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(54) Title: BIPHENYL DERIVATIVES AS MODULATORS OF THE HISTAMINE-H3 RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

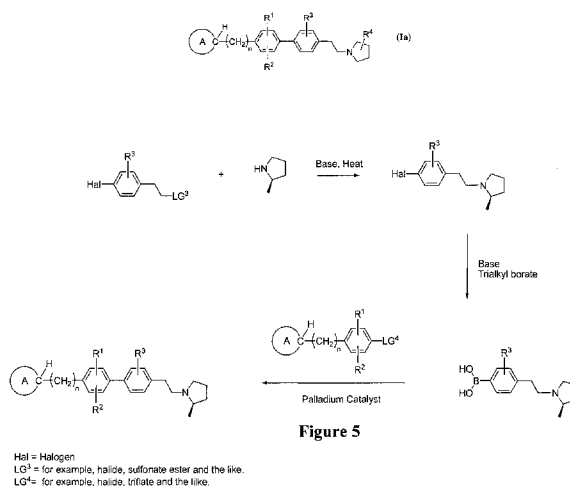


Figure 5

(57) **Abstract:** Biphenyl derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the H3 histamine receptor. (Ia) Compounds of the present invention and pharmaceutical compositions thereof are directed to methods useful in the treatment of histamine H3-associated disorders, such as cognitive disorders, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, such as narcolepsy, shift-work syndrome, drowsiness as a side effect from a medication, maintenance of vigilance to aid in 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 and the like.

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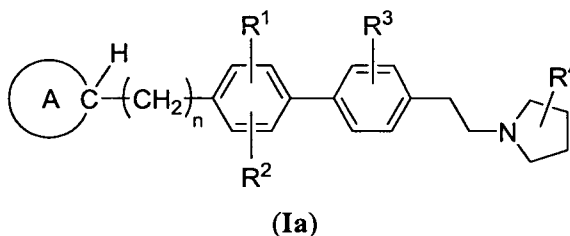
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FIELD OF THE INVENTION

The present invention relates to certain compounds of Formula (Ia) and pharmaceutical compositions 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, such as, cognitive disorders, epilepsy, brain
10 trauma, depression, obesity, disorders of sleep and wakefulness such as narcolepsy, shift-work syndrome, drowsiness as a side effect from a medication, maintenance of vigilance to aid in 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
15 disease, pain and the like.

SUMMARY OF THE INVENTION

One aspect of the present invention encompasses certain biphenyl derivatives selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates and hydrates
20 thereof:



wherein:

ring A is heterocyclyl optionally substituted with one, two or three substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆
25 alkoxy substituent;

R¹ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

R² is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

R³ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

R⁴ is H or C₁-C₄ alkyl; and

30

n is 0, 1 or 2.

One aspect of the present invention pertains to methods for treating a histamine H₃-receptor associated disorder in an individual comprising administering to said 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 histamine H3-receptor associated disorder selected from a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, 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 and pain.

One aspect of the present invention pertains to methods for treating a disorder of sleep and wakefulness.

One aspect of the present invention pertains to methods for treating a cognitive disorder.

One aspect of the present invention pertains to methods for treating cataplexy.

One aspect of the present invention pertains to methods for inducing wakefulness.

One aspect of the present invention pertains to methods for treating pain.

One aspect of the present invention pertains to the use of a compound of the present invention 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 in the manufacture of a medicament for the treatment of a disorder selected from a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, 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 and pain.

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

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

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a histamine H3-receptor associated disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a histamine H3-receptor associated disorder selected from a
5 cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease and pain.

One aspect of the present invention pertains to compounds of the present invention for
10 use in a method for the treatment of a disorder of sleep and wakefulness.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a cognitive disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of cataplexy.

15 One aspect of the present invention pertains to compounds of the present invention for use in a method of inducing wakefulness.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treating pain.

One aspect of the present invention pertains to compounds for preparing a composition
20 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.

25 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows two representative methods for preparing intermediates that are useful in the synthesis of the compounds of the present invention. The first method involves the reduction of an aryl amino acid derivative followed by cyclization of the resulting amino alcohol with triphosgene to give a 4-substituted cyclic carbamate. The second method involves the
30 reduction of an aryl amino ketone derivative followed by cyclization of the resulting amino alcohol with triphosgene to give a 5-substituted oxazolidinone.

Figure 2 shows two representative methods of introducing a substituent R⁵ onto the nitrogen of a heterocycle, ring A. Both processes involve the reaction of a cyclic carbamate with an alkyl or alkoxyalkyl derivative in the presence of a base. The step can be carried out either
35 before or after the formation of the biphenyl moiety.

Figure 3 shows a general synthesis of compounds of Formula (Ia). The first step is the conversion of an aryl halide derivative into a boronic acid with a trialkyl borate in the presence

of a base. Next, a palladium-catalyzed coupling is used to form the biphenyl moiety. Then, the silyl protecting group is removed and replaced with a leaving group. Finally, reaction between the biphenyl derivative and a cyclic amine in the presence of base, gives the molecule of Formula (Ia).

5 **Figure 4** shows a general method for preparing an aryl triflate for use in the palladium-catalyzed coupling reaction. First, a hydroxyphenyl amino acid derivative is esterified and the amine is converted to a *tert*-butyl carbamate in one pot. The ester function is reduced and the alcohol is converted to the cyclic carbamate with thionyl chloride. Finally the phenol group is converted to a triflate using triflic anhydride and a base.

10 **Figure 5** shows a general method for preparing a molecule of Formula (Ia) in which the right hand side of the molecule is (*R*)-2-methylpyrrolidine. First, (*R*)-2-methylpyrrolidine is reacted in the presence of a base with an arylalkyl derivative activated with a leaving group. The resulting (*R*)-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl halide is converted to an aryl boronic acid and undergoes a palladium-catalyzed coupling to give the final product.

15 **Figure 6** shows a general method for preparing an aryl triflate for use in the palladium-catalyzed coupling reaction. Reaction of a phenol derivative with 2-benzamidoacetic acid first provides an aryl amino acid. This is esterified and Boc protected followed by reduction to the alcohol. Cyclization is achieved by reaction with thionyl chloride and the resulting oxazolidinyl-phenol is converted to the aryl triflate with triflic anhydride.

20 **Figure 7** shows a general synthesis of compounds of Formula (Ia). A 2-(4-hydroxyphenyl)acetic acid derivative is esterified and then reduced to the diol. The pyrrolidine moiety is introduced by reaction of the primary alcohol with a secondary amine in the presence of triflic anhydride, with concomitant triflation of the phenol. This triflate is coupled to a boronic acid derivative, which itself is prepared from another aryl triflate or an aryl halide.

25 **Figure 8** shows three methods for preparing intermediates useful in preparing the compounds of the present invention. In the first of these methods, 5-oxopyrrolidine-2-carboxylic acid is reacted with anisole in the presence of phosphorus pentoxide and methanesulfonic acid to give 5-(4-methoxyphenyl)pyrrolidin-2-one, which in turn is converted to the triflate. The second
30 of these methods involves the conversion of a 4-amino-3-(4-chlorophenyl)butanoic acid derivative to a 4-(4-chlorophenyl)pyrrolidin-2-one by aluminum oxide-mediated cyclization. Finally, chlorinated aryl triflate intermediates useful in the preparation of chlorinated compounds of the present invention may be prepared by treating phenol derivatives with *N*-chlorosuccinimide followed by triflation.

35 **Figure 9** shows a representative synthesis of aryl triflate intermediates useful in the preparation of compounds of the present invention. A 2-(4-hydroxyphenyl)acetic acid derivative is esterified and then the phenol is protected with a *p*-methoxybenzyl group. The ester is then

reduced and the primary alcohol is converted to a leaving group which is displaced by a pyrrolidine derivative to give a tertiary amine. The PMB group is then removed with TFA and the phenol converted to the triflate.

Figure 10 shows a representative synthesis of aryl triflate intermediates useful in the preparation of compounds of the present invention. In the first step, a 2-(4-methoxyphenyl)acetic acid derivative is reduced to the corresponding primary alcohol. Next the free hydroxyl is activated with a leaving group which is displaced with a secondary amine. Next the methoxy group is removed with boron tribromide and the free phenol is converted to the triflate.

Figure 11 shows a general synthesis of compounds of Formula (Ia), wherein Ring A is 2-oxo-1,3-dioxolan-4-yl. First, a 1-(4-bromophenyl)ethane-1,2-diol is converted to the corresponding dimethyldioxolane and then coupled to an aryl boronic acid derivative using a palladium catalyst. The diol is then reformed by treatment with acid and subsequent reaction with 1,1'-carbonyldiimidazole (CDI) gives the desired heterocycle.

Figure 12 shows three general methods for preparing intermediates useful in the preparation of compounds of the present invention. The first method provides 2-oxo-1,3-oxazinan-6-yl intermediates by the reduction of aryl-3-oxopropanenitrile derivatives followed by treatment of the resulting hydroxy amine with CDI. The second method provides 2-oxo-1,3-oxazinan-4-yl intermediates via reaction of 1-amino-3-hydroxypropyl aryl derivatives with CDI. The third method provides 5-oxomorpholin-3-yl intermediates from 1,2-dihydroxyethyl aryl derivatives via the secondary amine by treatment first with sulfuric acid and acetonitrile and then ethyl chloroacetate in the presence of sodium hydride.

Figure 13 shows a general method for preparing compounds of Formula (Ia), wherein Ring A is 2-oxo-1,3-dioxolan-4-yl of the present invention. Palladium catalyzed coupling of a 4-hydroxymethyl aryl halide with a boronic acid derivative gives a biphenyl intermediate which is oxidized and reacted with ethyl acetate in the presence of LDA. The resulting ester is reduced to the 1,3-diol and converted to the 2-oxo-1,3-dioxan-4-yl derivative by treatment with CDI.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

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

The term “**agonists**” is intended to mean moieties that interact and activate the receptor, such as the H3 histamine 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**” is intended to mean 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**” is intended to mean bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, “contacting” a H3 histamine 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 H3 histamine receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a H3 histamine 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**” is intended to mean 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**” is intended to mean 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**” is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term “**pharmaceutical composition**” is intended to mean 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**” is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue,
5 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
10 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-C₆ alkoxy**” is intended to mean a C₁-C₆ alkyl radical, as defined herein, attached directly to an oxygen atom, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, *sec*-butoxy and the like.

The term “**C₁-C₆ alkyl**” is intended to mean a straight or branched carbon radical containing 1 to 6 carbons. Some embodiments are 1 to 5 carbons. Some embodiments are 1 to 4 carbons. Some embodiments are 1 to 3 carbons. Some embodiments are 1 or 2 carbons. Some embodiments are 1 carbon. Examples of an alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl, *iso*-pentyl, *t*-pentyl, *neo*-pentyl,
30 1-methylbutyl [*i.e.*, -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [*i.e.*, -CH₂CH(CH₃)CH₂CH₃], *n*-hexyl and the like.

The term “**C₁-C₄ alkyl**” is intended to mean a straight or branched carbon radical containing 1 to 4 carbons. Some embodiments are 1 to 3 carbons. Some embodiments are 1 or 2 carbons. Some embodiments are 1 carbon. Examples of a C₁-C₄ alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl and *t*-butyl.

The term “**aryl**” is intended to mean an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term “**halogen**” or “**halo**” is intended to mean to a fluoro, chloro, bromo or iodo group.

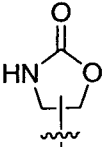
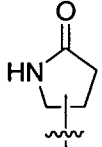
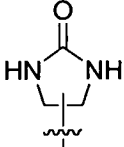
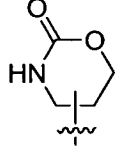
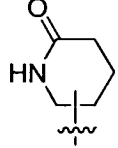
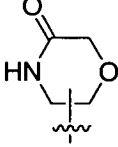
The term “**heterocyclic**” or “**heterocyclyl**” is intended to mean a non-aromatic, monocyclic ring containing 3 to 8 ring atoms wherein at least one ring atom is a heteroatom or substituted heteroatom selected from, but not limited to, for example, the group consisting of O, S, S(=O), S(=O)₂ and NH, wherein the N is optionally substituted as described herein. In some embodiments, the ring carbon atoms are optionally substituted with oxo thus forming a carbonyl group. In some embodiments, ring carbon atoms are optionally substituted with thioxo thus forming a thiocarbonyl group. In some embodiments the ring carbon atoms are optionally substituted with C₁-C₆ alkyl. In some embodiments the ring nitrogen atoms are optionally substituted with C₁-C₆ alkyl. In some embodiments the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy. In some embodiments a ring carbon is substituted with C₁-C₆ alkyl. In some embodiments a ring nitrogen is substituted with C₁-C₆ alkyl. In some embodiments the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy.

In some embodiments the heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered ring. Examples of a heterocyclic group include, but are not limited to, aziridin-2-yl, azetidin-2-yl, azetidin-3-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, piperzin-2-yl, piperzin-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, [1,3]-dioxolan-2-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl, 4-oxooxazolidin-2-yl, 4-oxooxazolidin-5-yl, 5-oxooxazolidin-2-yl, 5-oxooxazolidin-4-yl, 2-oxopyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, 3-oxopyrrolidin-2-yl, 3-oxopyrrolidin-4-yl, 3-oxopyrrolidin-5-yl, 2-oxoimidazolidin-4-yl, 4-oxoimidazolidin-2-yl, 4-oxoimidazolidin-5-yl, 2-oxopiperidin-3-yl, 2-oxopiperidin-4-yl, 2-oxopiperidin-5-yl, 2-oxopiperidin-6-yl, 3-oxopiperidin-2-yl, 3-oxopiperidin-4-yl, 3-oxopiperidin-5-yl, 3-oxopiperidin-6-yl, 4-oxopiperidin-2-yl, 4-oxopiperidin-3-yl, 2-oxomorpholin-3-yl, 2-oxomorpholin-5-yl, 2-oxomorpholin-6-yl, 3-oxomorpholin-2-yl, 3-oxomorpholin-5-yl, 3-oxomorpholin-6-yl, 2-oxo-1,3-oxazinan-4-yl, 2-oxo-1,3-oxazinan-5-yl, 2-oxo-1,3-oxazinan-6-yl, 4-oxo-1,3-oxazinan-2-yl, 4-oxo-1,3-oxazinan-5-yl, 4-oxo-1,3-oxazinan-6-yl, 5-oxo-1,3-oxazinan-2-yl, 5-oxo-1,3-oxazinan-4-yl, 5-oxo-1,3-oxazinan-6-yl, 6-oxo-1,3-oxazinan-2-yl, 6-oxo-1,3-oxazinan-4-yl, 6-oxo-1,3-oxazinan-5-yl and the like.

In some embodiments, the heterocyclic group is a 5- or 6-membered heterocyclic group. Examples of a 5- or 6-membered heterocyclic group include, but are not limited to, oxooxazolidinyl, oxopyrrolidinyl, oxoimidazolidinyl, oxopiperidinyl, oxomorpholinyl and oxo-1,3-oxazinanyl.

In some embodiments, examples of a 5- or 6-membered heterocyclic groups include, but are not limited to, 2-oxooxazolidinyl, 2-oxopyrrolidinyl, 2-oxoimidazolidinyl, 2-oxo-1,3-oxazinanyl, 2-oxopiperidinyl, 3-oxomorpholinyl and the like as shown in Table 1.

Table 1

Name	Structure
2-oxooxazolidinyl	
2-oxopyrrolidinyl	
2-oxoimidazolidinyl	
2-oxo-1,3-oxazinanyl	
2-oxopiperidinyl	
3-oxomorpholinyl	

It is understood that any one of the heterocyclic groups shown in Table 1 can be bonded
 5 at any available ring carbon as allowed by the respective formulae unless otherwise specified.

In some embodiments, examples of a 5- or 6-membered heterocyclic group include, but are not limited to, 2-oxooxazolidinyl, 2-oxo-1,3-oxazinanyl and the like.

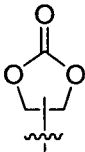
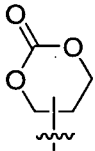
In some embodiments, examples of a 5- or 6-membered heterocyclic group include, but are not limited to, 2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl, 2-oxo-1,3-oxazinan-4-yl, 2-oxo-
 10 1,3-oxazinan-5-yl, 2-oxo-1,3-oxazinan-6-yl and the like.

In some embodiments, examples of a 5- or 6-membered heterocyclic group include, but are not limited to, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl and the like.

In some embodiments, examples of a 5- or 6-membered heterocyclic group include, but are not limited to, 2-oxo-1,3-dioxolanyl, 2-oxo-1,3-dioxanyl and the like as shown in Table 2.

5

Table 2

Name	Structure
2-oxo-1,3-dioxolanyl	
2-oxo-1,3-dioxanyl	

10 In some embodiments, examples of a 5- or 6-membered heterocyclic group include, but are not limited to, 2-oxo-1,3-dioxolan-4-yl, 2-oxo-1,3-dioxan-4-yl and the like.

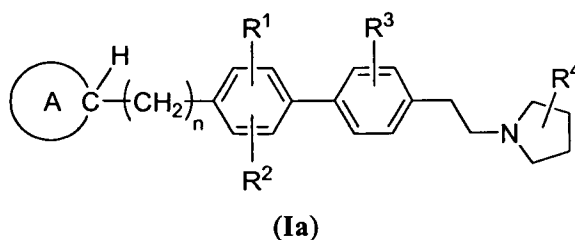
The term “**hydrate**” as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

15 The term “**oxo**” is intended to mean the substituent =O, accordingly, as a result, when a carbon is substituted by an “**oxo**” group the new group resulting from the carbon and oxo together is a carbonyl group.

20 The term “**solvate**” as used herein means a compound of the invention or a salt, thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

COMPOUNDS OF THE INVENTION:

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



and pharmaceutically acceptable salts, solvates and hydrates thereof;

wherein:

5 R^1 , R^2 , R^3 , R^4 , ring A and n 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^3 , R^4 , ring A and n) contained within the generic chemical formulae described herein, for example, (Ia), 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 Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

10 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 diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers 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 represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

15

The Group R¹

In some embodiments, R¹ is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

20 In some embodiments, R¹ is selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

In some embodiments, R¹ is selected from the group consisting of methoxy, methyl, chloro and fluoro.

In some embodiments, R¹ is H.

In some embodiments, R¹ is C₁-C₆ alkoxy.

25 In some embodiments, R¹ is C₁-C₆ alkyl.

In some embodiments, R¹ is halogen.

The Group R²

30 In some embodiments, R² is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

In some embodiments, R² is selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

In some embodiments, R² is selected from the group consisting of methoxy, methyl, chloro and fluoro.

35 In some embodiments, R² is H.

In some embodiments, R² is C₁-C₆ alkoxy.

In some embodiments, R² is C₁-C₆ alkyl.

In some embodiments, R² is halogen.

The Group R³

5 In some embodiments, R³ is selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

In some embodiments, R³ is selected from the group consisting of C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

In some embodiments, R³ is selected from the group consisting of methoxy, methyl, chloro and fluoro.

10 In some embodiments, R³ is H.

In some embodiments, R³ is C₁-C₆ alkoxy.

In some embodiments, R³ is C₁-C₆ alkyl.

In some embodiments, R³ is halogen.

15 The Group R⁴

In some embodiments, R⁴ is selected from the group consisting of H or C₁-C₄ alkyl.

In some embodiments, R⁴ is H.

In some embodiments, R⁴ is C₁-C₄ alkyl.

In some embodiments, R⁴ is methyl

20

The Ring A

In some embodiments, ring A is heterocyclyl optionally substituted with one substituent selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent.

25 In some embodiments, ring A is heterocyclyl optionally substituted with two substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is heterocyclyl optionally substituted with three substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent.

30

In some embodiments, ring A is heterocyclyl optionally substituted with one or two substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent.

35 In some embodiments, ring A is heterocyclyl optionally substituted with one, two or three substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from oxooxazolidinyl, oxopyrrolidinyl, oxoimidazolidinyl, oxopiperidinyl, oxomorpholinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

5 In some embodiments, ring A is selected from oxooxazolidinyl, oxopyrrolidinyl, oxoimidazolidinyl, oxopiperidinyl, oxomorpholinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

15 In some embodiments, ring A is selected from 2-oxooxazolidinyl, 2-oxopyrrolidinyl, 2-oxoimidazolidinyl, 2-oxopiperidinyl, 3-oxomorpholinyl and 2-oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from 2-oxooxazolidinyl, 2-oxopyrrolidinyl, 2-oxoimidazolidinyl, 2-oxopiperidinyl, 3-oxomorpholinyl and 2-oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is selected from 2-oxooxazolidinyl and 2-oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from 2-oxooxazolidinyl and 2-oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

30 In some embodiments, ring A is selected from 2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from 2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl; wherein each ring A is optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl.

5 In some embodiments, ring A is oxooxazolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is oxopyrrolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

10 In some embodiments, ring A is oxoimidazolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is oxopiperidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is oxomorpholinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

20 In some embodiments, ring A is oxo-1,3-oxazinanyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is oxooxazolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

25 In some embodiments, ring A is oxopyrrolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is oxoimidazolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is oxopiperidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

30 In some embodiments, ring A is oxomorpholinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is oxo-1,3-oxazinanyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

35 In some embodiments, ring A is 2-oxooxazolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is 2-oxopyrrolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

5 In some embodiments, ring A is 2-oxoimidazolidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is 2-oxopiperidinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

10 In some embodiments, ring A is 3-oxomorpholinyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

15 In some embodiments, ring A is 2-oxo-1,3-oxazinanyl optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is 2-oxooxazolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is 2-oxopyrrolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

20 In some embodiments, ring A is 2-oxoimidazolidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is 2-oxopiperidinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

25 In some embodiments, ring A is 3-oxomorpholinyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is 2-oxo-1,3-oxazinanyl optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

30 In some embodiments, ring A is 2-oxooxazolidin-4-yl, optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is 2-oxooxazolidin-5-yl, optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

35 In some embodiments, ring A is 2-oxo-1,3-oxazinan-4-yl, optionally substituted with a C₁-C₆ alkyl substituent; wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is 2-oxooxazolidin-4-yl, optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is 2-oxooxazolidin-5-yl, optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

5 In some embodiments, ring A is 2-oxo-1,3-oxazinan-4-yl, optionally substituted with a substituent selected from methyl, isopropyl and 2-methoxyethyl.

In some embodiments, ring A is 2-oxooxazolidin-4-yl.

In some embodiments, ring A is 3-methyl-2-oxooxazolidin-4-yl.

In some embodiments, ring A is 3-isopropyl-2-oxooxazolidin-4-yl.

10 In some embodiments, ring A is 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl.

In some embodiments, ring A is 2-oxooxazolidin-5-yl.

In some embodiments, ring A is 2-oxo-1,3-oxazinan-4-yl.

In some embodiments, ring A is selected from oxopyrrolidinyl, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl, oxomorpholinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.

In some embodiments, ring A is selected from oxopyrrolidinyl, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl, oxomorpholinyl and oxo-1,3-oxazinanyl.

20 In some embodiments, ring A is selected from 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, 2-oxo-1,3-dioxolan-4-yl, 2-oxo-1,3-dioxan-4-yl, 3-oxomorpholin-5-yl and 2-oxo-1,3-oxazinan-6-yl.

In some embodiments, ring A is 2-oxopyrrolidin-4-yl.

In some embodiments, ring A is 2-oxopyrrolidin-5-yl.

In some embodiments, ring A is 2-oxo-1,3-dioxolan-4-yl.

25 In some embodiments, ring A is 2-oxo-1,3-dioxan-4-yl.

In some embodiments, ring A is 3-oxomorpholin-5-yl.

In some embodiments, ring A is 2-oxo-1,3-oxazinan-6-yl.

