 8, wherein R^1 is C_1-C_4 alkyl.

10. A compound according to any one of claims 1 to 8, wherein R^1 is methyl.
11. A compound according to any one of claims 1 to 10, wherein R^2 is C_1 - C_4 alkoxy carbonyl.
12. A compound according to any one of claims 1 to 10, wherein R^2 is selected from the group: methoxycarbonyl and ethoxycarbonyl.
13. A compound according to any one of claims 1 to 10, wherein R^2 is carboxyl.
14. A compound according to any one of claims 1 to 10, wherein R^2 is 1*H*-tetrazol-5-yl.
15. A compound according to any one of claims 1 to 14, wherein each R^a is selected independently from the group: H, methyl, and amino.
16. A compound according to any one of claims 1 to 15, wherein each R^b is selected independently from the group: H, methyl, and fluoro.
17. A compound according to any one of claims 1 to 16, wherein X is CR^cR^c .
18. A compound according to any one of claims 1 to 16, wherein X is CR^cR^c , and each R^c is selected independently from the group: H, methyl, fluoro, and hydroxyl.
19. A compound according to any one of claims 1 to 16, wherein each R^a , R^b , and R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.
20. The compound according to claim 1, selected from compounds of Formula (IIe) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



30

wherein:

m, n, and p are each independently 0 or 1, provided that when m is 1 then both n and p are both 1;

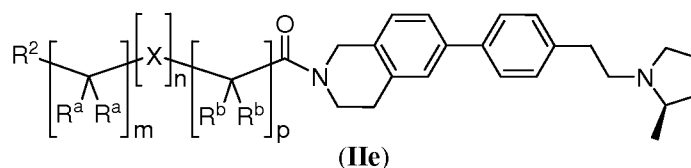
X is selected from the group: $-S-$, $-O-$, C_3 - C_6 cycloalkylene, and CR^cR^c ;

R^2 is selected from the group: C_1 - C_4 alkoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and

each R^a , R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, amino, halogen, and hydroxyl.

5

21. The compound according to claim 1, selected from compounds of Formula (IIe) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

10

m , n , and p are each independently 0 or 1, provided that when m is 1 then n and p are both 1;

X is selected from the group: $-S-$, $-O-$, cyclopropane-1,1-diyl, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, and CR^cR^c ;

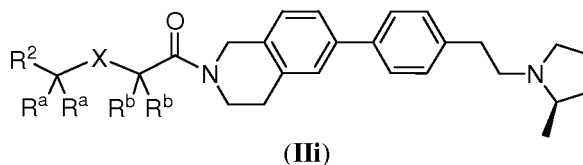
15

R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, carboxyl, and 1*H*-tetrazol-5-yl; and

each R^a , R^b , and R^c is independently selected from the group: H, methyl, amino, fluoro, and hydroxyl.

20

22. The compound according to claim 1, selected from compounds of Formula (Iii) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

X is selected from the group: $-S-$, $-O-$, C_3 - C_6 cycloalkylene, and CR^cR^c ;

25

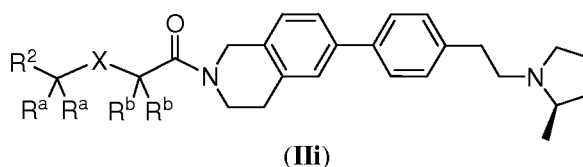
R^2 is selected from the group: C_1 - C_4 alkoxycarbonyl and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, amino, and hydroxyl.

30

23. The compound according to claim 1, selected from compounds of Formula (Iii) and pharmaceutically acceptable salts, solvates, and hydrates thereof:

80



wherein:

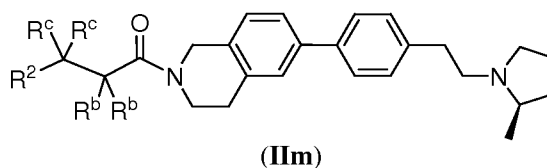
X is selected from the group: $-S-$, $-O-$, cyclopentane-1,1-diyl, cyclohexane-1,1-diyl, and CR^cR^c ;

5 R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and

each R^a , R^b , and R^c is independently selected from the group: H, methyl, amino, and hydroxyl.