The Variable n

30 In some embodiments, n is 0, 1 or 2.

In some embodiments, n is 0 or 1.

In some embodiments, n is 0 or 2.

In some embodiments, n is 1 or 2.

In some embodiments, n is 0.

35 In some embodiments, n is 1.

In some embodiments, n is 2.

Certain Combinations of the Present Invention:

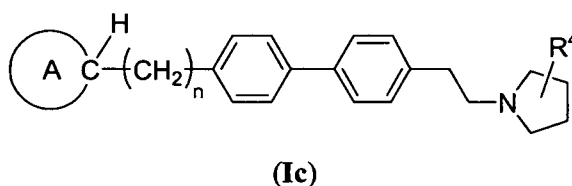
In some embodiments, R^1 and R^2 are both H.

In some embodiments, R^1 and R^3 are both H.

In some embodiments, R^2 and R^3 are both H.

5 In some embodiments, R^1 , R^2 and R^3 are all H.

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



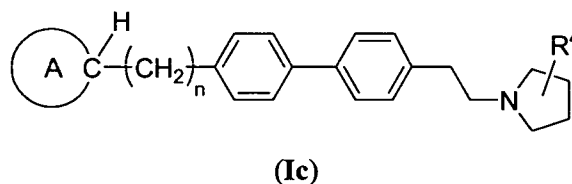
wherein:

10 R^4 is H or C_1 - C_4 alkyl;

ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C_1 - C_6 alkyl substituent; and wherein the C_1 - C_6 alkyl substituent is optionally substituted with a C_1 - C_6 alkoxy substituent; and

n is 0, 1 or 2.

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



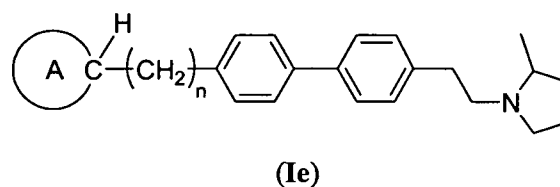
wherein:

R^4 is H or methyl;

20 ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl; and

n is 0, 1 or 2.

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

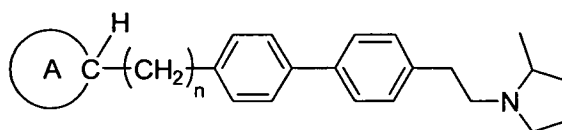


wherein:

ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent; and

n is 0, 1 or 2.

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



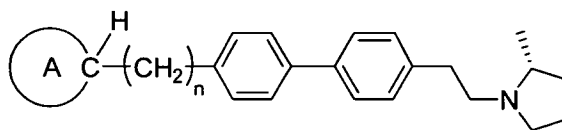
(Ie)

wherein:

- 10 ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazin-4-yl; and

n is 0, 1 or 2.

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



(Ig)

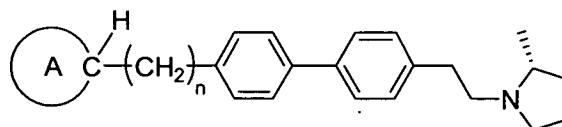
15

wherein:

ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent; and

- 20 n is 0, 1 or 2.

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



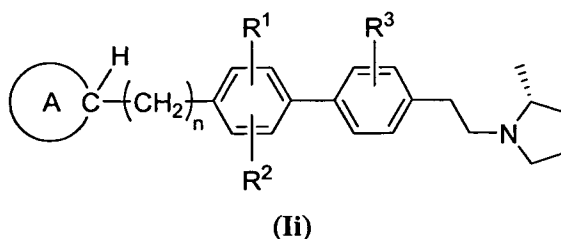
(Ig)

wherein:

- 25 ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazin-4-yl; and

n is 0, 1 or 2.

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



wherein:

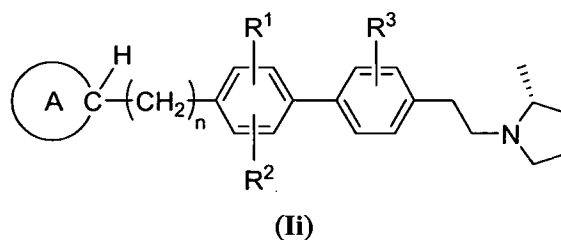
- 5 R^1 , R^2 and R^3 are each independently selected from H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl and halogen;

ring A is selected from oxooxazolidinyl, oxo-1,3-oxazinanyl, oxopyrrolidinyl, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl, oxomorpholinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C_1 - C_6 alkyl substituent; and wherein the C_1 - C_6 alkyl substituent is

10 optionally substituted with a C_1 - C_6 alkoxy substituent; and

n is 0, 1 or 2.

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



- 15 wherein:

R^1 , R^2 and R^3 are each independently selected from H, methoxy, methyl, chloro and fluoro;

ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl, 2-oxo-1,3-oxazinan-4-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, 2-oxo-1,3-dioxolan-4-yl, 2-oxo-1,3-dioxan-4-yl, 3-oxomorpholin-5-yl and 2-oxo-1,3-oxazinan-6-yl; and

20

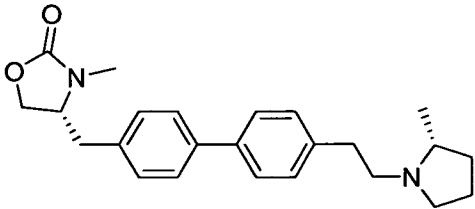
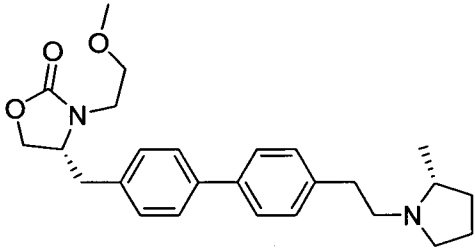
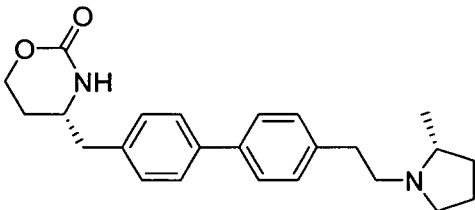
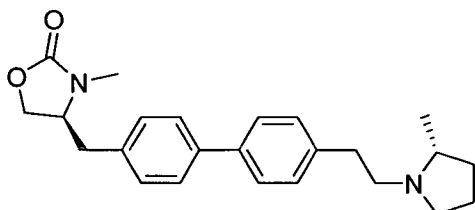
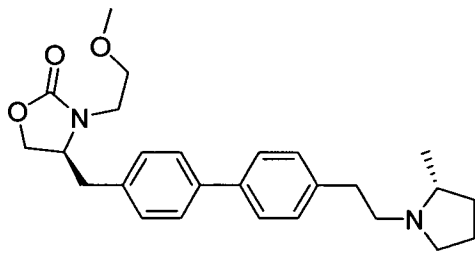
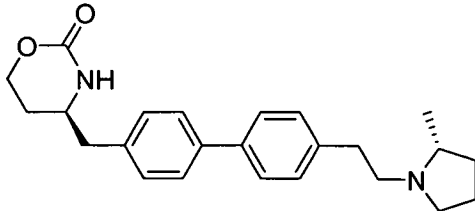
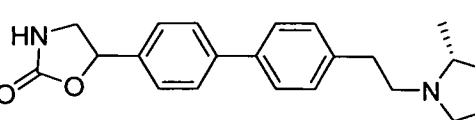
n is 0, 1 or 2.

Some embodiments of the present invention include every combination of one or more

25 compounds selected from the following group shown in TABLE A and TABLE B.

TABLE A

Cmpd No.	Chemical Structure	Chemical Name
1		(S)-4-((4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
2		(S)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
3		(R)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
4		(R)-4-((4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
5		(R)-3-methyl-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
6		(R)-3-(2-methoxyethyl)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
7		(R)-3-isopropyl-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one

Cmpd No.	Chemical Structure	Chemical Name
8		(<i>R</i>)-3-methyl-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
9		(<i>R</i>)-3-(2-methoxyethyl)-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
10		(<i>R</i>)-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one
11		(<i>S</i>)-3-methyl-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
12		(<i>S</i>)-3-(2-methoxyethyl)-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one
13		(<i>S</i>)-4-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one
14		5-((4'-(2-((<i>R</i>)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one

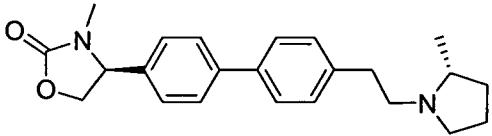
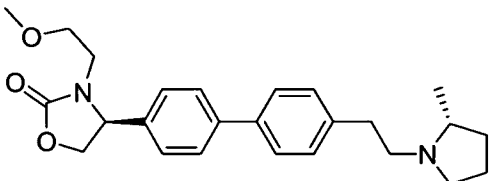
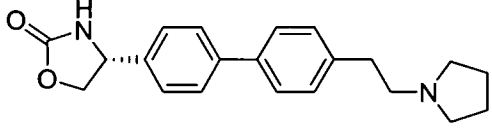
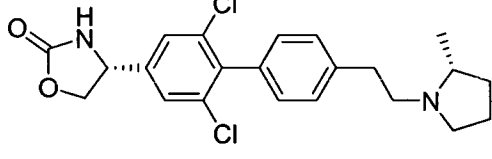
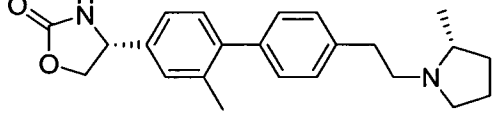
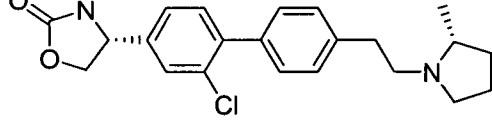
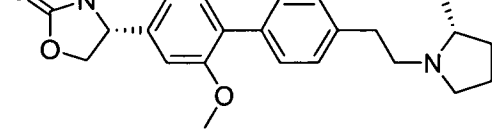
Cmpd No.	Chemical Structure	Chemical Name
15		(S)-3-methyl-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
16		(S)-3-(2-methoxyethyl)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
17		(R)-4-(4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one

TABLE B

Cmpd No.	Chemical Structure	Chemical Name
18		(R)-4-(2,6-dichloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
19		(R)-4-(2-methyl-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
20		(R)-4-(2-chloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
21		(R)-4-(2-methoxy-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one

Cmpd No.	Chemical Structure	Chemical Name
22		(S)-4-(2'-chloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
23		(S)-4-(3'-fluoro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
24		4-(3-methyl-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
25		4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one
26		4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxolan-2-one
27		6-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one
28		4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one
29		4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxan-2-one

Cmpd No.	Chemical Structure	Chemical Name
30		5-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one
31		5-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)morpholin-3-one
32		(S)-4-(2'-methyl-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one
33		(S)-4-(2'-methoxy-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in TABLE A and TABLE B including diastereomers 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]; incorporated herein by reference in its entirety).

It is understood that the present invention embraces each diastereomer, 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 diastereomeric 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

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 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, **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 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 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 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.

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 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 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 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 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), 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 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), 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 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
5 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, 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
10 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 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
15 compounds did not have a significant effect on the model of anxiety, a 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.

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
20 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 the year 2020, according to the World Health Organization.

Compounds of the present invention can be used in combination with various known
25 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), tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), escitalopram (Lexapro), and sertraline (Zoloft), norepinephrine
30 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
35 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."

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.

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.

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).

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 compound of the present invention and a pharmaceutically acceptable carrier.

5 Some embodiments of the present invention include a method of producing a 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.

10 Conventional excipients, such as binding agents, fillers, acceptable wetting agents, 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 (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.

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.*)

25 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.

30 The invention thus further provides pharmaceutical formulations comprising a 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.

35 Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (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
5 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
10 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,
15 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
20 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
25 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 H3
30 histamine receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and is intended to mean 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
35 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.

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
5 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.

In tablets, the active component is mixed with the carrier having the necessary binding
10 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, magnesium
15 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 without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are
20 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 therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized
25 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.

Liquid form preparations include solutions, suspensions and emulsions, for example,
30 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 injectable preparation may also be a sterile injectable solution or suspension in a nontoxic
35 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 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
5 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 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.
10 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.

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
15 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, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly
20 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, thickeners, solubilizing agents and the like.

For topical administration to the epidermis the compounds according to the invention
25 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 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.

30 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 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,
35 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 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), incorporated herein by reference in its entirety.

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.

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 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, both of which are hereby incorporated by reference in their entirety.

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.

It is noted that when the H3 histamine 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 H3 histamine receptor modulators, for the treatment of a H3-associated disease or disorder in companionship animals (*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

5 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. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned
10 herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, incorporated herein by reference in its entirety. Accordingly, one aspect of the present invention pertains to hydrates and solvates of compounds of Formula (Ia), as described herein, that can be
15 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.

OTHER UTILITIES

20 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 H3 histamine receptor in tissue samples, including human and for identifying H3 histamine receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel H3-receptor
25 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
30 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
35 example, for *in vitro* H3 histamine 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) or (Ii) 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 .

5 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
10 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
15 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
20 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,
25 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
30 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.

35 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.

10 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 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.

15 A radiolabeled H3 histamine receptor compound of Formula (Ia) can be used in a 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 H3 histamine receptor directly correlates to its binding affinity.

20 The labeled compounds of the present invention bind to the H3 histamine 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 embodiment the labeled inhibitor has an IC_{50} less than about 0.1 μM .

25 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.

30 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, 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

Example 1: Syntheses of compounds of the present invention.

35 Illustrated syntheses for compounds of the present invention are shown in Figures 1 through 13 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, dddd = doublet of 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 SynthesizerTM or an Emrys OptimizerTM (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 (R)-4-(4-Chlorophenyl)oxazolidin-2-one.

To an ice cooled solution of (R)-2-amino-2-(4-chlorophenyl)acetic acid (2.262 g, 12.19 mmol) in THF (49 mL) was added borane (1.0 M in tetrahydrofuran, 48.7 mL, 48.7 mmol) *via* a dropping funnel. The reaction mixture was stirred an additional 30 min before removal of the ice-bath and let stir overnight thereafter. Methanol (25 mL) was then added *via* a dropping funnel. After 30 min of stirring, the solvent was removed under reduced pressure. The residue was re-suspended in dichloromethane (122 mL), diisopropylethylamine (21.29 mL, 122 mmol) was added and the mixture was cooled in ice-bath. Triphosgene (3.98 g, 13.41 mmol) was then added resulting in rapid gas evolution. After 30 min, the ice bath was removed and the reaction mixture was let stir overnight. The solution was diluted with ethyl acetate (300 mL), washed twice with 1 M HCl, then brine, and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by chromatography on a silica column eluting with 40-100% ethyl acetate in hexanes to yield the title compound as a white solid (790 mg, 33%). ^1H NMR (400 MHz, CDCl_3) δ ppm 4.14 (dd, $J = 8.72, 6.95$ Hz, 1 H), 4.73 (t, $J = 8.72$ Hz, 1 H), 4.92 - 4.98 (m, 1 H), 6.32 (s, 1 H), 7.27 - 7.30 (m, 2 H), 7.36 - 7.40 (m, 2 H).

Example 1.2: Preparation of (R)-4-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 3).

A mixture of (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.192 g, 0.825 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (0.020 g, 0.041 mmol), (R)-4-(4-chlorophenyl)oxazolidin-2-one (0.163 g, 0.825 mmol), potassium phosphate (525 mg, 2.47 mmol), and palladium (II) acetate (3.70 mg, 0.016 mmol) in tetrahydrofuran (4 mL) was placed under microwave irradiation at 120 °C for 1 h. The reaction mixture was filtered and rinsed with acetonitrile. The filtrate was concentrated under reduced pressure and purified by preparative HPLC using a 25 x 250 mm C18 column, eluting with 10-75% acetonitrile in water containing 0.1% trifluoroacetic acid over 55 min. The resulting HPLC fractions were combined and acetonitrile was evaporated. The remaining aqueous solution was made basic with 2 M Na₂CO₃, saturated with sodium chloride and extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried with magnesium sulfate and filtered. HCl (1 M in ether, 1 mL) was added to the filtrate and the solvent was removed under reduced pressure. This material was then re-suspended in water, frozen and lyophilized to yield the hydrochloride salt of the title compound (121 mg, 38%). Exact mass calculated for C₂₂H₂₆N₂O₂: 350.5, Found: LCMS *m/z* = 351.3 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.34 (d, *J* = 6.57 Hz, 0.3 H), 1.51 (d, *J* = 6.57 Hz, 2.7 H), 1.72 - 1.84 (m, 1 H), 2.03 - 2.24 (m, 2 H), 2.31 - 2.42 (m, 1 H), 3.07 - 3.22 (m, 2 H), 3.25 - 3.33 (m, 2 H), 3.53 - 3.60 (m, 1 H), 3.61 - 3.71 (m, 1 H), 3.74 - 3.84 (m, 1 H), 4.19 (dd, *J* = 8.59, 6.57 Hz, 1 H), 4.82 (t, *J* = 8.72 Hz, 1 H), 5.07 (dd, *J* = 8.72, 6.44 Hz, 1 H), 7.42 - 7.50 (m, 4 H), 7.62 - 7.70 (m, 4 H).

Example 1.3: Preparation of (R)-4-(4-Bromobenzyl)oxazolidin-2-one.

From (R)-2-amino-3-(4-bromophenyl)propanoic acid (2.026 g, 8.30 mmol), using a similar method to the one described in **Example 1.1**, the title compound was obtained as a white solid (929 mg, 44%). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.84 (dd, *J* = 6.57, 2.78 Hz, 2 H), 4.02 - 4.15 (m, 2 H), 4.45 (t, *J* = 8.21 Hz, 1 H), 5.90 (s, 1 H), 7.04 - 7.09 (m, 2 H), 7.44 - 7.50 (m, 2 H).

Example 1.4: Preparation of (R)-4-((4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 4).

From (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.192 g, 0.825 mmol) and (R)-4-(4-bromobenzyl)oxazolidin-2-one (0.163 g, 0.825 mmol), using a similar method to the one described in **Example 1.2**, the hydrochloride salt of the title compound was obtained (96 mg, 53%). Exact mass calculated for C₂₃H₂₈N₂O₂: 364.5, Found: LCMS *m/z* = 365.5 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.31 (d, *J* = 6.57 Hz, 0.3 H), 1.50 (d, *J*

= 6.57 Hz, 2.7 H), 1.71 - 1.83 (m, 1 H), 2.03 - 2.22 (m, 2 H), 2.32 - 2.42 (m, 1 H), 2.88 - 2.98 (m, 2 H), 3.05 - 3.20 (m, 2 H), 3.23 - 3.33 (m, 2 H), 3.50 - 3.59 (m, 1 H), 3.67 (d, $J = 6.57$ Hz, 1 H), 3.73 - 3.82 (m, 1 H), 4.17 - 4.26 (m, 2 H), 4.40 - 4.48 (m, 1 H), 7.36 (d, $J = 8.34$ Hz, 2 H), 7.43 (d, $J = 8.34$ Hz, 2 H), 7.62 (dd, $J = 14.02, 8.21$ Hz, 4 H).

5

Example 1.5: Preparation of (*R*)-3-Methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 5).

To a solution of (*R*)-4-(4-chlorophenyl)oxazolidin-2-one (0.155 g, 0.784 mmol) in dimethylformamide (3 mL) under argon was added sodium hydride (0.047 g, 1.177 mmol).
10 Iodomethane (0.098 mL, 1.569 mmol) was then added. The reaction mixture was stirred overnight, diluted with ethyl acetate (50 mL), washed with 1 M HCl (10 mL twice), brine, dried with sodium sulfate and concentrated to give (*R*)-4-(4-chlorophenyl)-3-methyl-oxazolidin-2-one.

From (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.183 g, 0.784
15 mmol) and (*R*)-4-(4-chlorophenyl)-3-methyl-oxazolidin-2-one made above, using a similar method to the one described in **Example 1.2**, the hydrochloride salt of the title compound was obtained (153 mg, 49%). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 364.5, Found: LCMS $m/z = 365.6$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.35 (d, $J = 6.57$ Hz, 0.3 H), 1.51 (d, $J = 6.57$ Hz, 2.7 H), 1.72 - 1.84 (m, 1 H), 2.06 - 2.23 (m, 2 H), 2.32 - 2.43 (m, 1 H), 2.73 (s, 3 H),
20 3.07 - 3.22 (m, 2 H), 3.25 - 3.32 (m, 2 H), 3.53 - 3.60 (m, 1 H), 3.61 - 3.71 (m, 1 H), 3.75 - 3.82 (m, 1 H), 4.15 (dd, $J = 8.84, 7.07$ Hz, 1 H), 4.73 (t, $J = 8.72$ Hz, 1 H), 4.90 (dd, $J = 8.72, 7.20$ Hz, 1 H), 7.42 - 7.49 (m, 4 H), 7.65 - 7.75 (m, 4 H).

Example 1.6: Preparation of (*R*)-3-(2-Methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 6).

To a solution of (*R*)-4-(4-chlorophenyl)oxazolidin-2-one (0.157 g, 0.794 mmol) in dimethylformamide (3 mL) under argon was added sodium hydride (0.048 g, 1.192 mmol). 1-Bromo-2-methoxyethane (0.221 g, 1.589 mmol) was then added. The reaction mixture was stirred overnight, diluted with ethyl acetate (50 mL), washed with 1 M HCl (10 mL twice),
30 brine, dried with sodium sulfate and concentrated to give (*R*)-4-(4-chlorophenyl)-3-(2-methoxyethyl)-oxazolidin-2-one.

From (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.185 g, 0.794 mmol) and (*R*)-4-(4-chlorophenyl)-3-(2-methoxyethyl)-oxazolidin-2-one made above, using a similar method to the one described in **Example 1.2**, the hydrochloride salt of the title
35 compound was obtained (116 mg, 33%). Exact mass calculated for $C_{25}H_{32}N_2O_3$: 408.5, Found: LCMS $m/z = 409.4$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.35 (d, $J = 6.57$ Hz, 0.3 H), 1.51 (d, $J = 6.57$ Hz, 2.7 H), 1.72 - 1.85 (m, 1 H), 2.04 - 2.24 (m, 2 H), 2.32 - 2.42 (m, 1 H),

2.94 - 3.03 (m, 1 H), 3.06 - 3.24 (m, 2 H), 3.25 - 3.36 (m, 5 H), 3.48 (t, $J = 5.31$ Hz, 2 H), 3.52 - 3.70 (m, 3 H), 3.74 - 3.83 (m, 1 H), 4.18 (dd, $J = 8.84, 6.57$ Hz, 1 H), 4.74 (t, $J = 8.84$ Hz, 1 H), 5.11 (dd, $J = 8.97, 6.69$ Hz, 1 H), 7.46 (d, $J = 8.08$ Hz, 4 H), 7.69 (dd, 4 H).

5 **Example 1.7: Preparation of (*R*)-3-Isopropyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 7).**

To a solution of (*R*)-4-(4-chlorophenyl)oxazolidin-2-one (0.417 g, 2.110 mmol) in dimethylformamide (3 mL) under argon was added sodium hydride (0.048 g, 1.192 mmol) followed by 2-iodopropane (0.420 ml, 4.22 mmol). The reaction mixture was stirred overnight,
10 diluted with ethyl acetate (50 mL), washed with 1 M HCl (10 mL twice), brine, dried with sodium sulfate and concentrated to give (*R*)-4-(4-chlorophenyl)-3-isopropyl-oxazolidin-2-one.