10 24. The compound according to claim 23, wherein X is CR^cR^c ; and each R^a , R^b , and R^c is independently selected from the group: H, methyl, and hydroxyl.

25. The compound according to claim 1, selected from compounds of Formula **(IIIm)** and pharmaceutically acceptable salts, solvates, and hydrates thereof:



15

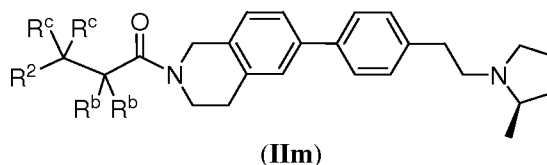
wherein:

R^2 is selected from the group: C_1 - C_4 alkoxy carbonyl and carboxyl; and

each R^b , and R^c is independently selected from the group: H, C_1 - C_3 alkyl, and halogen.

20

26. The compound according to claim 1, selected from compounds of Formula **(IIIm)** and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

25 R^2 is selected from the group: methoxycarbonyl, ethoxycarbonyl, and carboxyl; and

each R^b , and R^c is independently selected from the group: H, methyl, and fluoro.

27. A compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
- (*R*)-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)ethanone;
- 5 (*R*)-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;
- (*R*)-3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;
- (*R*)-2,2-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;
- 10 3-methyl-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;
- 3-hydroxy-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;
- 15 (*R*)-2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethylthio)acetic acid;
- (*R*)-2,2,3,3-tetrafluoro-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;
- (*R*)-2,2-dimethyl-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;
- 20 (*R*)-2-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethoxy)acetic acid;
- (*R*)-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoic acid;
- 25 (*R*)-methyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate;
- (*S*)-ethyl 2-amino-5-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate;
- (*R*)-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)(1*H*-tetrazol-5-yl)methanone;
- 30 (*R*)-ethyl 4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoate;
- (*R*)-methyl 2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoacetate;
- 35 (*R*)-2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclopentyl)acetic acid;

- (*R*)-2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetic acid;
 (1*S*,2*S*)-2-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
 5 (*R*)-methyl 3-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-oxopropanoate;
 (*R*)-methyl 1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylate;
 (*R*)-2-methyl-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(1*H*-tetrazol-5-yl)propan-1-one;
 10 (*R*)-methyl 3,3-dimethyl-5-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-5-oxopentanoate;
 (1*S*,3*R*)-methyl 3-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate;
 15 (1*r*,4*r*)-methyl 4-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate;
 (*R*)-1-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclopropanecarboxylic acid;
 (1*r*,4*r*)-4-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
 20 (1*S*,3*R*)-3-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylic acid;
 (*R*)-4-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-oxobutanoic acid;
 25 (*R*)-ethyl 2-(1-(2-(6-(4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-oxoethyl)cyclohexyl)acetate; and
 (1*R*,2*R*)-methyl 2-(6-(4-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexanecarboxylate.
- 30 28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27 and a pharmaceutically acceptable carrier.
29. A method for treating a histamine H3 receptor-associated disorder in an individual comprising administering to said individual in need thereof a therapeutically effective
 35 amount of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28.

30. A method for treating a histamine H3 receptor-associated disorder selected from the group: a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, and pruritus in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28.
31. A method for treating pruritus in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28.
32. A method according to claim 31, wherein said pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.
33. Use of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 in the manufacture of a medicament for the treatment of a histamine H3 receptor-associated disorder.
34. Use of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 in the manufacture of a medicament for the treatment of a disorder selected from the group: a cognitive disorder, epilepsy, brain trauma,

- depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, and pruritus.
- 5
35. Use of a compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 in the manufacture of a medicament for the treatment of pruritus.
- 10
36. Use of a compound or a pharmaceutical composition according to claim 35, wherein said pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice, lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch associated with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.
- 15
- 20
- 25
37. A compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 for use in a method of treatment of the human or animal body by therapy.
- 30
38. A compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 for use in a method for the treatment of a histamine H3 receptor-associated disorder.
- 35
39. A compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 for use in a method for the treatment of a histamine H3 receptor-associated disorder selected from the group: a cognitive disorder, epilepsy, brain