From (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.185 g, 0.794 mmol) and (*R*)-4-(4-chlorophenyl)-3-isopropyl-oxazolidin-2-one made above, using a similar method to the one described in **Example 1.2**, the hydrochloride salt of the title compound was
15 obtained (200 mg, 22%). Exact mass calculated for $C_{25}H_{32}N_2O_2$: 392.5, Found: LCMS $m/z = 393.3$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.01 (d, $J = 6.82$ Hz, 3 H), 1.29 (d, $J = 7.07$ Hz, 3 H), 1.34 (d, $J = 6.57$ Hz, 0.3 H), 1.51 (d, $J = 6.57$ Hz, 2.7 H) 1.73 - 1.84 (m, 1 H), 2.04 - 2.22 (m, 2 H), 2.32 - 2.43 (m, 1 H), 3.07 - 3.23 (m, 2 H), 3.25 - 3.33 (m, 2 H), 3.51 - 3.61 (m, 1 H), 3.61 - 3.71 (m, 1 H), 3.74 - 3.84 (m, 2 H), 4.15 (dd, $J = 8.59, 6.06$ Hz, 1 H), 4.68 (t, $J = 8.84$ Hz, 1 H), 5.04 (dd, $J = 8.97, 6.19$ Hz, 1 H), 7.48 (dd, $J = 20.21, 8.34$ Hz, 4 H), 7.69 (dd, $J = 14.27, 8.21$ Hz, 4 H).
20

Example 1.8: Preparation of (*R*)-3-Methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 8).

25 From (*R*)-4-(4-bromobenzyl)oxazolidin-2-one (0.204 g, 0.797 mmol), iodomethane (0.099 ml, 1.593 mmol), and (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.186 g, 0.796 mmol), using a similar method to the one described in **Example 1.5**, the hydrochloride salt of the title compound was obtained (179 mg, 54%). Exact mass calculated for $C_{24}H_{30}N_2O_2$: 378.5, Found: LCMS $m/z = 379.4$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.34 (d, $J = 6.32$ Hz, 0.3 H), 1.51 (d, $J = 6.32$ Hz, 2.7 H), 1.72 - 1.84 (m, 1 H), 2.03 - 2.23 (m, 2 H), 2.31 - 2.43 (m, 1 H), 2.83 - 2.96 (m, 4 H), 3.08 - 3.21 (m, 3 H), 3.24 - 3.32 (m, 2 H), 3.49 - 3.69 (m, 2 H), 3.78 (d, $J = 4.04$ Hz, 1 H), 4.06 - 4.17 (m, 2 H), 4.24 - 4.33 (m, 1 H), 7.35 (d, $J = 8.08$ Hz, 2 H), 7.43 (d, $J = 7.83$ Hz, 2 H), 7.62 (dd, $J = 11.75, 7.96$ Hz, 4 H).
30

35 **Example 1.9: Preparation of (*R*)-3-(2-Methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 9).**

From (*R*)-4-(4-bromobenzyl)oxazolidin-2-one (0.201 g, 0.785 mmol), 1-bromo-2-methoxyethane (0.148 ml, 1.570 mmol), and (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.183 g, 0.786 mmol), using a similar method to the one described in **Example 1.6**, the hydrochloride salt of the title compound was obtained (216 mg, 60%).

- 5 Exact mass calculated for $C_{26}H_{34}N_2O_3$: 422.6, Found: LCMS m/z = 423.2 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.32 (d, J = 6.57 Hz, 0.3 H), 1.48 (d, J = 6.57 Hz, 2.7 H) 1.71 - 1.82 (m, 1 H), 2.03 - 2.19 (m, 2 H), 2.29 - 2.40 (m, 1 H), 2.81 (dd, J = 13.64, 7.58 Hz, 1 H), 3.03 - 3.21 (m, 3 H), 3.22 - 3.31 (m, 2 H), 3.33 - 3.43 (m, 4 H), 3.48 - 3.79 (m, 6 H), 4.08 - 4.14 (m, 1 H), 4.21 - 4.32 (m, 2 H), 7.32 (d, J = 8.34 Hz, 2 H), 7.41 (d, J = 8.34 Hz, 2 H), 7.59 (dd, J =
10 12.88, 8.34 Hz, 4 H).

Example 1.10: Preparation of (*S*)-3-Methyl-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 11).

- To a solution of (*S*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one hydrochloride (0.202 g, 0.504 mmol) in dimethylformamide (2 mL)
15 under argon was first added sodium hydride (0.050 g, 1.260 mmol) followed by iodomethane (0.031 mL, 0.504 mmol). The reaction mixture was stirred overnight, diluted with ethyl acetate (20 mL), washed with 1 M HCl (2 mL twice), brine, dried with sodium sulfate and concentrated. The residue was purified by preparative HPLC using a 21.2 x 250 mm C18 column, eluting with
20 10-75% acetonitrile in water containing 0.1% trifluoroacetic acid over 55 min. The resulting HPLC fractions were combined and acetonitrile was evaporated. The remaining aqueous solution was made basic with 2 M Na_2CO_3 , saturated with sodium chloride and extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried with magnesium sulfate and filtered. HCl (1 M in ether, 1 mL) was added to the filtrate and the solvent was
25 removed under reduced pressure. This material was then re-suspended in water, frozen and lyophilized to yield the hydrochloride salt of the title compound (65 mg, 31%). Exact mass calculated for $C_{24}H_{30}N_2O_2$: 378.5, Found: LCMS m/z = 379.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.32 (d, J = 6.57 Hz, 0.3 H) 1.48 (d, J = 6.57 Hz, 2.7 H), 1.70 - 1.82 (m, 1 H), 2.00 - 2.22 (m, 2 H), 2.29 - 2.40 (m, 1 H), 2.83 - 2.93 (m, 4 H), 3.04 - 3.18 (m, 3 H), 3.22 -
30 3.30 (m, 2 H), 3.46 - 3.58 (m, 1 H), 3.58 - 3.69 (m, 1 H), 3.70 - 3.80 (m, 1 H), 4.05 - 4.15 (m, 2 H), 4.24 - 4.32 (m, 1 H), 7.33 (d, J = 8.34 Hz, 2 H), 7.41 (d, J = 8.08 Hz, 2 H), 7.55 - 7.64 (m, 4 H).

- Example 1.11: Preparation of (*S*)-3-(2-Methoxyethyl)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 12).**
35

From (*S*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one hydrochloride (0.209 g, 0.521 mmol) and 1-bromo-2-methoxyethane (0.098 ml, 1.043

mmol), using a similar method to the one described in **Example 1.10**, the hydrochloride salt of the title compound was obtained (90 mg, 38%). Exact mass calculated for $C_{26}H_{34}N_2O_3$: 422.6, Found: LCMS $m/z = 423.2$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.32 (d, $J = 6.57$ Hz, 0.3 H), 1.48 (d, $J = 6.57$ Hz, 2.7 H), 1.71 - 1.82 (m, 1 H), 2.02 - 2.19 (m, 2 H), 2.29 - 2.39 (m, 1 H), 2.81 (dd, $J = 13.64$, 7.58 Hz, 1 H), 3.08 - 3.18 (m, 3 H), 3.22 - 3.31 (m, 2 H), 3.33 - 3.43 (m, 4 H), 3.48 - 3.80 (m, 6 H), 4.08 - 4.15 (m, 1 H), 4.21 - 4.33 (m, 2 H), 7.32 (d, $J = 8.08$ Hz, 2 H), 7.41 (d, $J = 8.08$ Hz, 2 H), 7.59 (dd, $J = 12.76$, 8.21 Hz, 4 H).

Example 1.12: Preparation of (*R*)-4-(4-Bromobenzyl)-1,3-oxazinan-2-one.

From (*R*)-3-amino-4-(4-bromophenyl)butanoic acid (1.000 g, 3.87 mmol), using a similar method to the one described in **Example 1.1**, the title compound was obtained as a white solid (749 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.13 (t, $J = 6.82$ Hz, 1 H), 1.69 - 1.82 (m, 2 H), 1.91 - 2.02 (m, 1 H), 3.63 - 3.75 (m, 1 H), 4.15 - 4.27 (m, 1 H), 4.30 - 4.38 (m, 1 H), 5.82 (s, 1 H), 7.07 (d, $J = 8.34$ Hz, 2 H), 7.46 (d, $J = 8.34$ Hz, 2 H).

Example 1.13: Preparation of (*R*)-4-((4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one (Compound 10).

In a 5 mL vial was placed (*R*)-4-(4-bromobenzyl)-1,3-oxazinan-2-one (0.147 g, 0.544 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.127 g, 0.544 mmol), tetrakis (triphenylphosphine)palladium (0) (0.019 g, 0.016 mmol), benzene (3 mL), ethanol (1 mL), and 2 M sodium carbonate (1 mL). The reaction mixture was heated under microwave irradiation for 1 h at 100 °C. The top organic phase was separated and filtered. After removal of solvent from the filtrate, the residue was purified by preparative HPLC using a 25 x 250 mm C18 column, eluting with 10-75% acetonitrile in water containing 0.1% trifluoroacetic acid over 55 min. The resulting HPLC fractions were combined and acetonitrile was evaporated. The remaining aqueous solution was made basic with 2 M Na_2CO_3 , saturated with sodium chloride and extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried with magnesium sulfate and filtered. HCl (1 M in ether, 1 mL) was added to the filtrate and the solvent was removed under reduced pressure. This material was then re-suspended in water, frozen and lyophilized to yield the hydrochloride salt of the title compound (17 mg, 8%). Exact mass calculated for $C_{24}H_{30}N_2O_2$: 378.5, Found: LCMS $m/z = 379.5$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.32 (d, $J = 6.32$ Hz, 0.3 H), 1.48 (d, $J = 6.32$ Hz, 2.7 H), 1.67 - 1.82 (m, 2 H), 1.87 - 1.96 (m, 1 H), 2.02 - 2.20 (m, 2 H), 2.30 - 2.40 (m, 1 H), 2.78 (dd, $J = 13.26$, 8.21 Hz, 1 H), 2.98 (dd, $J = 13.39$, 5.31 Hz, 1 H), 3.03 - 3.19 (m, 2 H), 3.23 - 3.31 (m, 2 H), 3.50 - 3.57 (m, 1 H), 3.58 - 3.69 (m, 1 H), 3.70 - 3.80 (m, 2 H), 4.16 - 4.24 (m, 1 H), 4.27 - 4.36 (m, 1 H), 7.33 (d, $J = 7.83$ Hz, 2 H), 7.41 (d, $J = 8.08$ Hz, 2 H), 7.60 (dd, $J = 14.53$, 7.96 Hz, 4 H).

Example 1.14: Preparation of (S)-4-(4-Bromobenzyl)-1,3-oxazinan-2-one.

From (S)-3-amino-4-(4-bromophenyl)butanoic acid (1.025 g, 3.97 mmol), using a similar method to the one described in **Example 1.1**, the title compound was obtained as a white solid (730 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.68 - 1.82 (m, 1 H), 1.91 - 2.01 (m, 1 H), 2.78 (d, *J* = 6.82 Hz, 2 H), 4.15 - 4.24 (m, 1 H), 4.30 - 4.38 (m, 1 H), 5.91 (s, 1 H), 7.07 (d, *J* = 8.08 Hz, 2 H), 7.46 (d, *J* = 8.34 Hz, 2 H).

Example 1.15: Preparation of (S)-4-((4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one (Compound 13).

From (S)-4-(4-bromobenzyl)-1,3-oxazinan-2-one (0.137 g, 0.507 mmol) and (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.118 g, 0.507 mmol), using a similar method to the one described in **Example 1.13**, the hydrochloride salt of the title compound was obtained as a white solid (125 mg, 59%). Exact mass calculated for C₂₄H₃₀N₂O₂: 378.5, Found: LCMS *m/z* = 379.5 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.32 (d, *J* = 6.57 Hz, 0.3 H), 1.49 (d, *J* = 6.57 Hz, 2.7 H), 1.66 - 1.82 (m, 2 H), 1.87 - 1.96 (m, 1 H), 2.01 - 2.19 (m, 2 H), 2.29 - 2.41 (m, 1 H), 2.77 (dd, *J* = 13.39, 8.08 Hz, 1 H), 2.98 (dd, *J* = 13.39, 5.31 Hz, 1 H), 3.04 - 3.20 (m, 2 H), 3.22 - 3.31 (m, 2 H), 3.49 - 3.57 (m, 1 H), 3.58 - 3.68 (m, 1 H), 3.71 - 3.80 (m, 2 H), 4.17 - 4.24 (m, 1 H), 4.28 - 4.35 (m, 1 H), 7.32 (d, *J* = 8.34 Hz, 2 H), 7.41 (d, *J* = 8.08 Hz, 2 H), 7.59 (dd, *J* = 13.52, 8.21 Hz, 4 H).

Example 1.16: Preparation of 5-(4-Bromophenyl)oxazolidin-2-one.

To a slurry of 2-amino-1-(4-bromophenyl)ethanone (1.003 g, 4.69 mmol) in THF (19 mL) was added sodium borohydride (0.222 g, 5.86 mmol) followed by ethanol (10 mL). The reaction slurry was stirred overnight, diluted with ethyl acetate (100 mL), washed with water, dried with sodium sulfate and concentrated. The residue was suspended in dichloromethane (9.5 mL), triethylamine (1.306 mL, 9.37 mmol) was added, the mixture was cooled in an acetone/dry-ice bath and triphosgene (0.486 g, 1.639 mmol) was added. After 20 min, the ice bath was removed and the reaction was let stir 90 min. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 1 M HCl (10 mL) and brine, dried with sodium sulfate and concentrated. The residue was purified by chromatography on a silica column eluting with 25-75% ethyl acetate in dichloromethane to afford the title compound as a white solid (579 mg, 51%). ¹H NMR (400 MHz, CDCl₃) δ ppm 3.50 (t, *J* = 8.08 Hz, 1 H), 3.99 (t, *J* = 8.72 Hz, 1 H), 5.59 (t, *J* = 8.08 Hz, 1 H), 5.70 (s, 1 H), 7.27 (d, *J* = 3.79 Hz, 2 H), 7.52 - 7.57 (m, 2 H).

Example 1.17: Preparation of 5-((4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 14).

From 5-(4-bromophenyl)oxazolidin-2-one (0.142 g, 0.554 mmol) and (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.129 g, 0.554 mmol), using a similar method to the one described in **Example 1.13**, the hydrochloride salt of the title compound was obtained as a white solid (149 mg, 67%). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 350.5, Found: LCMS $m/z = 351.4$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.32 (d, $J = 6.57$ Hz, 0.3 H), 1.49 (d, $J = 6.57$ Hz, 2.7 H), 1.70 - 1.82 (m, 1 H), 2.02 - 2.20 (m, 2 H), 2.29 - 2.40 (m, 1 H), 3.05 - 3.19 (m, 2 H), 3.22 - 3.30 (m, 2 H), 3.48 - 3.57 (m, 2 H), 3.59 - 3.68 (m, 1 H), 3.72 - 3.80 (m, 1 H), 4.02 (t, $J = 8.84$ Hz, 1 H), 5.68 - 5.75 (m, 1 H), 7.42 (d, $J = 8.34$ Hz, 2 H), 7.49 (d, $J = 8.34$ Hz, 2 H), 7.65 (dd, $J = 14.27, 8.21$ Hz, 4 H).

Example 1.18: Preparation of 4-(2-(*tert*-Butyldimethylsilyloxy)ethyl)phenylboronic acid.

A solution of (4-bromophenethoxy) (*tert*-butyl)dimethylsilane (4.893 g, 15.52 mmol) in THF (39 mL) was cooled to $-78^\circ C$ in an ice/acetone bath. To this solution *n*-butyllithium (2.5 M in Hexanes, 8.07 mL, 20.17 mmol) was added slowly and stirred for 90 min. Triisopropyl borate (14.32 mL, 62.1 mmol) was then added and stirred an additional 2 h. The reaction was then allowed to warm to room temperature for 90 min. The resulting cloudy reaction was quenched by the addition of 1 M HCl (40 mL). The reaction mixture was then diluted with ethyl acetate (400 mL) and the aqueous layer was separated. The ethyl acetate layer was washed with brine, dried with sodium sulfate and concentrated. The residue was purified by chromatography on a silica column eluting with 20-50% ethyl acetate in dichloromethane to afford the title compound as a colorless oil (2.31 g, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.00 (s, 6 H), 0.88 (s, 9 H), 2.87 - 2.94 (t, $J = 6.95$ Hz, 2 H), 3.87 (t, $J = 6.95$ Hz, 2 H), 7.36 (d, $J = 7.83$ Hz, 2 H), 8.16 (d, $J = 7.83$ Hz, 2 H).

Example 1.19: Preparation of (*R*)-4-(4'-(2-(*tert*-Butyldimethylsilyloxy)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of (*R*)-4-(4-chlorophenyl)oxazolidin-2-one (0.205 g, 1.037 mmol), 4-(2-(*tert*-butyldimethylsilyloxy)ethyl)phenylboronic acid (0.291 g, 1.037 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (0.025 g, 0.052 mmol), potassium phosphate (0.661 g, 3.11 mmol), and palladium (II) acetate (4.66 mg, 0.021 mmol), in tetrahydrofuran (4 mL) was heated under microwave irradiation at $120^\circ C$ for 1 h. The reaction mixture was filtered and the solid was rinsed with acetonitrile. The filtrate was concentrated and the residue was purified by chromatography on a silica column eluting with 20-60% ethyl acetate in hexanes to afford the title compound as a colorless oil (134 mg, 30%). Exact mass calculated for $C_{23}H_{31}NO_3Si$: 397.6, Found: LCMS $m/z = 398.3$ $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.0 (s, 6 H), 0.88 (s, 9 H), 2.86 (t, $J = 6.95$ Hz, 2 H), 3.84 (t, $J = 6.95$ Hz, 2 H), 4.16 - 4.27 (m, 1 H), 4.75 (q, $J = 8.84$ Hz, 1 H), 4.92 - 5.02 (m, 1 H), 7.29 (d, $J = 8.08$ Hz, 2 H),

7.35 (d, $J = 1.77$ Hz, 1 H), 7.40 (d, $J = 8.34$ Hz, 2 H), 7.49 (d, $J = 8.08$ Hz, 2 H), 7.61 (d, $J = 8.34$ Hz, 2 H).

Example 1.20: Preparation of (*R*)-4-(4'-(2-Hydroxyethyl)biphenyl-4-yl)oxazolidin-2-one.

5 To a solution of (*R*)-4-(4'-(2-(tert-butyldimethylsilyloxy)ethyl)biphenyl-4-yl)oxazolidin-2-one (0.130 g, 0.327 mmol) in IPA (1.3 mL) was added HCl (4 M in dioxane, 1.226 mL, 4.90 mmol). The reaction mixture was stirred for 1 h. After removal of the solvent under reduced pressure, the title compound was obtained (105 mg, 100%). Exact mass calculated for $C_{17}H_{17}NO_3$: 283.3, Found: LCMS $m/z = 284.4$ $[M+H]^+$, TLC Rf = 0.32 in 1:1, 10 dichloromethane:ethyl acetate.

Example 1.21: Preparation of (*R*)-2-(4'-(2-Oxooxazolidin-4-yl)biphenyl-4-yl)ethyl methanesulfonate.

To a solution of (*R*)-4-(4'-(2-hydroxyethyl)biphenyl-4-yl)oxazolidin-2-one (0.105 g, 15 0.371 mmol) in DCM (1.5 mL) was added triethylamine (0.129 mL, 0.927 mmol) followed by methanesulfonyl chloride (0.058 mL, 0.741 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 1 M HCl (10 mL, twice), then brine, and dried with sodium sulfate. After removal of the solvent under reduced pressure, the title compound was obtained. TLC Rf = 0.51 in 1:1, dichloromethane:ethyl acetate. 20

Example 1.22: Preparation of (*R*)-4-(4'-(2-(Pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 17).

A mixture of (*R*)-2-(4'-(2-oxooxazolidin-4-yl)biphenyl-4-yl)ethyl methanesulfonate (0.04 g, 0.111 mmol), pyrrolidine (0.014 mL, 0.166 mmol) and potassium carbonate (0.076 g, 25 0.553 mmol) slurried in acetonitrile (2 mL) in a vial was heated under microwave irradiation at 120 °C for 2 h. The reaction mixture was dissolved in water and lyophilized. The residue was purified by preparative HPLC using a 21.2 x 250 mm C18 column, eluting with 5-50% acetonitrile in water containing 0.1% trifluoroacetic acid over 55 min. The HPLC fractions were lyophilized to afford the TFA salt of the title compound (7.5 mg, 15%). Exact mass calculated 30 for $C_{21}H_{24}N_2O_2$: 336.4, Found: LCMS $m/z = 337.5$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.77 - 1.86 (m, 2 H), 1.92 - 2.02 (m, 2 H), 2.84 - 2.98 (m, 4 H), 3.24 - 3.31 (m, 2 H), 3.44 - 3.53 (m, 2 H), 3.97 (dd, $J = 8.59, 6.57$ Hz, 1 H), 4.59 (t, $J = 8.72$ Hz, 1 H), 4.84 (dd, $J = 8.72, 6.44$ Hz, 1 H), 7.22 (dd, $J = 19.96, 8.34$ Hz, 4 H), 7.39 - 7.48 (m, 4 H).

35 **Example 1.23: Preparation of (*S*)-3-Methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 15).**

Step A: Preparation of (*S*)-4-(4-Chlorophenyl)-3-methyloxazolidin-2-one.

To a solution of (*S*)-4-(4-chlorophenyl)oxazolidin-2-one (250 mg, 1.27 mmol) in DMF (5.0 mL) was added sodium hydride (60% dispersion in mineral oil) (76 mg, 1.90 mmol) followed by iodomethane (0.159 mL, 2.53 mmol). The resulting mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL), washed with 1 M HCl (2 x 10 mL), extracted twice with EtOAc and washed with brine. The combined organics were dried over MgSO₄, filtered, and concentrated to afford the title compound as a yellow oil in 100% crude yield. Exact mass calculated for C₁₀H₁₀ClNO₂: 211.0, Found: LCMS *m/z* = 211.8 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm, 2.71 (s, 3 H), 4.05 (dd, *J* = 7.83, 6.32 Hz, 1 H), 4.56 - 4.72 (m, 2 H), 7.25 (d, *J* = 8.59 Hz, 2 H), 7.41 (d, *J* = 8.34 Hz, 2 H).

Step B: Preparation of (*S*)-3-Methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 15).

To a vial was added (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (295 mg, 1.266 mmol), (*S*)-4-(4-chlorophenyl)-3-methyloxazolidin-2-one (268 mg, 1.266 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (30 mg, 0.063 mmol), potassium phosphate (806 mg, 3.80 mmol) and palladium (II) acetate (5.69 mg, 0.025 mmol) dissolved in THF (4.0 mL). The resulting reaction mixture was heated under microwave irradiation at 120 °C for 1 hr. After 1 hr, LCMS indicated the reaction was complete. The reaction mixture was diluted with water and the organics separated. The aqueous layer was extracted with EtOAc. The combined organics were concentrated, dissolved in ACN/H₂O (with AcOH) and purified by HPLC (0.1% TFA in acetonitrile/0.1% TFA in water). The combined fractions were basified with 2 M Na₂CO₃ and extracted 3 times with EtOAc. The combined organics were dried over MgSO₄, filtered, and concentrated. The residue was dissolved in MeOH (5 mL). Then, HCl (1 M in Et₂O, 1 mL) was added followed by EtOAc (5 mL). The resulting mixture was concentrated to afford the hydrochloride salt of the title compound as a white solid (408 mg, 55% yield). Exact mass calculated for C₂₃H₂₈N₂O₂: 364.2, Found: LCMS *m/z* = 365.5 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm, 1.38 (d, *J* = 6.32 Hz, 3 H), 1.62 - 1.76 (m, 1 H), 1.94 - 2.11 (m, 2 H), 2.17 - 2.32 (m, 1 H), 2.65 - 2.75 (m, 3 H), 2.92 - 3.16 (m, 4 H), 3.18 - 3.35 (m, 2 H), 3.39 - 3.52 (m, 1 H), 3.53 - 3.65 (m, 1 H), 4.13 (dd, *J* = 8.72, 6.95 Hz, 1 H), 4.70 (t, *J* = 8.84 Hz, 1 H), 7.34 - 7.47 (m, 4 H), 7.55 - 7.76 (m, 4 H).