- 5 trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, shift-work sleep disorder, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, excessive daytime sleepiness, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease, pain, and pruritus.
40. A compound according to any one of claims 1 to 27 or a pharmaceutical composition according to claim 28 for use in a method for the treatment of pruritus.
- 10 41. A compound or a pharmaceutical composition according to claim 40, wherein said pruritus is associated with a disorder selected from eczema, atopic eczematous dermatitis, seborrheic dermatitis, atopic dermatitis, contact dermatitis, irritant dermatitis, xerosis (dry skin), psoriasis, a fungal infection, athlete's foot, a yeast infection, diaper rash, vaginal itch, parasitic infections, parasitic infestations including scabies and lice,
- 15 lichen planus, lichen simplex, lichen simplex chronicus, lichen sclerosis, itch secondary to medications, senile itch, uremia, idiopathic itch, itch associated with liver cirrhosis, itch associated with inflammation, itch associated with allergies, itch associated with cancer, itch associated with chemotherapy, itch associated with kidney disease, itch associated with haemodialysis, burns, scalds, sunburn, wound healing, itch associated
- 20 with an insect bite, itch associated with a flea bite, itch associated with an insect sting, itch associated with a mosquito sting, itch associated with a mite bite, urticaria, urticaria caused by a plant, urticaria caused by poison ivy, urticaria caused by stinging nettle, sweat gland abnormalities, bullous pemphigoid, photodermatoses, skin blisters, adult acne, chicken pox, and dermatitis herpetiformis.
- 25 42. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 27 and a pharmaceutically acceptable carrier.