Example 1.24: Preparation of (*S*)-3-(2-Methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 16).

Step A: Preparation of (*S*)-4-(4-Chlorophenyl)-3-(2-methoxyethyl)oxazolidin-2-one.

To a solution of (*S*)-4-(4-chlorophenyl)oxazolidin-2-one (250 mg, 1.27 mmol) in DMF (5.0 mL) was added sodium hydride (60% dispersion in mineral oil) (76 mg, 1.90 mmol) followed by 1-bromo-2-methoxyethane (0.235 mL, 2.53 mmol). The resulting mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL)

washed with 1 M HCl (2 x 10 mL), extracted twice with EtOAc and washed with Brine. The combined organics were dried over MgSO₄, filtered, and concentrated to give a yellow oil in 100% crude yield. Exact mass calculated for C₁₂H₁₄ClNO₃: 255.1, Found: LCMS *m/z* = 256.5 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm, 2.84 - 2.98 (m, 1 H), 3.29 (s, 3 H), 3.36 - 3.45 (m, 1 H), 3.49 - 3.67 (m, 2 H), 4.07 (dd, *J* = 8.84, 6.57 Hz, 1 H), 4.63 (t, *J* = 8.84 Hz, 1 H), 4.97 (dd, *J* = 8.84, 6.82 Hz, 1 H), 7.25 (d, *J* = 8.34 Hz, 2 H), 7.39 (d, *J* = 8.34 Hz, 2 H).

Step B: Preparation of (S)-3-(2-Methoxyethyl)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 16).

To a vial was added (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (294 mg, 1.263 mmol), (S)-4-(4-chlorophenyl)-3-(2-methoxyethyl)oxazolidin-2-one (323 mg, 1.263 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (30 mg, 0.063 mmol), potassium phosphate (804 mg, 3.79 mmol), palladium (II) acetate (5.67 mg, 0.025 mmol) and THF (4.0 mL). The resulting reaction mixture was heated at 120 °C under microwave irradiation for 1 h. The reaction mixture was diluted with water and the organics separated. The aqueous layer was extracted with EtOAc. The combined organics were concentrated, dissolved in ACN/H₂O (with AcOH) and purified by HPLC (0.1% TFA in acetonitrile/0.1% TFA in water). The combined fractions were basified with 2 M Na₂CO₃ and extracted 3 times with EtOAc. The combined organics were dried over MgSO₄, filtered, and concentrated. The residue was dissolved in MeOH (5 mL). Then, HCl (1 M in Et₂O, 1 mL) was added followed by EtOAc (5 mL). The resulting mixture was concentrated to afford the hydrochloride salt of the title compound as a white solid (281 mg, 50% yield). Exact mass calculated for C₂₅H₃₂N₂O₃: 408.2, Found: LCMS *m/z* = 409.4 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.33 (d, *J* = 6.32 Hz, 3 H), 1.56 - 1.72 (m, 1 H), 1.89 - 2.04 (m, 2 H), 2.11 - 2.27 (m, 1 H), 2.81 - 3.14 (m, 6 H), 3.27 - 3.43 (m, 4 H), 3.45 (t, *J* = 5.31 Hz, 2 H), 3.47 - 3.63 (m, 2 H), 4.16 (dd, *J* = 8.72, 6.69 Hz, 1 H), 4.71 (t, *J* = 8.84 Hz, 1 H), 5.08 (dd, *J* = 8.84, 6.57 Hz, 1 H), 7.40 (dd, *J* = 16.04, 8.21 Hz, 4 H), 7.61 (d, *J* = 8.08 Hz, 2 H), 7.68 (d, *J* = 8.34 Hz, 2 H).

Example 1.25: Preparation of (S)-4-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 2).

Step A: Preparation of (S)-2-Amino-2-(4-chlorophenyl)ethanol.

To a solution of (S)-2-amino-2-(4-chlorophenyl)acetic acid (10.0 g, 53.9 mmol) in THF (216 mL) was added 1.0 M borane tetrahydrofuran complex (216 mL, 216 mmol) *via* addition funnel over 45 min at 0 °C. The ice-bath was removed and the reaction mixture was stirred for 3.25 h at room temperature. Water (6.79 mL, 377 mmol) was added followed by sodium hydroxide solution (40.4 mL, 202 mmol) (dropwise over 15 min). The reaction was heated to 65 °C and stirred for 18 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (500 mL) and the organic phase was separated and washed with

water (200 mL). The aqueous phase was further extracted with DCM (2 x 250 mL). The organics were combined, dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound as a white solid (8.55 g, 92% yield). Exact mass calculated for C₈H₁₀ClNO: 171.1, Found: LCMS *m/z* (%) = 172.2 ([M+H]⁺, ³⁵Cl, 100), 174.2 ([M+H]⁺, ³⁷Cl, 33). ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 3.47 - 3.57 (m, 1 H), 3.59 - 3.69 (m, 1 H), 3.93 (dd, *J* = 7.58, 5.05 Hz, 1 H), 7.23 - 7.42 (m, 4 H).

Step B: Preparation of (*S*)-4-(4-Chlorophenyl)oxazolidin-2-one.

To a solution of (*S*)-2-amino-2-(4-chlorophenyl)ethanol hydrochloride (2.00 g, 9.61 mmol) and diisopropylethylamine (6.71 mL, 38.4 mmol) in DCM (40 mL) was added triphosgene (3.14 g, 10.6 mmol) at 25 °C resulting in an evolution of a large volume of gas. The mixture was stirred for 18 h and concentrated under reduced pressure. The solid residue was dissolved in 5% HCl (50 mL) solution and extracted with EtOAc (2 x 75 mL). The organic phase was washed with brine (60 mL), dried over Na₂SO₄, filtered and concentrated under reduce pressure. The crude residue was purified by flash chromatography (40-100% EtOAc/Hexane) to give the title compound as a clear oil (0.400 g, 21% yield). Exact mass calculated for C₉H₈ClNO₂: 197.0, Found: LCMS *m/z* = 198.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 4.13 (dd, *J* = 8.59, 6.82 Hz, 1 H), 4.72 (t, *J* = 8.72 Hz, 1 H), 4.91 - 4.97 (m, 1 H), 6.44 (s, 1 H), 7.27 (d, *J* = 8.34 Hz, 2 H), 7.37 (d, *J* = 8.59 Hz, 2 H).

Step C: Preparation of (*S*)-4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 2).

To a solution of (*S*)-4-(4-chlorophenyl)oxazolidin-2-one (0.150 g, 0.759 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.212 g, 0.911 mmol), potassium acetate (0.483 mL, 2.28 mmol), and 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (18.1 mg, 0.038 mmol) in anhydrous THF (4 mL) was added palladium (II) acetate (3.41 mg, 0.015 mmol). The reaction was heated at 120 °C under microwave irradiation for 45 min. The reaction mixture was filtered through Celite™ and the filter cake was washed with EtOAc (30 mL). The filtrate was concentrated. The residue was purified by preparative HPLC. The combined fractions were lyophilized to give the trifluoroacetic acid salt of the title compound (0.100 g, 29% yield). The trifluoroacetic acid salt was converted to the hydrochloride salt, which was a white solid. Exact mass calculated for C₂₂H₂₆N₂O₂: 350.2, Found: LCMS *m/z* = 351.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.23 (s, 0.3 H), 1.40 (d, *J* = 5.31 Hz, 2.7 H), 1.54 - 1.70 (m, 1 H), 1.87 - 2.04 (m, 2 H), 2.11 - 2.27 (bs, 1 H), 2.96 - 3.23 (m, 4 H), 3.27 - 3.71 (m, 2 H), 4.04 (dd, *J* = 8.34, 6.32 Hz, 1 H), 4.70 (t, *J* = 8.59 Hz, 1 H), 4.96 - 5.03 (m, 1 H), 7.42 (t, *J* = 7.58 Hz, 4 H), 7.68 (dd, *J* = 17.31, 8.21 Hz, 4 H), 8.22 (s, 1 H), 10.15 (s, 1 H).

Example 1.26: Preparation of (*S*)-4-((4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 1).

Step A: Preparation of (S)-2-Amino-3-(4-bromophenyl)propan-1-ol.

The title compound was prepared in a similar manner as described in **Example 1.25**,

Step A. Exact mass calculated for $C_9H_{12}BrNO$: 229.0, Found: LCMS m/z (%) = 230.2; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.84 (d, J = 6.82 Hz, 3 H), 4.04 - 4.15 (m, 2 H), 4.46 (t, J = 8.21 Hz, 1 H), 5.62 (s, 1 H), 7.07 (d, J = 8.34 Hz, 2 H), 7.45 - 7.50 (m, 2 H).

Step B: Preparation of (S)-4-(4-Bromobenzyl)oxazolidin-2-one.

The title compound was prepared in a similar manner as described in **Example 1.25**,

Step B. Exact mass calculated for $C_{10}H_{10}BrNO_2$: 255.0, Found: LCMS m/z (%) = 256.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.75 - 2.92 (m, 2 H), 4.00 - 4.19 (m, 2 H), 4.43 (t, J = 8.21 Hz, 1 H), 5.94 - 6.07 (m, 1 H), 7.06 (d, J = 8.34 Hz, 2 H), 7.46 (d, J = 8.34 Hz, 2 H).

Step C: Preparation of (S)-4-((4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one (Compound 1).

To a solution of (S)-4-(4-bromobenzyl)oxazolidin-2-one (0.150 g, 0.586 mmol), (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid (0.137 g, 0.586 mmol), and 2.0 M aqueous sodium carbonate (0.586 mL, 1.17 mmol) solution in a mixture of ethanol/benzene (4 mL, 1:3 EtOH:benzene) was added tetrakis (triphenylphosphine)palladium (0) (20.3 mg, 0.018 mmol). The reaction was heated at 100 °C under microwave irradiation for 1 h. The organic phase was separated and the aqueous phase was extracted with EtOAc (25 mL). The combined organics were concentrated under reduced pressure. The residue was purified by preparative HPLC. The combined pure fractions were lyophilized to give the trifluoroacetic acid salt of the title compound (0.152 g, 56% yield). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 364.2, Found: LCMS m/z = 365.2 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.34 (d, J = 6.82 Hz, 0.3 H), 1.50 (d, J = 6.57 Hz, 2.7 H), 1.72 - 1.85 (m, 1 H), 2.01 - 2.22 (m, 2 H), 2.31 - 2.43 (m, 1 H), 2.87 - 2.99 (m, 2 H), 3.05 - 3.22 (m, 2 H), 3.24 - 3.31 (m, 2 H), 3.50 - 3.60 (m, 1 H), 3.60 - 3.71 (m, 1 H), 3.73 - 3.82 (m, 1 H), 4.15 - 4.26 (m, 2 H), 4.44 (s, 1 H), 7.35 (d, J = 8.08 Hz, 2 H), 7.43 (d, J = 8.08 Hz, 2 H), 7.62 (dd, J = 13.26, 8.21 Hz, 4 H).

Example 1.27: Preparation of (R)-4-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride Salt (Compound 3).

Step A: Preparation of (R)-Methyl 2-(tert-Butoxycarbonylamino)-2-(4-hydroxyphenyl)acetate.

To a suspension of (R)-(4-hydroxy)phenylglycine (83.58 g, 500.0 mmol) in methanol (500 mL), cooled in an ice bath, was added dropwise thionyl chloride (36.5 mL, 500 mmol). The reaction mixture was stirred at reflux for 18 h, and then cooled to room temperature. *N,N*-diisopropylethylamine (87 mL, 500 mmol) was then added, followed by a solution of di-*tert*-butyl dicarbonate (109 g, 500 mmol) in methanol (200 mL), added dropwise over 1 h. A mild exotherm resulted, which was controlled by gradual addition, and the reaction temperature was

maintained below reflux at all times. After stirring for 2 h, the reaction appeared to be incomplete by LCMS, with the formation of about 5% of the free acid of the product. The pH of the reaction mixture (initially 10) had dropped to 4. Additional *N,N*-diisopropylethylamine was added until the pH was 9-10. Additional di-*tert*-butyl dicarbonate (3.2 g, 15 mmol) in methanol (10 mL) was added, and stirring was continued for one additional hour. The solvent was then reduced to half the original volume, and the resulting solution was poured into water (1.2 L), forming a white precipitate. After swirling manually and allowing the resulting suspension to stand for 1 h, a white solid was collected by filtration. This material was then dissolved in hot isopropanol (200 mL, 60 °C), and then cooled to 10 °C in an ice bath, seeding the solution with a small amount of pure product. Upon standing for 1 h with occasional agitation, a white solid was collected by filtration, rinsing with cold isopropanol (50 mL). The filtrate was concentrated to about 100 mL, chilled in an ice bath, and then filtered to furnish a second crop. The combined solids were dried to constant weight in a vacuum oven at 60 °C to afford the title compound as a white solid (119.6 g, 85%). Exact mass calculated for C₁₄H₁₉NO₅: 281.3; found: LCMS *m/z* = 282.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.38 (s, 9 H), 3.59 (s, 3 H), 5.06 (d, *J* = 7.84 Hz, 1 H), 6.71 (d, *J* = 8.43 Hz, 2 H), 7.82 (d, *J* = 8.48 Hz, 2 H), 7.61 (d, *J* = 7.82 Hz, 1 H), 9.49 (s, 1 H).

Step B: Preparation of (*R*)-*tert*-Butyl 2-Hydroxy-1-(4-hydroxyphenyl)ethylcarbamate.

A solution of (*R*)-methyl 2-(*tert*-butoxycarbonylamino)-2-(4-hydroxyphenyl)acetate (56.3 g, 200.0 mmol) in anhydrous THF (2.0 L) was cooled to 5 °C in an ice bath. Lithium aluminum hydride (23.6 g, 620 mmol) was added slowly over 1 h, maintaining an internal reaction temperature of less than 25 °C. Stirring was continued for 1 h, and then the reaction was carefully quenched with 1 N NH₄Cl (150 mL) over 45 min, maintaining a temperature less than 30 °C, followed by 0.3 N HCl (400 mL). The resulting suspension was then filtered through Celite™ and rinsed with ethyl acetate (2.0 L). 1 N HCl (250 mL) was added to the filtrate in order to acidify the aqueous layer to pH 1. The aqueous extract was discarded, and the organic extract was rinsed with water (400 mL), brine (200 mL), and dried over MgSO₄. Solvent removal, followed by drying in a vacuum oven at 60 °C gave a white solid (46.2 g, 91%). Exact mass calculated for C₁₃H₁₉NO₄: 253.2; found: LCMS *m/z* = 254.3 [M+H]⁺; ¹H NMR (400 MHz DMSO-*d*₆) δ 1.36 (s, 9 H), 3.42 (t, *J* = 5.88 Hz, 2 H), 4.41 (m, 1 H), 4.69 (t, *J* = 5.70 Hz, 1 H), 6.67 (d, *J* = 8.36 Hz, 2 H), 7.06 (m, 3 H), 9.22 (s, 1 H).

Step C: Preparation of (*R*)-4-(4-Hydroxyphenyl)oxazolidin-2-one.

A solution of (*R*)-*tert*-butyl 2-hydroxy-1-(4-hydroxyphenyl)ethylcarbamate (35 g, 138 mmol) in THF (420 mL) was cooled to 1.2 °C (internal; ice bath). Thionyl chloride (11.09 mL, 152 mmol) was added slowly with cooling and there was a mild exotherm to 3.0 °C. After the addition the mixture was cooled to 0.5 °C, held at that temperature for 10-12 min, gradually

warmed up to room temperature and stirred overnight. The reaction mixture was concentrated to approximately 35 mL by distillation under reduced pressure (385 mL collected). The residual slurry was stirred in room temperature and MTBE (40 mL) was added. The product started to crystallize out. The slurry was stirred for 15 min and filtered. The filter cake was washed twice with MTBE. The solid was dried in a vacuum oven at 50 °C to afford the title compound (15.05 g, 60.8%). Exact mass calculated for $C_9H_9NO_3$, 179.06; found: LCMS m/z = 180.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 3.93 (dd, J_1 = 8 Hz, J_2 = 12 Hz, 1 H), 4.59 (t, J = 8 Hz, 1 H), 4.81 (t, J = 8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 2 H), 7.12 (d, J = 8.4 Hz, 2 H), 8.05 (s, 1 H), 9.48 (s, 1 H).

Step D: Preparation of (*R*)-4-(2-Oxooxazolidin-4-yl)phenyl Trifluoromethanesulfonate.

To a slurry of (*R*)-4-(4-hydroxyphenyl)oxazolidin-2-one (15.05 g, 84 mmol) in acetonitrile (180 mL) was added pyridine (20.38 mL, 252 mmol). The mixture was stirred under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (17.03 mL, 101 mmol) was added slowly maintaining the reaction temperature at 17 to 20 °C (ice bath). The reaction mixture was stirred at 16 to 20 °C for 30 min, followed by 1.5 h at room temperature. The solvent was removed under reduced pressure. Water (150 mL) was added and the mixture was stirred for 30 min. The solid precipitate was collected by filtration, washed twice with water and dried in air under reduced pressure to obtain a solid cake (29.26 g). The above solid was dissolved in warm EtOH (125 mL) at 25 °C, water (80 mL) was added slowly and the mixture was stirred well, maintaining the internal temperature at 17 to 18 °C. The mixture was stirred overnight at 17-19 °C. The solid precipitate was collected by filtration, washed twice with 1:1 EtOH/H₂O and dried overnight in a vacuum oven at 50 °C to give the first crop of the title compound (18.7 g). The mother liquor was diluted with more water and a second crop of solids was isolated by filtration and dried to give the title compound (2.77 g). Exact mass for $C_{10}H_8F_3NO_5S$: 311.01; found: LCMS m/z = 312.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 4.02 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 1 H), 4.68 (t, J = 8 Hz, 1 H), 5.01 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1 H), 7.55 (s, 4 H), 8.28 (s, 1 H).

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

To a solution of 4-bromophenethyl methanesulfonate (120 g, 0.43 mol) in acetonitrile (1.2 L) was added (*R*)-2-methylpyrrolidine tartrate (121 g, 0.516 mol) followed by potassium carbonate (184 g, 1.33 mol). The mixture was heated to 60 °C, water (60 mL) was added and the mixture was stirred under nitrogen overnight. The mixture was cooled to room temperature, filtered and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (400 mL) and the ethyl acetate layer was washed with water (2 x 150 mL). The organic layer was extracted with 2 N HCl (2 x 150 mL). The aqueous acid layer was basified with 50% aq. NaOH to pH 12-14 and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with water (2 x 100 mL), dried over MgSO₄ and concentrated to give the

title compound (104.4g, 90% yield). Exact mass calculated for $C_{13}H_{18}BrN$, 267.06; found: LCMS m/z = 268.2. ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, J = 6 Hz, 3 H), 1.38-1.48 (m, 1 H), 1.66-1.96 (m, 3 H), 2.14-2.34 (m, 3 H), 2.7-2.83 (m, 2 H), 2.97 (m, 1 H), 3.22 (m, 1 H), 7.09 (d, J = 6.4Hz, 2 H), 7.39 (d, J = 6.4Hz, 2 H).

5 **Step F: Preparation of (*R*)-4-(2-(2-Methylpyrrolidin-1-yl)ethyl)phenylboronic Acid Hydrochloride Salt.**

A solution of (*R*)-1-(4-bromophenethyl)-2-methylpyrrolidine (30.0 g, 112 mmol) in anhydrous THF (300 mL) was purged with argon and cooled in a dry ice/acetone bath at -78 °C. n-Butyllithium (91 mL, 145 mmol) was added dropwise to maintain the reaction temperature at
10 -72 °C to -68 °C. Additional anhydrous THF (50 mL) was used to rinse the funnel. After addition of butyllithium was completed, the mixture was stirred for 15 min. Triisopropyl borate (104 mL, 447 mmol) was added at -72 °C to -66 °C. Additional THF (50 mL) was again used to rinse the funnel. After addition of triisopropyl borate was completed, the reaction mixture was gradually brought to room temperature (over 20 min) and stirred at the room temperature for 1
15 h. HCl (2 M, 130 mL) was added dropwise until an off-white suspension formed and the mixture was acidic. The mixture was stirred overnight. The white solid crystals were filtered, washed with THF (150 mL), and dried under reduced pressure to give the HCl salt of the title compound (26.538 g, 88%); Exact mass calculated for $C_{13}H_{20}BNO_2$ 233.1; found, LCMS m/z = 234.3 $[M+H]^+$.

20 **Step G: Preparation of (*R*)-4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.**

(*R*)-4-(2-Oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (8.25 g, 26.5 mmol) was transferred to a 500 mL 3-necked round-bottomed flask fitted with a temperature probe, condenser and nitrogen inlet. (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid
25 hydrochloride (7.86 g, 29.2 mmol) was added, followed by toluene (100 mL). The mixture was stirred and a solution of sodium carbonate (8.99 g, 85 mmol) in water (33.0 mL) was added at 21 °C (there was an exotherm to 33 °C). The mixture was stirred under nitrogen and heated up to 40 °C. $Pd(PPh_3)_4$ (0.919 g, 0.795 mmol) was added (at approximately 40 °C) and the reaction mixture was heated to 90 °C till a mild refluxing was observed. The mixture was stirred for 80
30 min. The mixture was cooled to room temperature and stirred overnight. The solid precipitate was filtered, washed with water several times and dried in a vacuum oven at 50 °C for 3 h to afford the title compound (9.11 g, 98%) as a free base. Exact mass calculated for $C_{22}H_{26}N_2O_2$, 350.2; found: LCMS m/z = 351.2 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 1.0 (d, J = 6 Hz, 3 H), 1.28 (m, 1 H), 1.63 (m, 2 H), 1.85 (m, 1 H), 2.11 (q, J_1 = 17.6 Hz, J_2 = 8.8 Hz, 1 H), 2.24 (m, 2 H), 2.67-2.83 (m, 2 H), 2.97 (m, 1 H), 3.13 (m, 1 H), 4.04 (dd, J_1 = 8.4 Hz, J_2 = 8.4 Hz, 1 H),
35 4.69 (t, J = 8.4 Hz, 1 H), 4.98 (t, J = 8 Hz, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.41 (d, J = 8 Hz, 2 H), 7.57 (d, J = 8 Hz, 2 H), 7.68 (d, J = 8 Hz, 2 H), 8.22 (s, 1 H).

Step H: Preparation of (*R*)-4-(4'-(2-(*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride Salt.