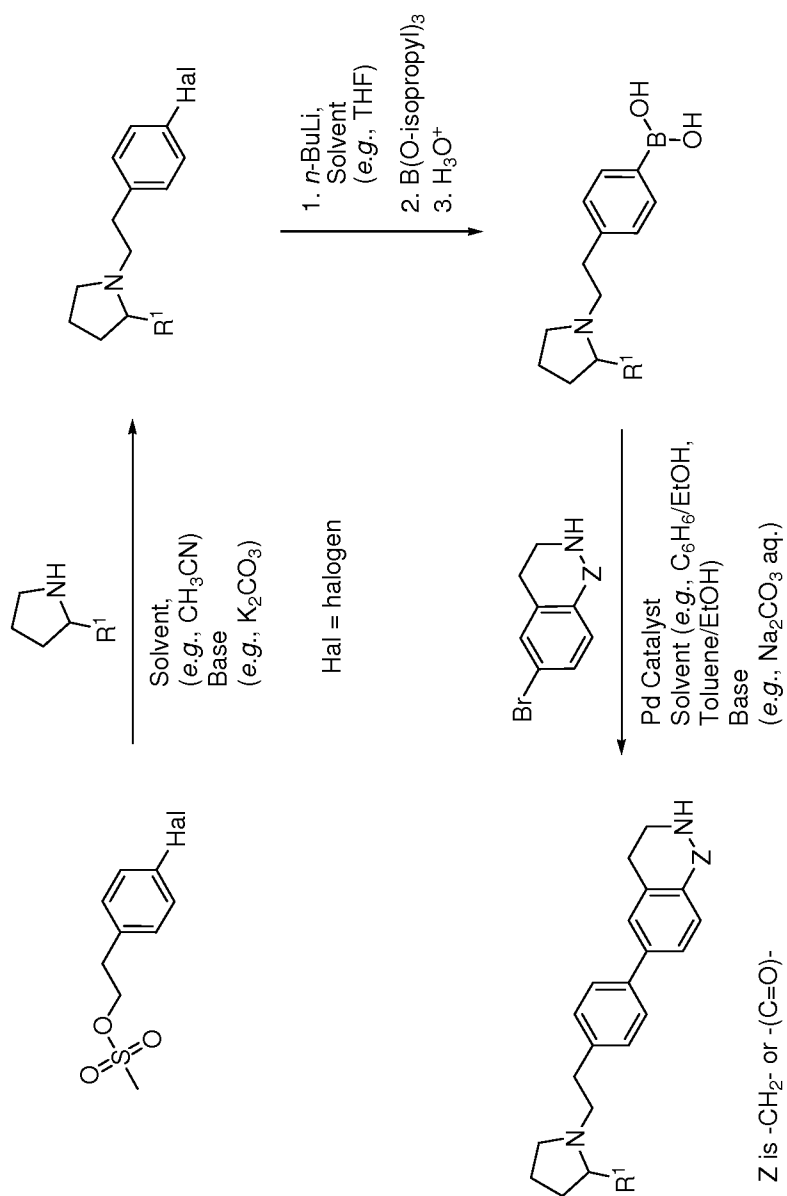


Figure 1

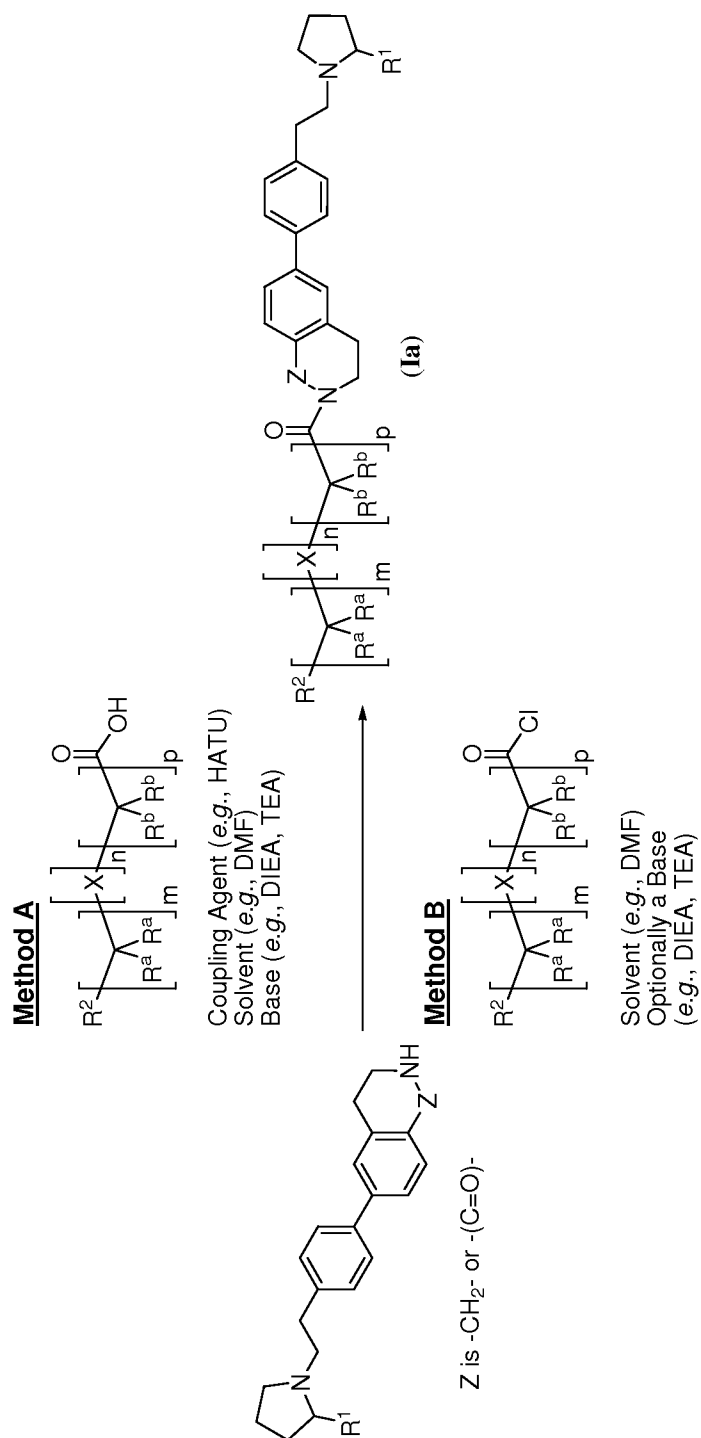


Figure 2

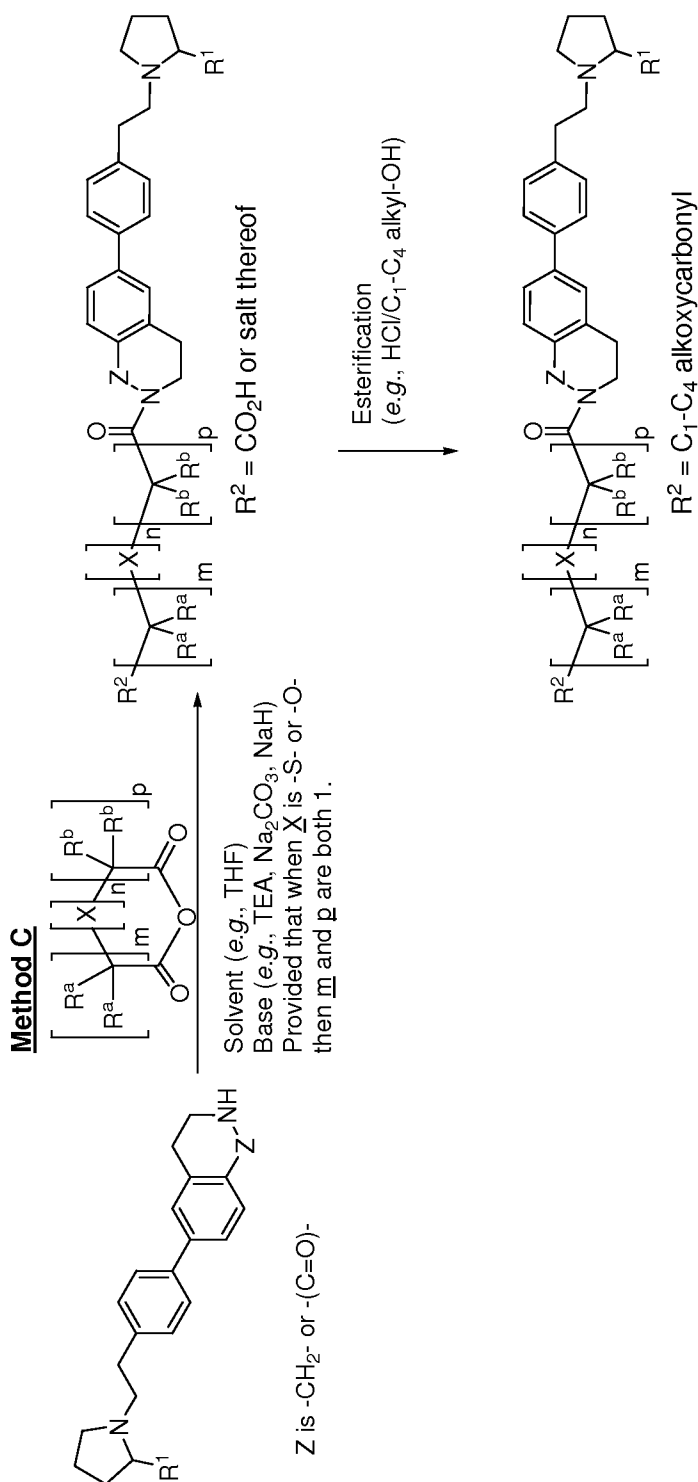


Figure 3

ADMINISTRATION OF COMPOUND 1
INHIBITS CHRONIC DNFB-MEDIATED ALLERGIC PRURITUS

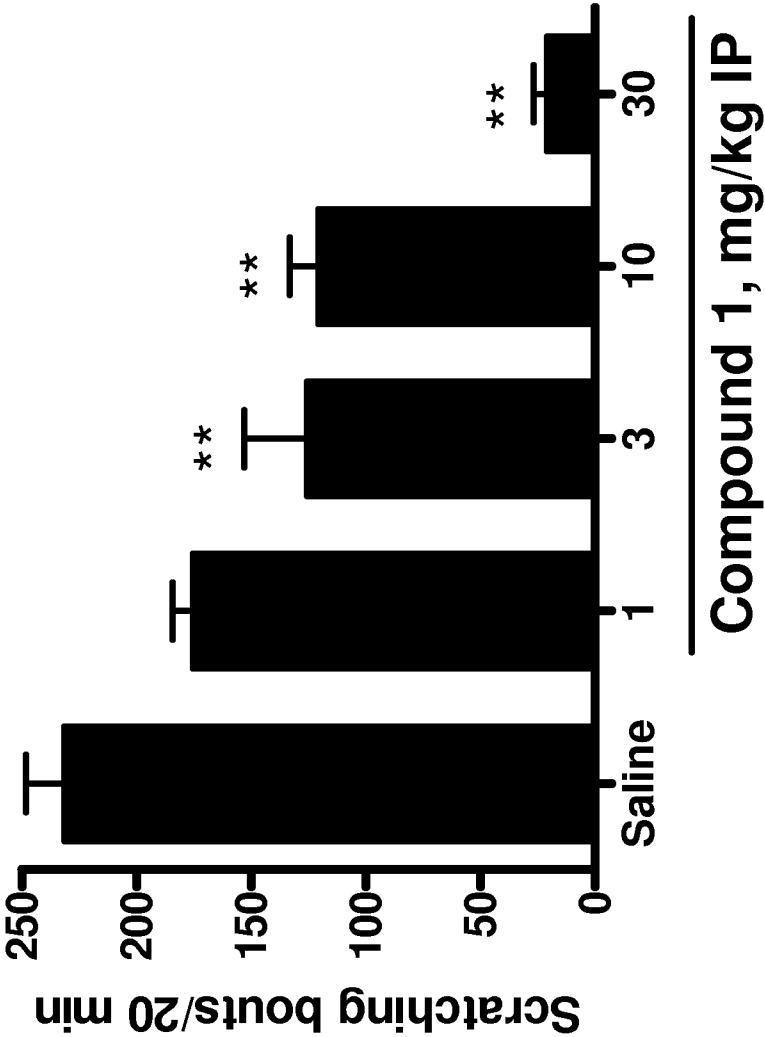


Figure 4

**ADMINISTRATION OF COMPOUND 1
INHIBITS HISTAMINE-INDUCED PRURITUS**

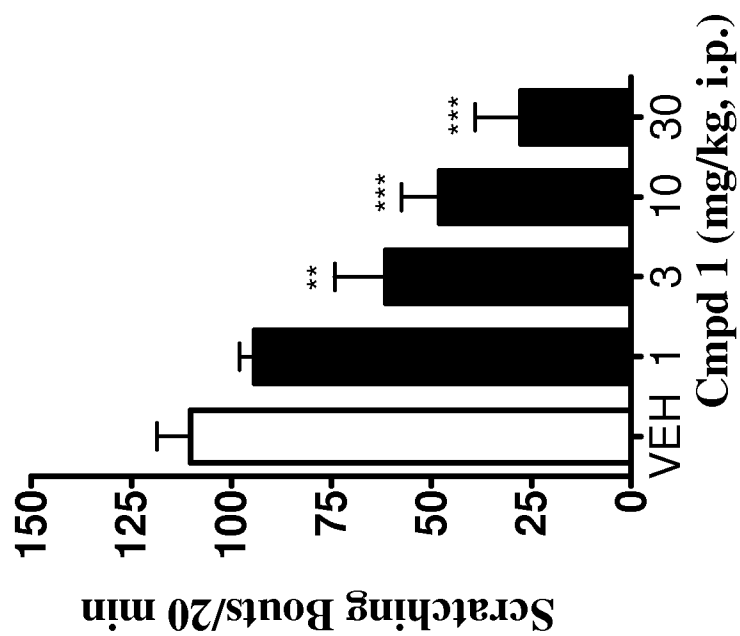


Figure 5

ADMINISTRATION OF COMPOUND 3