The freebase of (*R*)-4-(4'-(2-(*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (9.11 g, 26.0 mmol) was transferred to a 250 mL 3-necked round-bottomed flask fitted with a temperature probe, an addition funnel and nitrogen inlet. Ethanol (91 mL) was added, the slurry was warmed to 40 °C and a clear solution was obtained. It was further heated to 45 °C and hydrochloric acid (1.25 M in EtOH; 42.4 mL, 53.0 mmol) was added dropwise. The HCl salt started to crystallize out when approximately 85% of the HCl solution has been added. After addition was completed, the slurry was stirred for 5 min at 47-48 °C, gradually cooled to room temperature and stirred overnight. The volume of the mixture was reduced to approximately 58 mL by distilling off EtOH under reduced pressure and the residue became a paste. EtOH (10 mL) was added to make it a slurry, which was filtered. The solid cake was washed with EtOH (10 mL), MTBE, and dried in a vacuum oven at 50 °C for 3 h. The above solid (8.47 g) was recrystallized from EtOH (160 mL) to give the title compound (7.68 g, 80% yield). Exact mass calculated for C₂₂H₂₆N₂O₂: 350.2 (free base); found: LCMS *m/z* = 351.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.42 (d, *J* = 6.4 Hz, 3 H), 1.64 (m, 1 H), 1.95 (m, 2 H), 2.18 (m, 1 H), 3.13 (m, 4 H), 3.35-3.52 (m, 2 H), 3.62 (m, 1 H), 4.04 (dd, *J*₁ = 8.4 Hz, *J*₂ = 8.4 Hz, 1 H), 4.69 (t, *J* = 8.4 Hz, 1 H), 4.98 (t, *J* = 8 Hz, 1 H), 7.41 (dd, *J*₁ = 6.8 Hz, *J*₂ = 6.8 Hz, 4 H), 7.65 (d, *J* = 8 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 8.25 (s, 1 H), 10.67 (bs, 1 H).

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Example 1.28: Preparation of (*R*)-3-(2-Methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride (Compound 6).

Step A: Preparation of (*R*)-3-(2-Methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

To a slurry of sodium hydride (0.279 g, 11.63 mmol) (465 mg, 60% dispersion in mineral oil) in DMF (15 mL) was added (*R*)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one hydrochloride (1.5 g, 3.88 mmol) under N₂, with efficient stirring followed by 1-bromo-2-methoxyethane (0.437 mL, 4.65 mmol). The reaction mixture was stirred for 5 h at room temperature. LCMS analysis showed 51.8% product (*m/z* 409.4; [M+H]⁺) formation and 48.2% of starting material remained. 1-Bromo-2-methoxypropane (128 μL) was added and the reaction was stirred overnight at room temperature. LCMS analysis showed 92.6% product formed. The mixture was diluted with water (35 mL) and extracted with ethyl acetate (2 x 30 mL). The ethyl acetate layer was extracted with 2 N aqueous HCl (2 x 25 mL). The aqueous phases were combined and washed with ethyl acetate (1 x 25 mL) followed by heptane (1 x 25 mL). The aqueous phase was cooled (ice water bath) and basified to pH 12-14 by slow addition of 50% aqueous NaOH solution and extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with water

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(2 x 25 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure to obtain a brown oil.

Step B: Preparation of (R)-3-(2-methoxyethyl)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride Salt.

5 The product of **Example 1.28, Step A** was dissolved in ethanol (1.5 mL) and the solution was stirred well. Hydrochloric acid (6.20 mL, 7.75 mmol) (1.25 M in ethanol) was added and the mixture was stirred overnight. MTBE was added and the mixture was left at ~4 °C for two days. Solvents were removed under reduced pressure and the residue was dried overnight under reduced pressure to obtain the HCl salt as a foamy solid (1.02 g, 59%). Exact
10 mass calculated for C₂₅H₃₂N₂O₃ (free base), 408.53; found, 409.5 [M+H]⁺; ¹H NMR (Bruker, 400 MHz, DMSO-*d*₆) δ 1.43 (d, 3 H, *J* = 6.4 Hz), 1.95 (m, 2 H), 1.64 (m, 1 H), 2.17 (m, 1 H), 2.80 (m, 1 H), 3.12 (m, 4 H), 3.19 (s, 3 H), 3.36 (m, 3 H), 3.50 (m, 2 H), 3.62 (m, 1 H), 4.05 (dd, *J*₁ = 6.8 Hz, *J*₂ = 6.8 Hz, 1 H), 4.65 (t, *J* = 8.8 Hz, 1 H), 5.02 (t, *J* = 8 Hz, 1 H), 7.41 (dd, *J*₁ = 8 Hz, *J*₂ = 8 Hz, 4 H), 7.66 (d, *J* = 8 Hz, 2 H), 7.72 (d, *J* = 8 Hz, 2 H), 10.85 (bs, 1 H).

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Example 1.29: Preparation of (R)-3-Isopropyl-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride (Compound 7).

Step A: Preparation of (R)-3-Isopropyl-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

20 To a slurry of sodium hydride (0.279 g, 11.63 mmol) (465 mg, 60% dispersion in mineral oil) in DMF (15 mL) was added (R)-4-(4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one hydrochloride (1.5 g, 3.88 mmol) under N₂ and the mixture was stirred well. 2-Iodopropane (0.465 mL, 4.65 mmol) was added and the mixture was stirred at room temperature for 4 h. LCMS analysis showed ~18% of product. The reaction
25 mixture was heated to 55 °C and stirred overnight. LCMS analysis showed ~60.5% product and ~39.5% starting material remained. Sodium hydride (0.186 g, 60% dispersion) was added followed by 2-iodopropane (0.155 mL) and the reaction was stirred at 55 °C for 2 h. More NaH (0.186 g, 60% dispersion) and 2-iodopropane (0.155 mL) was added after 2 h. Another batch of NaH (0.186 g, 60% dispersion) and 2-iodopropane (0.155 mL) was added and the mixture was
30 allowed to stir overnight. LCMS analysis showed 79.4% product and ~20% starting material. The final portions of NaH (0.186 g, 60% dispersion) and 2-iodopropane (0.155 mL) were added and the reaction mixture was stirred overnight. LCMS analysis showed ~95% product. The reaction mixture was cooled to room temperature and diluted with water (35 mL). The aqueous mixture was extracted with ethyl acetate (2 x 30 mL). The ethyl acetate layer was extracted with
35 2 N aqueous HCl (2 x 25 mL). The HCl phase was washed with ethyl acetate (1 x 25 mL) followed by heptane (1 x 25 mL). The aqueous phase was cooled (ice bath) and slowly basified with 50% aqueous NaOH and extracted with ethyl acetate (2 x 25 mL). The ethyl acetate layer

was washed with water (2 x 25 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure to obtain the product (free base) as a waxy solid, 1.02 g. Exact mass for C₂₅H₃₂N₂O₂, 392.53; found 393.3 [M+H]⁺; ¹H NMR (Bruker, 400 MHz, DMSO-*d*₆) δ 0.89 (d, *J* = 8 Hz, 3 H), 1.0 (d, *J* = 6.4 Hz, 3 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 1.28 (m, 1 H), 1.62 (m, 2 H), 1.84 (m, 1 H), 2.11 (q, *J* = 8.8 Hz, 1 H), 2.24 (m, 2 H), 2.83-2.69 (m, 2 H), 2.97 (m, 1 H), 3.13 (m, 1 H), 3.62 (m, 1 H), 4.02 (dd, *J*₁ = 6.4 Hz, *J*₂ = 6.4 Hz, 1 H), 4.59 (t, *J*₁ = 8.8 Hz, 1 H), 4.99 (dd, *J*₁ = 6.4 Hz, *J*₂ = 6.4 Hz, 1 H), 7.32 (d, *J* = 8 Hz), 7.47 (d, 2 H, *J* = 8.4 Hz), 7.59 (d, 2 H, *J* = 8 Hz), 7.69 (d, 2 H, *J* = 8 Hz).

Step B: Preparation of (*R*)-3-Isopropyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one Hydrochloride.

The free base of **Example 1.29, Step A** was dissolved in ethanol (1.5 mL) and HCl (1.25 M in ethanol; 4.15 mL; 2 eq.) was added slowly with stirring. MTBE was added until the solution was cloudy. The mixture was stirred overnight at room temperature. The solvents were removed under reduced pressure and the residue was dried under reduced pressure, to obtain the HCl salt as a foamy solid (1.09 g 65.5%, 95.5% purity by LCMS). ¹H NMR (Bruker, 400 MHz, DMSO-*d*₆) δ 0.89 (d, *J* = 6.8 Hz, 3 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 1.42 (d, *J* = 6.4 Hz, 3 H), 1.62 (m, 1 H), 1.95 (m, 2 H), 2.19 (m, 1 H), 3.19-3.05 (m, 5 H), 3.50 (m, 1 H), 3.63 (m, 2 H), 4.01 (dd, *J*₁ = 6.4 Hz, *J*₂ = 6.4 Hz, 1 H), 4.59 (t, *J* = 8.8 Hz, 1 H), 5.0 (dd, *J*₁ = 6.4 Hz, *J*₂ = 6.4 Hz, 1 H), 7.41 (d, *J* = 8 Hz, 2 H), 7.48 (d, *J* = 8 Hz, 2 H), 7.67 (d, *J* = 8 Hz, 2 H), 7.71 (d, *J* = 8 Hz, 2 H), 10.50 (bs, 1 H).

Example 1.30: Preparation of (*R*)-4-(2-Methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 19).

Step A: Preparation of 2-Benzamido-2-(4-hydroxy-3-methylphenyl)acetic Acid.

To a suspension of α-hydroxyhippuric acid (4.0 g, 21 mmol) in concentrated sulfuric acid (2 mL) and glacial acetic acid (18 mL) at 0 °C was added *o*-cresol (5.5 g, 51 mmol). The cold bath was allowed to expire while stirring continued overnight. The reaction was quenched by pouring into a beaker containing ice and NaHCO₃ (40 g). The reaction was extracted with EtOAc (thrice), and the aqueous phase was acidified with concentrated HCl to pH 2. A precipitate formed was collected, washed with water, and then dried under reduced pressure to give the title compound as a pale peach-colored powder (2.9 g, 50%). Exact mass calculated for C₁₆H₁₅NO₄: 285.1, found: LCMS *m/z* = 286.3 [M+H]⁺.

Step B: Preparation of 2-Amino-2-(4-hydroxy-3-methylphenyl)acetic Acid.

A solution of 2-benzamido-2-(4-hydroxy-3-methylphenyl)acetic acid (1.0 g, 3.5 mmol) in 10% aqueous HCl (10 mL) was heated at reflux for 1 week. After cooling to room temperature, the mixture was washed once with MTBE and then the aqueous phase was concentrated to give a brown solid residue. The residue was diluted with acetonitrile and water,

frozen, and lyophilized to give the hydrochloride salt of the title compound (0.67 g, 88%). Exact mass calculated for $C_9H_{11}NO_3$: 181.1, found: LCMS m/z = 182.2 $[M+H]^+$.

Step C: Preparation of Methyl 2-(*tert*-Butoxycarbonylamino)-2-(4-hydroxy-3-methylphenyl)acetate.

5 A stirring suspension of 2-amino-2-(4-hydroxy-3-methylphenyl)acetic acid hydrochloride (0.70 g, 3.2 mmol) in MeOH (4 mL) was cooled to 0 °C. Thionyl chloride (0.25 mL, 3.4 mmol) was added dropwise, and then the ice bath was allowed to expire while stirring the red solution overnight. *N*-ethyl-*N*-isopropylpropan-2-amine (2.8 mL, 16 mmol) was added dropwise, then the mixture was placed into a 0 °C ice bath. Di-*tert*-butyldicarbonate (0.77 g, 3.5 mmol) was added in portions. The mixture was stirred for 2 h at 0 °C, before removing the ice bath and stirring for another 2 h at room temperature. The mixture was concentrated to give a solid residue. The solid material was loaded onto a fritted funnel and washed with water while under reduced pressure. The solid which remained was partitioned between EtOAc and water at pH 8. The aqueous phase was extracted twice more with EtOAc. The combined organics were washed with brine, dried over sodium sulfate, and concentrated to give the title compound as a pale pink solid (0.9 g, 95%). Exact mass calculated for $C_{15}H_{21}NO_5$: 295.1, found: LCMS m/z = 296.4 $[M+H]^+$.

Step D: Preparation of *tert*-Butyl 2-Hydroxy-1-(4-hydroxy-3-methylphenyl)ethylcarbamate.

20 To a stirring 0 °C solution of methyl 2-(*tert*-butoxycarbonylamino)-2-(4-hydroxy-3-methylphenyl)acetate (0.87 g, 3.0 mmol) in THF (20 mL) was added lithium aluminum hydride (3.0 mL of 1 M THF solution, 3.0 mmol). The cold bath was removed and the mixture was stirred overnight. The reaction was quenched by pouring onto ice. The slurry was diluted with EtOAc and the solution was adjusted to pH 2 with 10% aqueous HCl. The organic phase was separated and washed with brine, then dried over sodium sulfate. The volatiles were evaporated to give the title compound (0.60 g, 76%). Exact mass calculated for $C_{14}H_{21}NO_4$: 267.2, found: LCMS m/z = 268.4 $[M+H]^+$.

Step E: Preparation of 4-(4-Hydroxy-3-methylphenyl)oxazolidin-2-one.

30 To a stirring 0 °C solution of *tert*-butyl 2-hydroxy-1-(4-hydroxy-3-methylphenyl)ethylcarbamate (0.60 g, 2.2 mmol) in THF (7 mL) was added thionyl chloride (0.18 mL, 2.5 mmol) dropwise. The ice bath was removed and the mixture was stirred overnight at room temperature. The solvents were evaporated. The residue was washed with MTBE, decanted and dried to give the title compound (0.37 g, 84%). Exact mass calculated for $C_{10}H_{11}NO_3$: 193.1, found: LCMS m/z = 194.2 $[M+H]^+$.

35 **Step F: Preparation of 2-Methyl-4-(2-oxooxazolidin-4-yl)phenyl Trifluoromethanesulfonate.**

To a stirred slurry of 4-(4-hydroxy-3-methylphenyl)oxazolidin-2-one (0.40 g, 2.1 mmol) in acetonitrile (6 mL) was added pyridine (0.67 mL, 8.3 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.53 mL, 3.1 mmol) was added dropwise. The ice bath was removed and the clear red solution was stirred at room temperature. LCMS after 2 h indicated the reaction was incomplete, so another equivalent of Tf₂O (0.35 mL, 2.1 mmol) was added. The reaction was stirred for another 30 min. The solvent was evaporated and the residue was diluted with aqueous HCl. The slurry was extracted with EtOAc (thrice), the combined organics were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel flash column chromatography to give the title compound (with minor impurities, 48 mg). Exact mass calculated for C₁₁H₁₀F₃NO₅S: 325.0, found: LCMS *m/z* = 326.2 [M+H]⁺.

Step G: Preparation of 4-(2-Methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of 2-methyl-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (48 mg, 0.15 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (40 mg, 0.15 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mg, 4 μmol), sodium carbonate (0.22 mL of 2.0 M aqueous solution, 0.44 mmol), benzene (1 mL), and ethanol (0.3 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 90 min. The mixture was filtered through a pad of Celite® with EtOAc, and the filtrate was concentrated. The residue was purified by preparative HPLC. The appropriate fractions were combined and lyophilized to give the title compound as a TFA salt (14 mg, 26%). Exact mass calculated for C₂₃H₂₈N₂O₂: 364.2, found: LCMS *m/z* = 365.5 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.38 (d, *J* = 6.5 Hz, 3H), 1.61 (dddd, *J* = 12.9, 9.0, 9.0, 9.0 Hz, 1H), 2.10-1.86 (m, 2H), 2.28-2.17 (m, 1H), 3.10-2.91 (m, 2H), 3.29-3.16 (m, 2H), 3.60-3.40 (m, 2H), 3.66 (dddd, *J* = 11.5, 8.0, 5.5, 5.5 Hz, 1H), 3.78 (s, 3H), 4.07 (dd, *J* = 8.6, 6.6 Hz, 1H), 4.70 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.98 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 8.20 (s, 1H), 9.38 (bs, 1H).

Example 1.31: Preparation of 4-(3-Methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 24).

Step A: Preparation of 2-Benzamido-2-(4-hydroxy-2-methylphenyl)acetic Acid.

To a suspension of 2-benzamido-2-hydroxyacetic acid (4.0 g, 21 mmol) in concentrated sulfuric acid (2 mL) and glacial acetic acid (18 mL) at 0 °C was added *m*-cresol (5.4 mL, 51 mmol). The cold bath was allowed to expire while stirring continued overnight. The reaction was quenched by pouring into a beaker containing ice and NaHCO₃ (40 g). The reaction was extracted with EtOAc (thrice). The aqueous phase was acidified with concentrated HCl to pH 1 and extracted with EtOAc (thrice). The combined organic phase from the acidified extraction

was washed with brine, dried over sodium sulfate, and concentrated. Half of the residue was purified by silica gel flash column chromatography followed by preparative HPLC to give the title compound as a white solid (0.63 g, 11%). Exact mass calculated for $C_{16}H_{15}NO_4$: 285.1, found: LCMS m/z = 286.1 $[M+H]^+$.

5 **Step B: Preparation of 2-Amino-2-(4-hydroxy-2-methylphenyl)acetic Acid.**

A solution of 2-benzamido-2-(4-hydroxy-2-methylphenyl)acetic acid (0.63 g, 2.2 mmol) in 10% aqueous HCl (10 mL) was heated at reflux for 6 days. After cooling to room temperature, the mixture was washed with MTBE (4 times) and then the aqueous phase was evaporated to give the hydrochloride salt of the title compound as a tan powder which was used
10 in the next reaction without further purification. Exact mass calculated for $C_9H_{11}NO_3$: 181.1, found: LCMS m/z = 182.2 $[M+H]^+$.

Step C: Preparation of Methyl 2-(tert-Butoxycarbonylamino)-2-(4-hydroxy-2-methylphenyl)acetate.

A stirring suspension of 2-amino-2-(4-hydroxy-2-methylphenyl)acetic acid
15 hydrochloride (0.48 g, 2.2 mmol) in MeOH (2.2 mL) was cooled to 0 °C. Thionyl chloride (0.17 mL, 2.3 mmol) was added dropwise, then the ice bath was allowed to expire while stirring overnight. The mixture was placed into a 0 °C ice bath and *N*-ethyl-*N*-isopropylpropan-2-amine (1.3 mL, 7.3 mmol) was added dropwise, followed by the addition of di-*tert*-butyldicarbonate (0.48 g, 2.2 mmol) in portions. The mixture was stirred for 20 h before another equivalent of di-
20 *tert*-butyldicarbonate (0.48 g, 2.2 mmol) was added. After additional 16 h, the reaction mixture was concentrated and the residue was dissolved in EtOH (5 mL). Sodium bicarbonate (0.61 g, 7.3 mmol) was added and the mixture was stirred at room temperature over the weekend. After 60 h the reaction mixture was concentrated and the residue was diluted with DCM and treated with dilute HCl to pH 2. The aqueous phase was extracted twice with DCM. The combined
25 organic phase was washed with brine, dried over sodium sulfate, and concentrated to give the title compound as an off-white solid (0.56 g, 86%). Exact mass calculated for $C_{15}H_{21}NO_5$: 295.1, found: LCMS m/z = 296.2 $[M+H]^+$.

Step D: Preparation of *tert*-Butyl 2-Hydroxy-1-(4-hydroxy-2-methylphenyl)ethylcarbamate.

30 To a stirring 0 °C solution of methyl 2-(*tert*-butoxycarbonylamino)-2-(4-hydroxy-2-methylphenyl)acetate (0.55 g, 1.9 mmol) in THF (12 mL) was added lithium aluminum hydride (1.9 mL of 1 M THF solution, 1.9 mmol). The cold bath was removed and the mixture was stirred overnight. The reaction was quenched by pouring onto ice. The slurry was diluted with EtOAc and the solution was adjusted to pH 2 with 10% aqueous HCl. The organic phase was
35 separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated to give the title

compound (0.47 g, 94%). Exact mass calculated for $C_{14}H_{21}NO_4$: 267.2, found: LCMS m/z = 268.4 $[M+H]^+$.

Step E: Preparation of 4-(4-Hydroxy-2-methylphenyl)oxazolidin-2-one.

To a stirring 0 °C solution of *tert*-butyl 2-hydroxy-1-(4-hydroxy-2-methylphenyl)ethylcarbamate (0.46 g, 1.7 mmol) in THF (6 mL) was added thionyl chloride (0.14 mL, 1.9 mmol). The ice bath was removed and the mixture was stirred overnight at room temperature. The solvents were evaporated and the residue was washed with MTBE. The MTBE solution was collected and concentrated to give the title compound (with minor impurities, 0.37 g). Exact mass calculated for $C_{10}H_{11}NO_3$: 193.1, found: LCMS m/z = 194.2 $[M+H]^+$.

Step F: Preparation of 3-Methyl-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate.

To a stirred slurry of 4-(4-hydroxy-2-methylphenyl)oxazolidin-2-one (0.10 g, 0.52 mmol) in acetonitrile (2 mL) was added pyridine (0.17 mL, 2.1 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.13 mL, 0.78 mmol) was added dropwise. After 30 min the solvent was evaporated and the residue was washed with (10:1) MTBE/EtOAc. The decanted liquid was collected and evaporated to give the title compound as an oily solid (with minor impurities, 0.18 g). Exact mass calculated for $C_{11}H_{10}F_3NO_5S$: 325.0, found: LCMS m/z = 326.3 $[M+H]^+$.

Step G: Preparation of 4-(3-Methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of 3-methyl-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (0.17 g, 0.52 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.14 g, 0.52 mmol), tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.017 mmol), sodium carbonate (0.83 mL of 2.0 M aqueous solution, 1.7 mmol), benzene (2.2 mL), and ethanol (0.62 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 30 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt (0.055 g, 29% yield). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 364.2, found: LCMS m/z = 365.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.38 (d, J = 6.5 Hz, 3H), 1.68 (dddd, J = 12.9, 9.0, 9.0, 9.0 Hz, 1H), 2.06-1.87 (m, 2H), 2.27-2.17 (m, 1H), 2.33 (s, 3H), 3.11-2.93 (m, 2H), 3.28-3.16 (m, 2H), 3.60-3.40 (m, 2H), 3.65 (dddd, J = 11.4, 8.0, 5.5, 5.5 Hz, 1H), 3.97 (dd, J = 8.4, 6.2 Hz, 1H), 4.77 (dd, J = 8.6, 8.6 Hz, 1H), 5.18 (dd, J = 8.5, 6.5 Hz, 1H), 7.43-7.38 (m, 3H), 7.57-7.49 (m, 2H), 7.65 (d, J = 8.3 Hz, 2H), 8.14 (s, 1H), 9.36 (bs, 1H).

Example 1.32: Preparation of (*S*)-4-(2'-Methyl-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 32).

Step A: Preparation of Ethyl 2-(4-Hydroxy-3-methylphenyl)acetate.

To a stirring solution of 2-(4-hydroxy-3-methylphenyl)acetic acid (5.0 g, 30 mmol) in absolute ethanol (150 mL) was added concentrated sulfuric acid (1.6 mL, 30 mmol). The mixture was heated to 75 °C for 3 h, and then the heat was removed and the mixture was stirred at room temperature overnight. After 18 h, the volatiles were evaporated and the residue was diluted with water and extracted into EtOAc (thrice). The combined organic extract was washed with brine, dried over sodium sulfate, and the solvents were evaporated to give the title compound as an oil (5.8 g, 100%). Exact mass calculated for C₁₁H₁₄O₃: 194.1, found: LCMS $m/z = 195.2$ [M+H]⁺.

Step B: Preparation of 4-(2-Hydroxyethyl)-2-methylphenol.

To a stirring solution of ethyl 2-(4-hydroxy-3-methylphenyl)acetate (5.8 g, 30 mmol) in THF (149 mL) at 0 °C was added lithium aluminum hydride (30 mL of 1.0M THF solution, 30 mmol). The cold bath was removed and the mixture was stirred at ambient temperature. After 2.5 h, the reaction was quenched with ice water and the slurry was treated with concentrated sulfuric acid to pH 3. The mixture was extracted 4 times with EtOAc. The combined organic extract was washed with a concentrated aqueous solution of Rochelle's salt and then with brine. The extract was dried over sodium sulfate and concentrated to give the title compound as a faintly pink solid (4.6 g). Exact mass calculated for C₉H₁₂O₂: 152.1, found: LCMS $m/z = 135.2$ [M - H₂O + H]⁺.

Step C: Preparation of 2-Methyl-4-(2-(pyrrolidin-1-yl)ethyl)phenyl trifluoromethanesulfonate.

To a stirred slurry of 4-(2-hydroxyethyl)-2-methylphenol (2.0 g, 13 mmol) in acetonitrile (44 mL) was added pyrrolidine (5.5 mL, 66 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (6.7 mL, 39 mmol) was added dropwise. After 2.5 h the cold bath was removed and the mixture was stirred at ambient temperature. After 1 h, more triflic anhydride (3.0 mL, 18 mmol) was added. After another 30 min, the reaction mixture was again charged with triflic anhydride (3.0 mL, 39 mmol). After an additional 1 h, the solvent was evaporated to give a dark residue which was extracted with EtOAc (thrice). The combined organic extract was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative HPLC to give the title compound as a TFA salt. The salt was dissolved in water and EtOAc, then the mixture was treated with a 50% aqueous sodium hydroxide solution to pH 9. The layers were separated, and the aqueous phase was extracted twice more with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated to give the title compound as an oil (0.52 g, 12%). Exact mass calculated for C₁₄H₁₈F₃NO₃S: 337.1, found: LCMS $m/z = 338.5$ [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.71-1.63 (m, 4H), 2.30 (s, 3H), 2.51-2.45 (m, 4H), 2.66-2.60 (m, 2H), 2.78-2.72 (m, 2H), 7.28-7.21 (m, 2H), 7.34-7.31 (m, 1H).

Step D: Preparation of (S)-4-(2'-Methyl-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of 2-methyl-4-(2-(pyrrolidin-1-yl)ethyl)phenyl trifluoromethanesulfonate (0.23 g, 0.69 mmol), (S)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-2-one (0.20 g, 0.69 mmol), tetrakis(triphenylphosphine)palladium(0) (0.024 g, 0.021 mmol), sodium carbonate (0.70 mL of 2.0 M aqueous solution, 1.4 mmol), benzene (1.8 mL), and ethanol (0.5 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 3 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC. The appropriate fractions were combined and neutralized with 50% aqueous sodium hydroxide. The slurry was extracted with EtOAc (thrice). The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to provide the title compound as an oil (0.15 g, 62%). Exact mass calculated for C₂₂H₂₆N₂O₂: 350.2, found: LCMS *m/z* = 351.4 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.88-1.80 (m, 4H), 2.23 (s, 3H), 2.72-2.65 (m, 4H), 2.91-2.76 (m, 4H), 4.25 (dd, *J* = 8.6, 6.9 Hz, 1H), 4.76 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.99 (dd, *J* = 8.6, 7.1 Hz, 1H), 6.28 (bs, 1H), 7.13-7.06 (m, 3H), 7.40-7.32 (m, 4H).

Example 1.33: Preparation of (R)-4-(2,6-Dichloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 18).

Step A: Preparation of (R)-4-(3,5-Dichloro-4-hydroxyphenyl)oxazolidin-2-one.

To a solution of (R)-4-(4-hydroxyphenyl)oxazolidin-2-one (0.100 g, 0.558 mmol) in DCM (10 mL) in an appropriate microwave vial was added *N*-chlorosuccinimide (0.224 g, 1.67 mmol). The mixture was irradiated under microwave conditions at 100 °C for 3 h. The reaction was quenched with water and extracted with DCM (thrice). The combined organics were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative HPLC to give the title compound as a white solid (35 mg, 25%). Exact mass calculated for C₉H₇Cl₂NO₃: 247.0, found: LCMS *m/z* = 247.9, [M+H]⁺.

Step B: Preparation of (R)-2,6-Dichloro-4-(2-oxooxazolidin-4-yl)phenyl Trifluoromethanesulfonate.

To a stirred slurry of (R)-4-(3,5-dichloro-4-hydroxyphenyl)oxazolidin-2-one (0.40 g, 1.6 mmol) in acetonitrile (5 mL) was added pyridine (0.52 mL, 6.5 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.41 mL, 2.4 mmol) was added dropwise. The ice bath was removed and the clear red solution was stirred at room temperature. After 2 h the solvent was evaporated to give a white residue which was washed with MTBE/EtOAc (10:1). The decanted solvents were treated with diluted aqueous HCl, and then the mixture was extracted with EtOAc (thrice). The combined organics were washed with brine, dried over

sodium sulfate and concentrated to provide the title compound (with minor impurities, 0.72 g). Exact mass calculated for $C_{10}H_6Cl_2F_3NO_5S$: 378.9, found: LCMS m/z = 380.1 $[M+H]^+$.

Step C: Preparation of (*R*)-4-(2,6-Dichloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

5 A mixture of (*R*)-2,6-dichloro-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (0.6 g, 1.6 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.4 g, 1.6 mmol), tetrakis(triphenylphosphine)palladium(0) (0.06 g, 0.04 mmol), sodium carbonate (2.4 mL of 2.0 M aqueous solution, 4.8 mmol), benzene (3.8 mL), and ethanol (1.1 mL) were combined in a
10 suitable microwave vial and irradiated under microwave conditions at 100 °C for 90 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC. The appropriate fractions were combined and concentrated. The residue was treated with 50% aqueous NaOH to pH 14, and then extracted with DCM (thrice). The combined organics were washed with brine, dried over sodium sulfate,
15 and concentrated to give the title compound, which was then treated with 1 M HCl in Et₂O to give a hydrochloride salt (0.04 g, 6%). Exact mass calculated for $C_{22}H_{24}Cl_2N_2O_2$: 418.1, found: LCMS m/z = 419.3 $[M+H]^+$; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.13 (d, *J* = 6.0 Hz, 3H), 1.51-1.39 (m, 1H), 2.01-1.66 (m, 3H), 2.22 (ddd, *J* = 8.8, 8.8, 8.8 Hz, 1H), 2.41-2.31 (m, 2H), 2.96-2.80 (m, 2H), 3.09 (ddd, *J* = 11.4, 11.4, 5.8 Hz, 1H), 3.27 (ddd, *J* = 8.8, 8.8, 2.4 Hz, 1H), 4.22
20 (dd, *J* = 8.4, 7.0 Hz, 1H), 4.77 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.98-4.91 (m, 1H), 6.63 (bs, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 2H).

Example 1.34: Preparation of (*R*)-4-(2-Chloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 20)

25 **Step A: Preparation of (*R*)-4-(3-Chloro-4-hydroxyphenyl)oxazolidin-2-one.**

To a solution of (*R*)-4-(4-hydroxyphenyl)oxazolidin-2-one (0.50 g, 2.8 mmol) in DCM (20 mL) was added *N*-chlorosuccinimide (0.37 g, 2.8 mmol). The mixture was stirred at room temperature for 18 h. The reaction was quenched with water and extracted with DCM (thrice). The combined organics were washed with brine and dried over sodium sulfate. The solvents were
30 evaporated and the solid residue was washed with MeOH. The decanted MeOH was concentrated to give a crude title compound (0.26 g). Exact mass calculated for $C_9H_8ClNO_3$: 213.0, found: LCMS m/z = 214.1, $[M+H]^+$.

Step B: Preparation of (*R*)-2-Chloro-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate.

35 To a stirred slurry of impure (*R*)-4-(3-chloro-4-hydroxyphenyl)oxazolidin-2-one (0.26 g, 1.2 mmol) in acetonitrile (4 mL) was added pyridine (0.39 mL, 4.9 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.31 mL, 1.8 mmol) was added

dropwise. The clear red solution was stirred at 0 °C. After 1 h the solvent was evaporated to give a white residue which was diluted with EtOAc and dilute aqueous HCl. The mixture was extracted with EtOAc (thrice). The combined organics were washed with brine, dried over sodium sulfate, and concentrated to provide the title compound with impurities (0.30 g). Exact mass calculated for C₁₀H₇ClF₃NO₅S: 345.0, found: LCMS *m/z* = 345.9 [M+H]⁺.

Step C: Preparation of (R)-4-(2-Chloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture (R)-2-chloro-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (0.3 g, 0.9 mmol) from above, (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.2 g, 0.9 mmol), tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.03 mmol), sodium carbonate (1.3 mL of 2.0 M aqueous solution, 2.6 mmol), benzene (2.0 mL), and ethanol (0.57 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 90 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to provide the title compound as a TFA salt (0.09 g, 28%). Exact mass calculated for C₂₂H₂₅ClN₂O₂: 384.2, found: LCMS *m/z* = 385.3 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.48 (d, *J* = 6.6 Hz, 3H), 1.76 (dddd, *J* = 13.2, 9.1, 9.1, 9.1, Hz, 1H), 2.25-2.01 (m, 2H), 2.41-2.30 (m, 1H), 3.21-3.03 (m, 2H), 3.33-3.23 (m, 2H), 3.53 (dddd, *J* = 15.8, 6.8, 6.8, 6.8 Hz, 1H), 3.66 (ddd, *J* = 12.5, 11.0, 5.8 Hz, 1H), 3.77 (ddd, *J* = 13.1, 8.0, 5.3 Hz, 1H), 4.18 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.80 (dd, *J* = 8.8, 8.8 Hz, 1H), 5.05 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.43-7.36 (m, 6H), 7.52-7.50 (m, 1H).

Example 1.35: Preparation of (S)-4-(2'-Chloro-4'-(2-((R)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 22).

Step A: Preparation of Methyl 2-(3-Chloro-4-hydroxyphenyl)acetate.

To a solution of 2-(3-chloro-4-hydroxyphenyl)acetic acid (10.0 g, 53.6 mmol) in MeOH (250 mL) was added concentrated sulfuric acid. The resulting mixture was heated at reflux for 16 h. The MeOH was evaporated to give an oil which was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (thrice). The combined organics were washed with brine, dried over sodium sulfate, and then evaporated to give the title compound (10.5 g, 98%) as an amber oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.57 (s, 2H), 3.64 (s, 3H), 6.09 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.23 (d, *J* = 2.1 Hz, 1H), 10.03 (s, 1H).

Step B: Preparation of Methyl 2-(3-Chloro-4-(4-methoxybenzyloxy)phenyl)acetate.

To a stirring solution of methyl 2-(3-chloro-4-hydroxyphenyl)acetate (2.19 g, 10.9 mmol) in acetone (27 mL) was added PMBCl (*p*-methoxybenzyl chloride) (1.88 g, 12.0 mmol), tetrabutylammonium iodide (TBAI) (4.03 g, 10.9 mmol), and potassium carbonate (2.26 g, 16.4 mmol). The mixture was heated at 55 °C for 60 h. The reaction mixture was diluted with a

solution of 10% acetone in hexanes and a small amount of DCM, heated briefly, and then cooled to room temperature and passed through a column of Celite®/silica gel. The column was washed with 10-20% acetone/hexanes (700 mL), and the colorless eluent was concentrated to give the title compound as an off-white solid (3.4 g, 97%) with minor impurities. TLC (20% acetone/hexanes) $R_f = 0.27$.

Step C: Preparation of 2-(3-Chloro-4-(4-methoxybenzyloxy)phenyl)ethanol.

To a stirring 0 °C solution of methyl 2-(3-chloro-4-(4-methoxybenzyloxy)phenyl)acetate (0.50 g, 1.6 mmol) in THF (15 mL) was added lithium aluminum hydride (1.6 mL of 1 M THF solution, 1.6 mmol). The cold bath was allowed to expire while the reaction stirred overnight. The reaction was quenched by pouring onto ice, then the slurry was extracted with EtOAc (thrice). The combined organics were washed with brine, dried over sodium sulfate, and concentrated to give the title compound (with minor impurities, 0.49 g).

Step D: Preparation of 3-Chloro-4-(4-methoxybenzyloxy)phenethyl

Methanesulfonate.

To a stirring 0 °C solution of methyl 2-(3-chloro-4-(4-methoxybenzyloxy)phenyl)ethanol (0.49 g, 1.7 mmol) in DCM (4 mL) was added triethylamine (0.70 mL, 5.0 mmol) and MsCl (0.16 mL, 1.2 mmol). After stirring 1 h, the reaction was quenched by the addition of 10% aqueous HCl (2 mL). The mixture was diluted with water and extracted with DCM (thrice). The combined organics were washed with brine, dried over sodium sulfate, and concentrated to give the title compound as an amber oil (with minor impurities, 0.62 g). TLC (50% acetone/hexanes) $R_f = 0.60$.

Step E: Preparation of (R)-1-(3-Chloro-4-(4-methoxybenzyloxy)phenethyl)-2-methylpyrrolidine.

To a stirring solution of impure 3-chloro-4-(4-methoxybenzyloxy)phenethyl methanesulfonate (0.60 g, 1.6 mmol) was added (R)-2-methylpyrrolidine, benzene sulfonate (0.47, 1.9 mmol) and potassium carbonate (0.49 g, 3.6 mmol). The mixture was heated at 60 °C for 18 h. The white heterogeneous mixture was cooled to room temperature, filtered, and the filtrate was concentrated. The residue was dissolved in EtOAc and water, treated with 10% HCl to pH 2, and then the aqueous phase was separated and washed twice more with EtOAc. The aqueous phase was then basified with 50% NaOH to pH 9, followed by extraction with EtOAc (thrice). The combined organic phase from the basic extraction was washed with brine, dried over sodium sulfate, and concentrated to give the title compound as an orange oil (with minor impurities, 0.29 g, 50%). Exact mass calculated for $C_{21}H_{26}ClN_2O_2$: 359.2, found: LCMS $m/z = 360.4$ $[M+H]^+$.

Step F: Preparation of (R)-2-Chloro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenol.

To a stirring solution of (*R*)-1-(3-chloro-4-(4-methoxybenzyloxy)phenethyl)-2-methylpyrrolidine (0.26 g, 0.72 mmol) in DCM (1.5 mL) was added 2,2,2-trifluoroacetic acid (1.5 mL, 20 mmol). After 10 min, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and adjusted to pH 9. The mixture was extracted with DCM (thrice), washed with brine, and dried over sodium sulfate. The solvents were evaporated to give the title compound (70 mg). Exact mass calculated for $C_{13}H_{18}ClNO$: 239.1, found: LCMS m/z = 240.1 $[M+H]^+$.

Step G: Preparation of (*R*)-2-Chloro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl Trifluoromethanesulfonate.

To a stirred slurry of (*R*)-2-chloro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenol (0.070 g, 0.29 mmol) in acetonitrile (1 mL) was added pyridine (0.094 mL, 1.2 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.074 mL, 0.44 mmol) was added dropwise. After 2 h the mixture was evaporated to give a solid residue which was washed with MTBE/EtOAc (10:1). The resulting white solid contained no desired product and was discarded. To the filtrate was added dilute aqueous HCl. The acidified mixture was then extracted with EtOAc (thrice), the combined organic fractions were washed with brine, and then dried over sodium sulfate. The solvent was evaporated to give the title compound (0.11 g). Exact mass calculated for $C_{14}H_{17}ClF_3NO_3S$: 371.1, found: LCMS m/z = 372.2 $[M+H]^+$.

Step H: Preparation of (*S*)-4-(2'-Chloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of (*R*)-2-chloro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl trifluoromethanesulfonate (0.085 g, 0.29 mmol), (*S*)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-2-one (0.11 g, 0.29 mmol), tetrakis(triphenylphosphine)palladium(0) (0.010 g, 0.0088 mmol), sodium carbonate (0.29 mL of 2.0 M aqueous solution, 0.59 mmol), benzene (1.0 mL), and ethanol (0.29 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 15 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to provide the title compound as a TFA salt (2.2 mg, 20%). Exact mass calculated for $C_{22}H_{25}ClN_2O_2$: 384.2, found: LCMS m/z = 385.2 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.48 (d, J = 6.6 Hz, 3H), 1.81-1.70(m, 1H), 2.22-2.02 (m, 2H), 2.41-2.32 (m, 1H), 3.10-3.01 (m, 1H), 3.20-3.11 (m, 1H), 3.37-3.23 (m, 3H), 3.54 (dddd, J = 15.6, 6.6, 6.6, 6.6 Hz, 1H), 3.66 (ddd, J = 12.6, 11.1, 5.9 Hz, 1H), 3.76 (ddd, J = 13.2, 8.1, 5.3 Hz, 1H), 4.20 (dd, J = 8.7, 6.4 Hz, 1H), 4.84-4.75 (m, 1H), 5.07 (dd, J = 8.8, 6.4 Hz, 1H), 7.38-7.32 (m, 2H), 7.47-7.44 (m, 4H), 7.53-7.51 (m, 1H).

Example 1.36: Preparation of (*S*)-4-(3'-Fluoro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 23).

Step A: Preparation of 2-(2-Fluoro-4-methoxyphenyl)ethanol.

To a stirring 0 °C solution of 2-(2-fluoro-4-methoxyphenyl)acetic acid (5.0 g, 27 mmol) in THF (11 mL) was added borane-THF complex (27 mL of 1.0 M solution in THF, 27 mmol). The cold bath was allowed to expire naturally while stirring overnight. After 16 h the reaction was quenched by the careful addition of water until effervescence ceased. The solution was neutralized by stirring with a saturated solution of sodium carbonate. The mixture was then extracted with MTBE (thrice). The combined organics were washed with brine, dried over sodium sulfate, and concentrated to give the title compound as a colorless oil (4.3 g, 93%). Exact mass calculated for C₉H₁₁FO₂: 170.1, found: LCMS m/z = 153.2 [M - H₂O + H]⁺.

Step B: Preparation of 2-Fluoro-4-methoxyphenethyl Methanesulfonate.

To a stirring 0 °C solution of 2-(2-fluoro-4-methoxyphenyl)ethanol (2.0 g, 12 mmol) in THF (30 mL) was added triethylamine (4.9 mL, 35 mmol) and methanesulfonyl chloride (1.1 mL, 14 mmol). The cold bath was allowed to expire naturally while stirring overnight. After 16 h the reaction was quenched by the careful addition of dilute HCl. The mixture was extracted with DCM (thrice). The combined organic fractions were washed with brine, dried over sodium sulfate, and concentrated to give the title compound as an amber oil (with minor impurities, 3.2 g, 110%). Exact mass calculated for C₁₀H₁₃FO₄S: 248.1, found: LCMS m/z = 153.2 [M - MsOH + H]⁺.

Step C: Preparation of (R)-1-(2-Fluoro-4-methoxyphenethyl)-2-methylpyrrolidine.

To a stirring solution of 2-fluoro-4-methoxyphenethyl methanesulfonate (1.5 g, 6.0 mmol) in acetonitrile (15 mL) was added (R)-2-methylpyrrolidine benzene sulfonate (1.8, 7.3 mmol) and potassium carbonate (1.8 g, 13 mmol). The mixture was heated at 60 °C for 18 h. The white heterogeneous mixture was cooled to room temperature, filtered, and the filtrate was evaporated. The residue was dissolved in EtOAc and water, treated with 10% HCl to pH 2, and then the aqueous phase was separated and washed twice more with EtOAc. The aqueous phase was then basified with 50% NaOH to pH 9, followed by extraction with EtOAc (thrice). The combined organic phase from the basic extraction was washed with brine, dried over sodium sulfate, and then concentrated to give the title compound as an orange oil (0.87 g, 62%). Exact mass calculated for C₁₄H₂₀FNO: 237.2, found: LCMS m/z = 238.0 [M+H]⁺.

Step D: Preparation of (R)-3-Fluoro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenol.

To a stirring -78 °C solution of (R)-1-(2-fluoro-4-methoxyphenethyl)-2-methylpyrrolidine (0.10 g, 0.42 mmol) in DCM (3 mL) was added dropwise boron tribromide (0.84 mL of 1 M solution in DCM, 0.84 mmol). After 1 h the cold bath was removed and the mixture was stirred for 3.5 h at room temperature. The mixture was cooled to 0 °C and quenched by the addition of 2 M aqueous sodium carbonate until the mixture reached pH 7. The mixture was extracted with DCM (thrice). The combined organic phase was washed with brine, dried over sodium sulfate, and then evaporated to give the title compound which was used directly in

the next reaction without further purification. Exact mass calculated for $C_{13}H_{18}FNO$: 223.1, found: LCMS m/z = 224.3 $[M+H]^+$.

Step E: Preparation of (*R*)-3-Fluoro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl.

To a stirred slurry of (*R*)-3-fluoro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenol (0.10 g, 0.45 mmol) in acetonitrile (1.5 mL) was added pyridine (0.15 mL, 1.8 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.11 mL, 0.67 mmol) was added dropwise. After 2 h the mixture was evaporated to give an oily residue which was washed with MTBE/EtOAc (10:1). The resulting white solid contained no desired product and was discarded. The filtrate was evaporated to give the title compound with minor impurities as an orange oily solid, which was used directly in the next reaction without further purification. Exact mass calculated for $C_{14}H_{17}CF_4NO_3S$: 355.1, found: LCMS m/z = 356.2 $[M+H]^+$.

Step F: Preparation of (*S*)-4-(3'-Fluoro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of (*R*)-3-fluoro-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenyl trifluoromethanesulfonate (0.13 g, 0.45 mmol), (*S*)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-2-one (0.16 g, 0.45 mmol), tetrakis(triphenylphosphine)palladium(0) (0.016 g, 0.014 mmol), sodium carbonate (0.45 mL of 2.0 M aqueous solution, 0.90 mmol), benzene (1.8 mL), and ethanol (0.50 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 3.5 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to provide the title compound as a TFA salt (49 mg, 24% yield). Exact mass calculated for $C_{22}H_{25}FN_2O_2$: 368.2, found: LCMS m/z = 369.2 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, J = 6.5 Hz, 3H), 1.81-1.70(m, 1H), 2.23-2.02 (m, 2H), 2.42-2.32 (m, 1H), 3.21-3.07 (m, 2H), 3.35-3.25 (m, 3H), 3.67-3.51 (m, 2H), 3.83-3.75 (m, 1H), 4.17 (dd, J = 8.7, 6.4 Hz, 1H), 4.85-4.74 (m, 1H), 5.05 (dd, J = 8.7, 6.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.50-7.42 (m, 3H), 7.68 (d, J = 8.4 Hz, 2H).

Example 1.37: Preparation of (*R*)-4-(2-Methoxy-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 21).

Step A: Preparation of Methyl 2-(*tert*-Butoxycarbonylamino)-2-(4-hydroxy-3-methoxyphenyl)acetate.

A stirring suspension of 2-amino-2-(4-hydroxy-3-methoxyphenyl)acetic acid (0.98 g, 5.0 mmol) in MeOH (6.5 mL) was cooled to 0 °C. Thionyl chloride (0.38 mL, 5.2 mmol) was added dropwise, and then the ice bath was allowed to expire while stirring overnight. After 16 h, *N,N*-diisopropylethylamine (4.3 mL, 25 mmol) was added dropwise and the mixture was placed into a 0 °C ice bath. Di-*tert*-butyldicarbonate (1.2 g, 5.5 mmol) was added in portions. After 2 h, the volatiles were evaporated and the residue was diluted with water, then extracted with EtOAc

(thrice). The combined organic phase was washed with brine, dried over sodium sulfate, and the solvents were evaporated to give the title compound as an amber oil. Exact mass calculated for $C_{15}H_{21}NO_6$: 311.1, found: LCMS $m/z = 312.2$ $[M+H]^+$.

Step B: Preparation of *tert*-Butyl 2-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)ethylcarbamate.