INHIBITS HISTAMINE-INDUCED PRURITUS

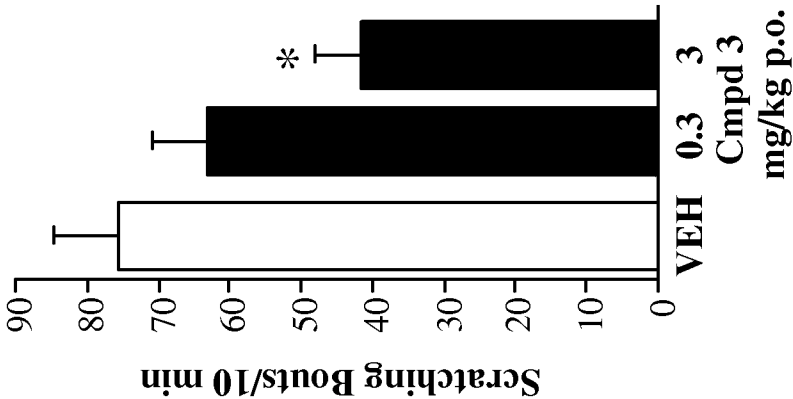


Figure 6

CENTRAL ADMINISTRATION OF COMPOUND A
DOES NOT INHIBIT HISTAMINE-INDUCED PRURITUS

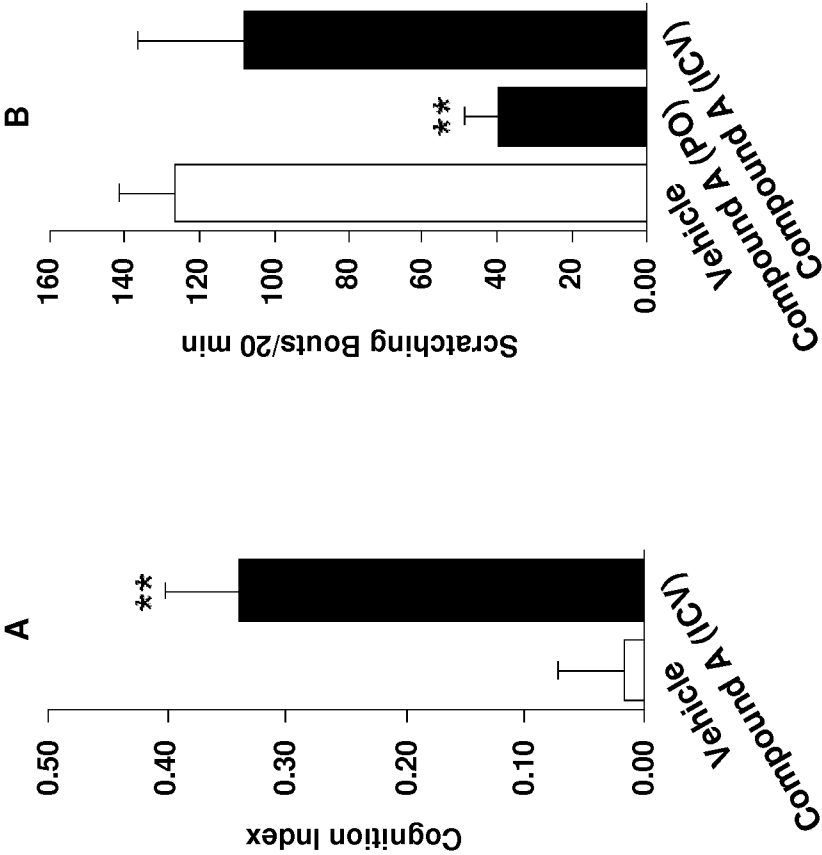


Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/054307

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D401/10 A61K31/4725 A61P17/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/331312 A1 (SANTORA VINCENT J [US] ET AL) 30 December 2010 (2010-12-30) Abstract; claims; page 6, paragraph 0147; examples e.g. pages 15-25, tables A, B. -----	1-42
A	LAZEWSKA ET AL.: "Recent advances in histamine H3 receptor antagonists/inverse agonists", EXPERT OPIN. THER. PATENTS, vol. 20, no. 9, 1 September 2010 (2010-09-01), pages 1147-1169, XP008127038, ISSN: 1354-3776, DOI: 10.1517/13543776.2010.509346 the whole document -----	1-42



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 September 2013

Date of mailing of the international search report

01/10/2013

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Authorized officer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/054307

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2714122 A1	27-08-2009
		CN 102007102 A	06-04-2011
		EP 2265587 A1	29-12-2010
		JP 2011512355 A	21-04-2011
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		WO 2009105206 A1	27-08-2009