To a stirring 0 °C solution of methyl 2-(*tert*-butoxycarbonylamino)-2-(4-hydroxy-3-methoxyphenyl)acetate (1.5 g, 4.8 mmol) in THF (50 mL) was added lithium aluminum hydride (5.8 mL of 1M THF solution, 5.8 mmol). The cold bath was removed and the mixture was stirred overnight. The reaction was quenched by pouring onto ice. The slurry was diluted with EtOAc and the solution was adjusted to pH 4 with 10% aqueous HCl. The organic phase was separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography to give the title compound as a tan solid (0.50 g, 36%). Exact mass calculated for $C_{14}H_{21}NO_5$: 283.1, found: LCMS $m/z = 284.4$ $[M+H]^+$.

Step C: Preparation of 4-(4-Hydroxy-3-methoxyphenyl)oxazolidin-2-one.

To a stirring 0 °C solution of *tert*-butyl 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)ethylcarbamate (0.5 g, 1.8 mmol) in THF (7 mL) was added thionyl chloride (0.14 mL, 1.9 mmol). The ice bath was removed and the mixture was stirred overnight at room temperature. The solvents were evaporated to give the title compound (with minor impurities, 0.37 g). Exact mass calculated for $C_{10}H_{11}NO_4$: 209.1, found: LCMS $m/z = 210.0$ $[M+H]^+$.

Step D: Preparation of 2-Methoxy-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate.

To a stirred slurry of 4-(4-hydroxy-3-methoxyphenyl)oxazolidin-2-one (0.37 g, 1.8 mmol) in acetonitrile (6 mL) was added pyridine (0.57 mL, 7.1 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.45 mL, 2.7 mmol) was added dropwise. After 30 min the ice bath was removed and the clear red solution was stirred at room temperature. After another 30 min the solvent was evaporated and the residue was extracted with (10:1) MTBE/EtOAc. To the decanted liquid was added dilute aqueous HCl. The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phase was washed with brine and dried over sodium sulfate. The solvents were evaporated to give the title compound as a red oil (with impurities, 0.77 g). Exact mass calculated for $C_{11}H_{10}F_3NO_6S$: 341.0, found: LCMS $m/z = 342.2$ $[M+H]^+$.

Step E: Preparation of 4-(2-Methoxy-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of 2-methoxy-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (0.75 g, 2.2 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.59 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (76 mg, 0.066 mmol), sodium

carbonate (3.3 mL of 2.0 M aqueous solution, 6.6 mmol), benzene (8 mL), and ethanol (2.3 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 90 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt (0.10 g). Exact mass calculated for $C_{23}H_{28}N_2O_3$: 380.2, found: LCMS m/z = 381.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.38 (d, J = 6.5 Hz, 3H), 1.61 (dddd, J = 12.9, 9.0, 9.0, 9.0 Hz, 1H), 2.08-1.86 (m, 2H), 2.28-2.18 (m, 1H), 3.10-2.92 (m, 2H), 3.28-3.15 (m, 2H), 3.60-3.40 (m, 2H), 3.66 (dddd, J = 11.4, 8.0, 5.5, 5.5 Hz, 1H), 3.78 (s, 3H), 4.08 (dd, J = 8.5, 6.6 Hz, 1H), 4.70 (dd, J = 8.6, 8.6 Hz, 1H), 4.98 (dd, J = 8.1, 8.1 Hz, 1H), 7.00 (dd, J = 7.8, 1.4 Hz, 1H), 7.09 (d, J = 1.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 8.20 (s, 1H), 9.38 (bs, 1H).

Example 1.38: Preparation of (S)-4-(2'-Methoxy-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one (Compound 33).

Step A: Preparation of 2-Methoxy-4-(2-(pyrrolidin-1-yl)ethyl)phenyl Trifluoromethanesulfonate.

To a stirred slurry of 4-(2-hydroxyethyl)-2-methoxyphenol (homovanillyl alcohol) (2.0 g, 12 mmol) in acetonitrile (40 mL) was added pyrrolidine (5.0 mL, 60 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (6.0 mL, 36 mmol) was added dropwise. After 3 h the cold bath was removed and the mixture was stirred at ambient temperature. After another 18 h, pyridine (5.0 mL, 62 mmol) and more triflic anhydride (5.0 mL, 30 mmol) were added. After another 1 h, the reaction mixture was again charged with triflic anhydride (5 mL, 30 mmol). After an additional 3 h, the solvent was evaporated to give a dark residue which was extracted with EtOAc (thrice). The combined organic extract was washed with brine, dried over sodium sulfate, and then the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt. The salt was dissolved in water and EtOAc, then the mixture was treated with a saturated aqueous sodium bicarbonate solution to pH 9. The layers were separated, and the aqueous phase was extracted twice more with EtOAc. The combined organic extract was washed with brine, dried over sodium sulfate, and then the solvent was evaporated to give the title compound as an oil (0.76 g, 18%). Exact mass calculated for $C_{14}H_{18}F_3NO_4S$: 353.1, found: LCMS m/z = 354.2 $[M+H]^+$.

Step B: Preparation of (S)-4-(2'-Methoxy-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

A mixture of 2-methoxy-4-(2-(pyrrolidin-1-yl)ethyl)phenyl trifluoromethanesulfonate (0.20 g, 0.57 mmol), (S)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-2-one (0.16 g, 0.57 mmol), tetrakis(triphenylphosphine)palladium(0) (0.020 g, 0.017 mmol), sodium carbonate (0.57 mL of 2.0 M aqueous solution, 1.1 mmol), benzene (1.5 mL), and

ethanol (0.4 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 12 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt (19 mg). Exact mass calculated for C₂₂H₂₆N₂O₃: 366.2, found:

5 LCMS m/z = 367.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.95-1.82 (m, 2H), 2.10-1.98 (m, 2H), 3.04-2.97 (m, 2H), 3.15-3.04 (m, 2H), 3.60-3.40 (m, 4H), 3.78 (s, 3H), 4.06 (dd, J = 8.5, 6.4 Hz, 1H), 4.70 (dd, J = 8.6, 8.6 Hz, 1H), 4.97 (dd, J = 7.5, 7.5 Hz, 1H), 6.96 (dd, J = 7.7, 1.4 Hz, 1H), 7.06 (d, J = 1.4 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 8.18 (s, 1H), 9.72 (bs, 1H).

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Example 1.39: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxolan-2-one (Compound 26).

Step A: Preparation of 4-(4-Bromophenyl)-2,2-dimethyl-1,3-dioxolane.

To a mixture of 1-(4-bromophenyl)ethane-1,2-diol (1.0 g, 4.6 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (11 mL, 92 mmol) was added pyridinium *p*-toluenesulfonate (PPTs) (0.12 g, 0.46 mmol). After 16 h, the reaction was quenched with water. The volatiles were evaporated and the aqueous slurry was extracted with DCM (thrice). The combined organic phase was washed with brine, dried over sodium sulfate, and then the solvent was evaporated to give the title compound as a yellow oil (1.2 g, 98%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 (s, 3H), 1.45 (s, 3H), 3.55 (dd, J = 8.0, 8.0 Hz, 1 H), 4.30 (dd, J = 8.0, 6.8 Hz, 1 H), 5.05 (dd, J = 6.8, 6.8 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H).

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Step B: Preparation of (2*R*)-1-(2-(4'-(2,2-Dimethyl-1,3-dioxolan-4-yl)biphenyl-4-yl)ethyl)-2-methylpyrrolidine.

A mixture of 4-(4-bromophenyl)-2,2-dimethyl-1,3-dioxolane (0.50 g, 2.0 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.52 g, 2.0 mmol), tetrakis(triphenylphosphine)palladium(0) (67 mg, 0.058 mmol), sodium carbonate (2.0 mL of 2.0 M aqueous solution, 3.9 mmol), benzene (7.6 mL), and ethanol (2.2 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 3 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated to give the title compound (with minor impurity, 0.76 g). Exact mass calculated for C₂₄H₃₁NO₂: 365.2, found: LCMS m/z = 366.4 [M+H]⁺.

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Step C: Preparation of 1-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)ethane-1,2-diol.

To a solution of crude (2*R*)-1-(2-(4'-(2,2-dimethyl-1,3-dioxolan-4-yl)biphenyl-4-yl)ethyl)-2-methylpyrrolidine (0.60 g, 1.6 mmol) in dioxane (20 mL) was added hydrogen chloride (5 mL of 4 M solution in dioxane, 20 mmol), and water (0.5 mL, 28 mmol). The mixture was stirred at room temperature for 60 h. The reaction was neutralized with 50%

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aqueous sodium hydroxide. The volatiles were evaporated and the residue was purified by preparative HPLC to provide the title compound containing a chloro-alcohol impurity. Exact mass calculated for $C_{21}H_{27}NO_3$: 325.2, found: LCMS m/z = 326.3 $[M+H]^+$.

Step D: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxolan-2-one.

To a solution of 1-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)ethane-1,2-diol (0.20 g, 0.62 mmol), containing a chloro-alcohol impurity, in THF (12 mL) was added CDI (0.60 g, 3.7 mmol). The mixture was stirred at 40 °C for 30 min, then cooled to room temperature before quenching with 10% aqueous HCl. The mixture was stirred for another 20 min, then the reaction was neutralized by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was extracted with MTBE (thrice) and the combined organic phase was washed with brine, and then dried over sodium sulfate. The volatiles were evaporated and the residue was purified by preparative HPLC to give the title compound as a TFA salt (3.1 mg). Exact mass calculated for $C_{22}H_{25}NO_3$: 351.2, found: LCMS m/z = 352.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, J = 6.5 Hz, 3H), 1.81-1.70 (m, 1H), 2.21-2.00 (m, 2H), 2.40-2.30 (m, 1H), 3.20-3.01 (m, 2H), 3.33-3.22 (m, 2H), 3.80-3.50 (m, 3H), 4.43 (dd, J = 8.6, 7.6 Hz, 1H), 4.89 (dd, J = 8.6, 8.6 Hz, 1H), 5.84 (dd, J = 7.9, 7.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H).

Example 1.40: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one (Compound 25).

Step A: Preparation of 4-(4-Chlorophenyl)pyrrolidin-2-one.

To a solution of 4-amino-3-(4-chlorophenyl)-butanoic acid (baclofen) (1.0 g, 4.7 mmol) in toluene (80 mL) was added neutral alumina (1.4 g, 14 mmol). The mixture was heated to reflux for 16 h, then cooled to room temperature and filtered. The filtrate was evaporated to give the title compound as a white solid (0.82 g, 90%). Exact mass calculated for $C_{10}H_{10}ClNO$: 195.1, found: LCMS m/z = 196.1 $[M+H]^+$.

Step B: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one.

A mixture of 4-(4-chlorophenyl)pyrrolidin-2-one (0.15 g, 0.77 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.21 g, 0.77 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (XPHOS) (18 mg, 0.038 mmol), potassium phosphate (0.49 g, 2.3 mmol), palladium acetate (3.4 mg, 0.015 mmol) and THF (1.0 mL) were combine in a sealed vial which was then heated in an oil bath at 100 °C for 26 h. The mixture was filtered through a pad of Celite® with acetonitrile, and the solvents were evaporated. The residue was dissolved in EtOAc and washed with 10% aqueous HCl. The aqueous phase was then treated with 50% aqueous NaOH to pH 12, and extracted with EtOAc

(thrice). The combined organic phase from the basic extraction was washed with brine, dried over sodium sulfate, and then the solvent was evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt (3.8 mg). Exact mass calculated for $C_{23}H_{28}N_2O$: 348.2, found: LCMS $m/z = 349.3$ $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, $J = 6.5$ Hz, 3H), 1.76 (dddd, $J = 13.2, 9.1, 9.1, 9.1$ Hz, 1H), 2.20-2.00 (m, 2H), 2.40-2.30 (m, 1H), 2.53-2.45 (m, 1H), 2.78-2.70 (m, 1H), 3.19-3.02 (m, 2H), 3.32-3.22 (m, 3H), 3.46-3.39 (m, 1H), 3.58-3.48 (m, 1H), 3.63 (dddd, $J = 10.7, 10.7, 10.7, 5.9$ Hz, 1H), 3.84-3.72 (m, 3H), 7.42-7.36 (m, 4H), 7.63-7.57 (m, 4H).

Example 1.41: Preparation of 5-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one (Compound 30).

Step A: Preparation of 5-(4-Methoxyphenyl)pyrrolidin-2-one.

To a stirring mixture of phosphorous pentoxide (0.64 g, 4.5 mmol), methanesulfonic acid (4.3 mL, 67 mmol), and anisole (0.93 mL, 8.5 mmol) was added (*S*)-5-oxopyrrolidine-2-carboxylic acid (pyroglutamic acid) (1.0 g, 7.8 mmol). The neat mixture was heated at 100 °C for 30 min. The reaction was quenched by pouring onto ice. The aqueous slurry was extracted with DCM (thrice). The organic extracts were combined, washed with brine, dried over sodium sulfate, and then the solvents were evaporated. The residue was purified by preparative HPLC. The appropriate fractions were combined and the solvents evaporated. The residue was extracted with DCM (thrice). The organic extracts were combined, washed with brine, dried over sodium sulfate, and then the solvents were evaporated to give the title compound as a white solid (0.40 g, 27%). Exact mass calculated for $C_{11}H_{13}NO_2$: 191.1, found: LCMS $m/z = 192.2$ $[M+H]^+$.

Step B: Preparation of 5-(4-Hydroxyphenyl)pyrrolidin-2-one.

To a stirring -78 °C solution of 5-(4-methoxyphenyl)pyrrolidin-2-one (0.38 g, 2.0 mmol) in DCM (13 mL) was added dropwise boron tribromide (2.6 mL of 1 M solution in DCM, 2.6 mmol). After 1 h the cold bath was removed and the mixture continued to stir at ambient temperature overnight. The solvent was evaporated to give a tan solid. The reaction was diluted with DCM and quenched by the addition of an aqueous sodium bicarbonate solution until pH 7. The mixture was filtered to collect the title compound as an off-white solid (0.20 g, 57%). Exact mass calculated for $C_{10}H_{11}NO_2$: 177.2, found: LCMS $m/z = 178.1$ $[M+H]^+$.

Step C: Preparation of 4-(5-Oxopyrrolidin-2-yl)phenyl trifluoromethanesulfonate.

To a stirred slurry of 5-(4-hydroxyphenyl)pyrrolidin-2-one (0.20 g, 1.1 mmol) in acetonitrile (4 mL) was added pyridine (0.37 mL, 4.5 mmol). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.29 mL, 1.7 mmol) was added dropwise. After 30 min the solvent was evaporated and the dark residue was washed with (10:1) MTBE/EtOAc. A solid precipitated which contained no desired product. The decanted liquid was evaporated to give the

title compound with impurities as an oily solid (0.30 g, 85%). Exact mass calculated for $C_{10}H_{11}NO_2$: 309.0, found: LCMS m/z = 310.4 $[M+H]^+$.

Step D: Preparation of 5-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one.

5 A mixture of 4-(5-oxopyrrolidin-2-yl)phenyl trifluoromethanesulfonate (0.30 g, 0.97 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.26 g, 0.97 mmol), tetrakis(triphenylphosphine)palladium(0) (0.034 g, 0.029 mmol), sodium carbonate (1.5 mL of 2.0 M aqueous solution, 2.9 mmol), benzene (2.5 mL), and ethanol (0.80 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 10 5 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was partitioned between water and DCM. The aqueous phase was extracted twice more with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and then the solvents were evaporated. The residue was purified by preparative HPLC. The appropriate fractions were combined and lyophilized to give the title 15 compound as a TFA salt (7.0 mg, 1.6%). Exact mass calculated for $C_{23}H_{28}N_2O$: 348.2, found: LCMS m/z = 349.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, J = 6.5 Hz, 3H), 1.76 (dddd, J = 13.2, 9.0, 9.0, 9.0 Hz, 1H), 2.02-1.91 (m, 1H), 2.18-2.02 (m, 2H), 2.40-2.30 (m, 1H), 2.48-2.42 (m, 2H), 2.62 (dddd, J = 12.8, 8.2, 8.2, 6.3 Hz, 1H), 3.19-3.02 (m, 2H), 3.35-3.22 (m, 3H), 3.59-3.49 (m, 1H), 3.64 (ddd, J = 16.6, 10.8, 5.9 Hz, 1H), 3.76 (ddd, J = 13.1, 8.0, 4.6 20 Hz, 1H), 4.87-4.82 (m, 1H), 7.43-7.38 (m, 4H), 7.65-7.60 (m, 4H).

Example 1.42: Preparation of 6-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one (Compound 27).

Step A: Preparation of 3-Amino-1-(4-bromophenyl)propan-1-ol.

25 A solution of 3-(4-bromophenyl)-3-oxopropanenitrile (1.0 g, 4.5 mmol) in THF (89 mL) was heated to reflux. Borane-THF complex (13 mL of 1 M solution, 13 mmol) was added dropwise. After 3.5 h the mixture was cooled to room temperature, then MeOH (20 mL) was added. The volatiles were evaporated to give a white residue, which was then dissolved in MTBE. The clear solution was treated with a 1 M ethereal HCl solution. The solvents were 30 evaporated and the residue was partitioned between water and DCM. The organic phase was set aside. The aqueous phase was neutralized with a 50% aqueous sodium hydroxide solution, and then extracted with DCM (thrice). The combined organic phase was washed with brine and dried over sodium sulfate. The solvent was evaporated to give the title compound in impure form as a colorless oil (0.85 g) which was used without further purification. Exact mass 35 calculated for $C_9H_{12}BrNO$: 229.0, found: LCMS m/z = 230.3 $[M+H]^+$.

Step B: Preparation of 6-(4-Bromophenyl)-1,3-oxazinan-2-one.

A solution of impure 3-amino-1-(4-bromophenyl)propan-1-ol (0.85 g, 3.7 mmol) and 1,1'-carbonyldiimidazole (3.6 g, 22 mmol) in THF (74 mL) was heated to 40 °C. After 18 h the solvent was evaporated and the residue was treated with water and extracted with DCM (thrice). The combined organic extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated. The residue was purified by preparative HPLC, the appropriate fractions were combined, and the volatiles were evaporated. The aqueous residue was extracted with DCM (thrice), the combined organic extract was washed with brine, and the solvent was evaporated to give the title compound (45 mg). Exact mass calculated for $C_{10}H_{10}BrNO_2$: 255.0, found: LCMS $m/z = 256.5 [M+H]^+$.

Step C: Preparation of 6-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one.

A mixture of 6-(4-bromophenyl)-1,3-oxazinan-2-one (0.045 g, 0.18 mmol), (R)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.047 g, 0.18 mmol), tetrakis(triphenylphosphine)palladium(0) (0.006 g, 0.005 mmol), sodium carbonate (0.18 mL of 2.0 M aqueous solution, 0.35 mmol), benzene (0.68 mL), and ethanol (0.20 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 3 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a white TFA salt (15 mg). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 364.2, found: LCMS $m/z = 365.6 [M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, $J = 6.5$ Hz, 3H), 1.75 (dddd, $J = 13.2, 9.0, 9.0, 9.0$ Hz, 1H), 2.21-2.00 (m, 3H), 2.30-2.23 (m, 1H), 2.41-2.31 (m, 1H), 3.20-3.02 (m, 2H), 3.38-3.23 (m, 4H), 3.59-3.42 (m, 2H), 3.70-3.60 (m, 1H), 3.75 (ddd, $J = 15.3, 12.6, 7.2$ Hz, 1H), 5.45 (dd, $J = 10.1, 2.6$ Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 7.67-7.61 (m, 4H).

Example 1.43: Preparation of 4-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one (Compound 28).

Step A: Preparation of 4-(4-Bromophenyl)-1,3-oxazinan-2-one.

A solution of 3-amino-3-(4-bromophenyl)propan-1-ol (0.10 g, 0.44 mmol) and 1,1'-carbonyldiimidazole (0.70 g, 0.44 mmol) in THF (9 mL) was heated to 40 °C. After 3 d the solvent was evaporated and the residue was partitioned between water and DCM. The aqueous phase was extracted twice more with DCM. The combined organic extract was washed with brine, dried over sodium sulfate and concentrated. The residue was subjected to acidic and basic extraction conditions. The organic extract was washed with brine and dried over sodium sulfate. The solvent of the extract was evaporated to give the title compound as a colorless oil. Exact mass calculated for $C_{10}H_{10}BrNO_2$: 255.0, found: LCMS $m/z = 256.4 [M+H]^+$.

Step B: Preparation of 4-(4'-(2-((R)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one.

A mixture of impure 4-(4-bromophenyl)-1,3-oxazinan-2-one (0.35 g, 1.4 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.37 g, 1.4 mmol), tetrakis(triphenylphosphine)palladium(0) (0.047 g, 0.041 mmol), sodium carbonate (2.1 mL of 2.0 M aqueous solution, 4.1 mmol), benzene (4.6 mL), and ethanol (1.3 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 24 h. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The residue was partitioned between water and DCM. The aqueous phase was extracted twice more with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and then the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a white TFA salt (3.0 mg). Exact mass calculated for C₂₃H₂₈N₂O₂: 364.2, found: LCMS *m/z* = 365.5 [M+H]⁺; ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm 1.47 (d, *J* = 6.5 Hz, 3H), 1.81-1.70 (m, 1H), 2.21-1.93 (m, 3H), 2.40-2.27 (m, 2H), 3.20-3.02 (m, 2H), 3.33-3.23 (m, 3H), 3.59-3.50 (m, 1H), 3.68-3.60 (m, 1H), 3.75 (ddd, *J* = 13.1, 7.9, 5.3 Hz, 1H), 4.38-4.25 (m, 2H), 4.73 (dd, *J* = 7.4, 5.3 Hz, 1H), 7.46-7.38 (m, 4H), 7.67-7.61 (m, 4H).

Example 1.44: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxan-2-one (Compound 29).

Step A: Preparation of (*R*)-(4'-(2-(2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methanol.

A mixture of (4-bromophenyl)methanol (0.50 g, 2.7 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.72 g, 2.7 mmol), tetrakis(triphenylphosphine)palladium(0) (0.093 g, 0.080 mmol), sodium carbonate (4.0 mL of 2.0 M aqueous solution, 8.0 mmol), benzene (10 mL), and ethanol (3 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 90 min. The mixture was filtered through a pad of Celite® with EtOAc, and the solvents were evaporated. The crude material was partitioned between water and DCM. The aqueous phase was extracted twice more with DCM. The combined organic phase was washed with brine, dried over sodium sulfate, and then the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a white TFA salt (0.35 g, 44%). Exact mass calculated for C₂₀H₂₅NO: 295.2, found: LCMS *m/z* = 296.3 [M+H]⁺.

Step B: Preparation of (*R*)-4'-(2-(2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-carbaldehyde.

To a stirring solution of (*R*)-(4'-(2-(2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methanol (0.35 g, 1.2 mmol) in DCM (5 mL) was added 4Å molecular sieves (0.60 g), NMO (0.21 g, 1.8 mmol), and TPAP (0.025 g, 0.071 mmol). After 3 days the mixture was filtered through a plug of Celite®/SiO₂, washing with DCM and EtOAc. The solvents were evaporated

to give the title compound as an oil (0.17 g, 49 %). Exact mass calculated for $C_{20}H_{23}NO$: 293.2, found: LCMS m/z = 294.0 $[M+H]^+$.

Step C: Preparation of Ethyl 3-Hydroxy-3-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)propanoate.

5 To a stirring solution of diisopropylethylamine (0.15 mL, 1.1 mmol) in THF (1 mL) at -78 °C was added *n*BuLi (0.44 mL of 2.5 M hexane solution, 1.1 mmol). After 15 min, a solution of EtOAc (0.11 mL, 1.1 mmol) in THF (0.2 mL) was added. After 30 min, a solution of (*R*)-4'-(2-(2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-carbaldehyde (0.16 g, 0.55 mmol) in THF (0.2 mL) was added. After 30 min, the cold bath was removed and the mixture was allowed to reach ambient temperature. After 2 h, the reaction was quenched with water and extracted with EtOAc (thrice). The combined organic extract was washed with brine and dried over sodium sulfate. The solvent was evaporated to give the title compound as an amber oil (0.19 g, 90%). Exact mass calculated for $C_{24}H_{31}NO_3$: 381.2, found: LCMS m/z = 382.5 $[M+H]^+$.

Step D: Preparation of 1-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)propane-1,3-diol.

15 To a stirring solution of ethyl 3-hydroxy-3-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)propanoate (0.19 g, 0.49 mmol) in THF (3 mL) at 0 °C was added lithium aluminum hydride (0.49 mL of 1.0 M THF solution, 0.49 mmol). The cold bath was removed and the mixture was stirred at ambient temperature overnight. After 16 h, the reaction was quenched with ice water and extracted with EtOAc (thrice). The combined organic extract was treated with dilute aqueous HCl to pH 1. The mixture was extracted with water (thrice), then the combined aqueous extract was basified with 50% NaOH to pH 10. The basic solution was extracted with EtOAc (thrice), then the combined organic extract was washed with brine and dried over sodium sulfate. The solvent was evaporated to give the title compound as an amber oil (0.13 g, 77%). Exact mass calculated for $C_{22}H_{29}NO_2$: 339.2, found: LCMS m/z = 340.4 $[M+H]^+$.

Step E: Preparation of 4-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxan-2-one.

30 To a stirring solution of 1-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)propane-1,3-diol (0.13 g, 0.38 mmol) in THF (8 mL) at 0 °C was added 1,1'-carbonyldiimidazole (CDI) (0.061 g, 0.38 mmol). After 1 h the cold bath was removed and the mixture was stirred overnight. After 18 h, more CDI (0.030 g, 0.19 mmol) was added. After 1 h, the solvent was evaporated and the residue was partitioned between water and EtOAc. The aqueous phase was extracted twice more with EtOAc. The combined organic extract was washed with brine and dried over sodium sulfate. The solvents were evaporated to give the title compound as an amber oil (0.16 g). This material was purified by preparative HPLC to give the title compound as a TFA salt (16 mg, 8.8%). Exact mass calculated for $C_{23}H_{27}NO_3$: 365.2,

found: LCMS m/z = 366.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol- d_4) δ ppm 1.47 (d, J = 6.5 Hz, 3H), 1.75 (dddd, J = 13.2, 9.1, 9.1, 9.1 Hz, 1H), 2.21-2.00 (m, 2H), 2.44-2.26 (m, 3H), 3.20-3.03 (m, 2H), 3.33-3.23 (m, 2H), 3.57-3.50 (m, 1H), 3.64 (ddd, J = 16.6, 10.8, 6.0 Hz, 1H), 3.76 (ddd, J = 13.1, 8.0, 5.3 Hz, 1H), 4.55-4.49 (m, 1H), 4.62 (ddd, J = 11.0, 11.0, 3.7 Hz, 1H), 5.69 (dd, J = 10.4, 3.6 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H).

Example 1.45: Preparation of 5-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)morpholin-3-one (Compound 31).

Step A: Preparation of 2-Amino-2-(4-bromophenyl)ethanol.

To a stirring solution of 1-(4-bromophenyl)ethane-1,2-diol (3.0 g, 14 mmol), in acetonitrile (25 mL), was added concentrated sulfuric acid (7.4 mL, 0.14 mol). The resulting solution was stirred at room temperature for 1 h, then heated to reflux. After 2 h, the mixture was cooled to room temperature and water (10 mL) was added. The acetonitrile was removed by rotary evaporation. The resulting aqueous slurry was heated to 100 °C. After 2 h, the mixture was cooled to room temperature and DCM was added. The mixture was stirred for 5 min before separating the layers. The organic layer was extracted once more with water, then the combined organic extract was set aside. The aqueous extract was treated with 50% aqueous NaOH to pH 10, then extracted with EtOAc (thrice). The combined EtOAc extracts were washed with brine, dried over sodium sulfate, and then the solvents were evaporated to give the title compound (1.9 g, 64%). Exact mass calculated for $C_8H_{10}BrNO$: 215.0, found: LCMS m/z = 216.3 $[M+H]^+$.

Step B: Preparation of 5-(4-Bromophenyl)morpholin-3-one.

To a stirring suspension of sodium hydride (1.3 g of 60% dispersion in mineral oil, 32 mmol) in benzene (50 mL) was added a solution of 2-amino-2-(4-bromophenyl)ethanol (1.7 g, 7.9 mmol) in benzene (50 mL). The mixture was stirred at room temperature for 30 min, then cooled to 0 °C. A cooled solution of ethyl chloroacetate in benzene (50 mL) was added dropwise at 0 °C. The mixture was stirred for 2.5 h. The reaction was quenched by pouring into ice/MTBE and then treating with 10% HCl to pH 1. The mixture was extracted with MTBE (thrice), washed with brine, and dried over sodium sulfate. The solvents were evaporated to give a yellow residue. The residue was purified by silica gel flash chromatography to give the title compound as a white solid (0.70 g, 35%). Exact mass calculated for $C_{10}H_{10}BrNO_2$: 255.0, found: LCMS m/z = 256.4 $[M+H]^+$.

Step C: Preparation of 5-(4'-(2-((*R*)-2-Methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)morpholin-3-one.

A mixture of 5-(4-bromophenyl)morpholin-3-one (0.10 g, 0.39 mmol), (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)phenylboronic acid hydrochloride (0.11 g, 0.39 mmol), tetrakis(triphenylphosphine)palladium(0) (0.014 g, 0.012 mmol), sodium carbonate (0.59 mL of

2.0 M aqueous solution, 1.2 mmol), benzene (1.0 mL), and ethanol (0.3 mL) were combined in a suitable microwave vial and irradiated under microwave conditions at 100 °C for 30 min. The mixture was filtered through a pad of Celite with EtOAc, and the solvents were evaporated. The residue was purified by preparative HPLC to give the title compound as a TFA salt (20 mg, 11%). Exact mass calculated for $C_{23}H_{28}N_2O_2$: 364.2, found: LCMS m/z = 365.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.38 (d, J = 6.5 Hz, 3H), 1.61 (dddd, J = 12.9, 8.9, 8.9, 8.9 Hz, 1H), 2.11-1.85 (m, 2H), 2.27-2.17 (m, 1H), 3.12-2.93 (m, 2H), 3.28-3.17 (m, 2H), 3.70-3.45 (m, 4H), 3.99 (dd, J = 11.6, 4.1 Hz, 1H), 4.11 (s, 2H), 4.70-4.65 (m, 1H), 7.45-7.40 (m, 4H), 7.69-7.63 (m, 4H), 8.46 (s, 1H), 9.34 (bs, 1H).

Example 1.46: Preparation of (S)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-2-one.

To a three-necked, round-bottom 500 mL flask equipped with a temperature probe, mechanical stirrer and nitrogen inlet was added (S)-4-(2-oxooxazolidin-4-yl)phenyl trifluoromethanesulfonate (20.0 g, 64.3 mmol) followed by toluene (250 mL). The mixture was stirred under N_2 and potassium acetate (13.87 g, 141 mmol) was added followed by 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (24.48 g, 96 mmol), triphenylphosphine (1.011 g, 3.86 mmol) and $PdCl_2(PPh_3)_2$ (1.353 g, 1.928 mmol). The reaction mixture was gradually heated (by an oil bath) to 100 °C (internal). There was a mild exotherm initially and the internal temperature went up to 110 °C. The reaction was cooled to ~100 °C and maintained at that temperature for 2 h. LCMS analysis showed there was less than 1% of starting material. The starting material and the product have the same retention time by LCMS; the product formation was analyzed by extracted ion chromatogram data.

The reaction was heated for 20 min more, cooled to ~30 °C, water (100 mL) was added and the mixture was stirred well for 30 min at room temperature. The product crystallized out and was collected by filtration. The filter cake was washed once with water followed by 1:1 toluene:heptane and dried overnight in a vacuum oven at ~50 °C to obtain the product as brown solid (16.09 g). Exact mass calculated for $C_{15}H_{20}BNO_4$: 289.15, found: LCMS m/z = 290.0 $[M+H]^+$; 92% purity by LCMS.

A solution of the above material (16.09 g) was dissolved in EtOAc (100 mL), acetonitrile (50 mL) and methanol (20 mL) with warming to ~35 °C. The solution was passed through a plug of silica. Then, the plug was eluted with EtOAc three times. The combined solvent (after plug filtration) was concentrated under reduced pressure. Heptane was added and the residual solvent was swapped with heptane. The heptane slurry was concentrated (approximately 2-3 volumes) and filtered. The filter cake was washed with heptane to obtain a beige solid, which was dried in a vacuum oven at ~50 ° to leave the title compound (14.35 g).

Exact mass calculated for $C_{15}H_{20}BNO_4$: 289.15, found: LCMS m/z = 290.0 $[M+H]^+$; 95.7% purity by LCMS.

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

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

The following table shows the observed activities for certain compounds of the present invention.

Compound No.	K_i Binding Assay (nM)
7	1.3
12	0.8
13	2.2
14	3.2
15	1.1

Certain other compounds of the invention had activity values ranging from 0.6 nM to 24.0 nM in this assay.

Example 3: Rat Polysomnography Protocol.

Animals: Male Sprague-Dawley rats (225-350 g) (Harlan, San Diego, CA) were singly housed and maintained in a humidity- (30-70%) and temperature- (20-22 °C) controlled facility on a 12 h:12 h light/dark cycle (lights on at 6:30 A.M.) with free access to food (Harlan-Teklad

Western Res., Orange, CA, Rodent Diet 8604) and water. Rats were allowed at least three days of habituation to the animal facility before surgery.

Procedures:

Rats were anaesthetized with a ketamine/xylazine mixture, and surgically prepared for EEG and EMG recording. After 2-3 weeks of post-surgical recovery, rats were habituated to polypropylene test cages for at least three days. On test days, the rats were placed in the test chambers and habituated overnight. At 10 am the next day, the rats were administered the test compound, connected to the recording apparatus, and placed back into the test chambers for 3 h.

Data analysis

EEG and EMG data were digitized and stored in 10 s epochs over the three hour test period. These data were then visually scored, and each 10 s epoch characterized as either a non-REM sleep, REM sleep, or waking episode. Total wake time over the three hour period was calculated for each rat after either vehicle administration or test compound. Percent increase in wakefulness was then derived for each rat.

The following table shows the observed percent increase in wakefulness over 1 h after oral administration of a representative compound at 1.0 mg/kg.

Cmpd No.	% Increase in wakefulness +/- s.e.
2	54.4 ± 15.8

Example 4: Human Histamine H₃-Receptor Binding Assay – MDS Pharma Services (Taiwan).

Compounds of the invention were tested for their ability to bind to the human histamine H₃-receptor using the MDS Pharma Services (Taiwan) assay, Catalogue No. 239810. Certain compounds of the present invention and their corresponding activity values are shown in following table.

Compound No.	Binding Assay (K _i , nM)
1	6.9
2	4.4

Certain other compounds of the invention had activity values ranging from about 4.4 nM to about 23 nM in this assay.

Example 5: Blockade of RAMH-Induced Drinking Assay.

When administered to rodents, H₃ agonists such as R- α -methyl-histamine (RAMH) induce a drinking response that is sensitive to reversal with an H₃ antagonist. Blockade of

RAMH-induced drinking can therefore be utilized as an *in vivo* assay for functional H3 antagonist activity. In this assay, male Sprague Dawley rats (250-350g) were 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 were individually housed in new cages and food was removed. 120 min later, rats were administered test article (vehicle or H3 antagonist, 0.3 mg/kg PO). 30 min later, water was removed, and RAMH (vehicle or RAMH 3 mg/kg salt SC) was administered. 10 min after administration of RAMH, weighed water bottles were placed in the cages, and drinking was allowed for 20 min. Water consumption was 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:

$$\frac{[(\text{VEH}/\text{RAMH}) - (\text{ANTAGONIST}/\text{RAMH})] / ((\text{VEH}/\text{RAMH}) - (\text{BASELINE DRINKING: 1mL}))}{1} * 100$$

Compound No.	% inhibition of RAMH-induced drinking
4	109.5
5	50.6
11	83.3

15

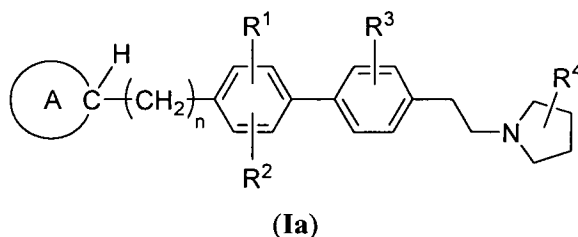
Those skilled in the art will recognize that various modifications, additions, substitutions and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications and provisional and regular patent applications, are incorporated herein by reference in their entirety.

20

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 ring A is heterocyclyl optionally substituted with one, two or three substituents selected from C₁-C₆ alkyl and oxo; wherein each C₁-C₆ alkyl is optionally substituted with a C₁-C₆ alkoxy substituent;

R¹ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

R² is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

R³ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl or halogen;

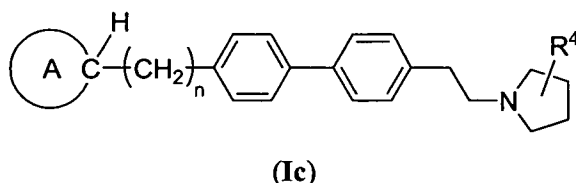
- 15 R⁴ is H or C₁-C₄ alkyl; and

n is 0, 1 or 2.

2. A compound according to any one of claims 1 to 2, wherein R¹, R² and R³ are all H.
- 20 3. A compound according to claim 1, wherein R¹ is selected from C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.
4. A compound according to claim 3, wherein R¹ is selected from methoxy, methyl, chloro and fluoro.
- 25 5. A compound according to claim 1, wherein R² is selected from C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.
6. A compound according to claim 5, wherein R² is selected from methoxy, methyl, chloro and fluoro.
- 30 7. A compound according to claim 1, wherein R³ is selected from C₁-C₆ alkoxy, C₁-C₆ alkyl and halogen.

8. A compound according to claim 7, wherein R³ is selected from methoxy, methyl, chloro and fluoro.
- 5 9. A compound according to any one of claims 1 to 8, wherein R⁴ is H.
10. A compound according to any one of claims 1 to 8, wherein R⁴ is C₁-C₄ alkyl.
11. A compound according to any one of claims 1 to 8, wherein R⁴ is methyl.
- 10 12. A compound according to any one of claims 1 to 11, wherein n is 0.
13. A compound according to any one of claims 1 to 11, wherein n is 1.
- 15 14. A compound according to any one of claims 1 to 11, wherein n is 2.
15. A compound according to any one of claims 1 to 14, wherein ring A is selected from oxooxazolidinyl, and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.
- 20 16. A compound according to any one of claims 1 to 14, wherein ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl.
- 25 17. A compound according to any one of claims 1 to 14, wherein ring A is selected from oxopyrrolidinyl, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl, oxomorpholinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C₁-C₆ alkyl substituent; and wherein the C₁-C₆ alkyl substituent is optionally substituted with a C₁-C₆ alkoxy substituent.
- 30 18. A compound according to any one of claims 1 to 14, wherein ring A is selected from 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, 2-oxo-1,3-dioxolan-4-yl, 2-oxo-1,3-dioxan-4-yl, 3-oxomorpholin-5-yl and 2-oxo-1,3-oxazinan-6-yl.
- 35

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

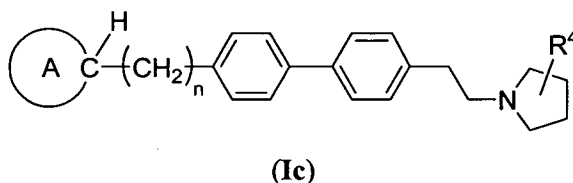


wherein:

- 5 R^4 is H or C_1 - C_4 alkyl;
 ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C_1 - C_6 alkyl substituent; and wherein the C_1 - C_6 alkyl substituent is optionally substituted with a C_1 - C_6 alkoxy substituent; and
 n is 0, 1 or 2.

10

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

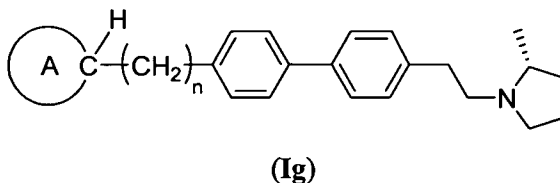


wherein:

- 15 R^4 is H or methyl;
 ring A is selected from 2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl and 2-oxo-1,3-oxazinan-4-yl; and
 n is 0, 1 or 2.

20

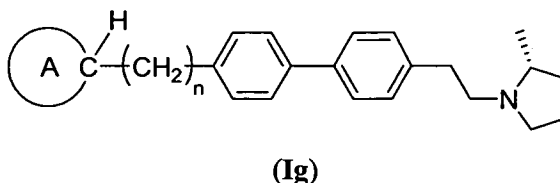
21. The compound according to claim 1, selected from compounds of Formula (Ig) and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

- 25 ring A is selected from oxooxazolidinyl and oxo-1,3-oxazinanyl; wherein each ring A is optionally substituted with a C_1 - C_6 alkyl substituent; and wherein the C_1 - C_6 alkyl substituent is optionally substituted with a C_1 - C_6 alkoxy substituent; and
 n is 0, 1 or 2.

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



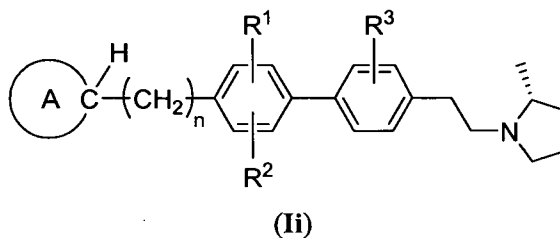
5 wherein:

ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl, 2-oxo-1,3-oxazinan-4-yl; and

n is 0, 1 or 2.

10

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



wherein:

15 R^1 , R^2 and R^3 are each independently selected from H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl and halogen;

ring A is selected from oxooxazolidinyl, oxo-1,3-oxazinanyl, oxopyrrolidinyl, oxo-1,3-dioxolanyl, oxo-1,3-dioxanyl, oxomorpholinyl and oxo-1,3-oxazinanyl;

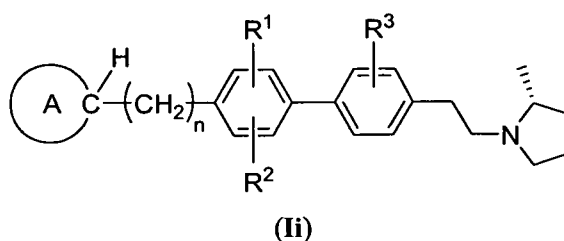
wherein each ring A is optionally substituted with a C_1 - C_6 alkyl substituent; and

20 wherein the C_1 - C_6 alkyl substituent is optionally substituted with a C_1 - C_6 alkoxy substituent; and

n is 0, 1 or 2.

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

25



wherein:

R^1 , R^2 and R^3 are each independently selected from H, methoxy, methyl, chloro and fluoro;

5 ring A is selected from 2-oxooxazolidin-4-yl, 3-methyl-2-oxooxazolidin-4-yl, 3-isopropyl-2-oxooxazolidin-4-yl, 3-(2-methoxyethyl)-2-oxooxazolidin-4-yl, 2-oxooxazolidin-5-yl, 2-oxo-1,3-oxazinan-4-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, 2-oxo-1,3-dioxolan-4-yl, 2-oxo-1,3-oxazinan-6-yl, 2-oxo-1,3-dioxan-4-yl and 3-oxomorpholin-5-yl; and

10 n is 0, 1 or 2.

25. A compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates and hydrates thereof:

15 (*S*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;

(*S*)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;

(*R*)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;

(*R*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;

20 (*R*)-3-methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;

(*R*)-3-(2-methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;

25 (*R*)-3-isopropyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;

(*R*)-3-methyl-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;

(*R*)-3-(2-methoxyethyl)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;

30 (*R*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one;

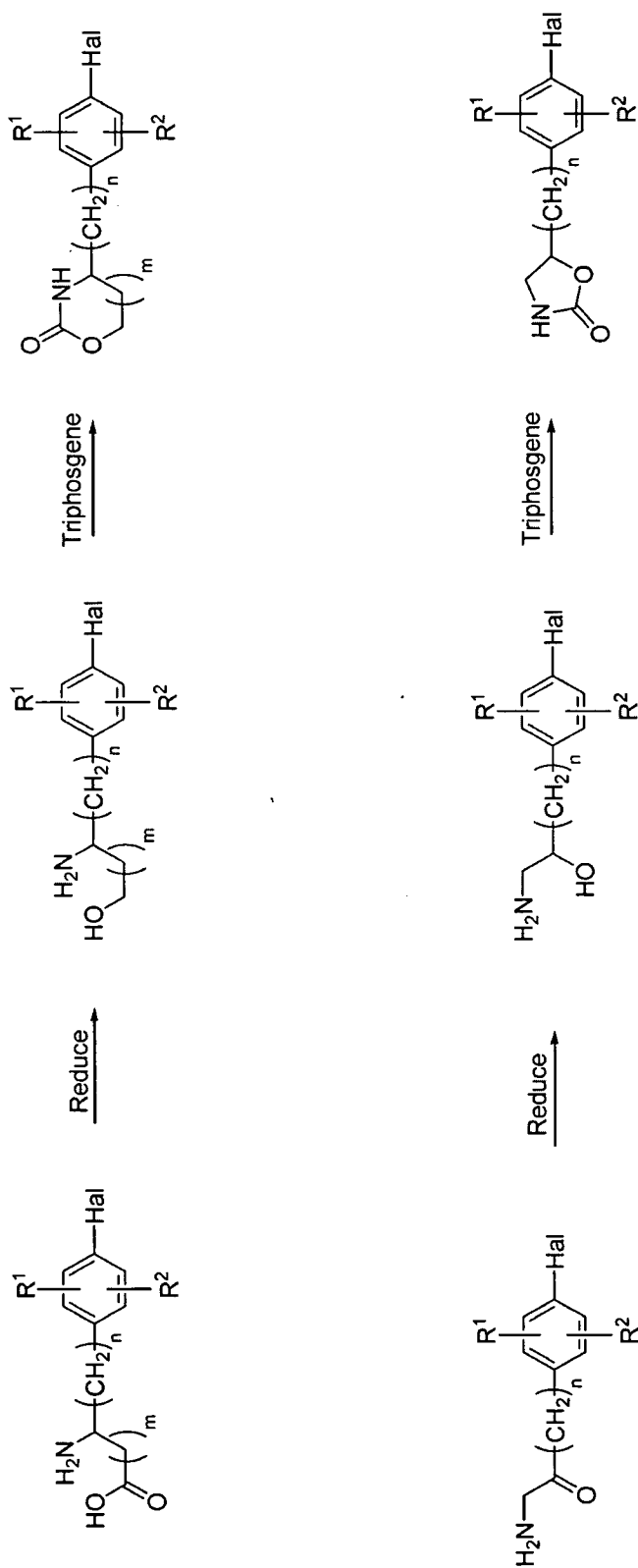
(*S*)-3-methyl-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;

- (*S*)-3-(2-methoxyethyl)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)oxazolidin-2-one;
- (*S*)-4-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)methyl)-1,3-oxazinan-2-one;
- 5 5-((4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*S*)-3-methyl-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*S*)-3-(2-methoxyethyl)-4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one; and
- 10 (*R*)-4-(4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.
26. A compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates and hydrates thereof:
- 15 (*R*)-4-(2,6-dichloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*R*)-4-(2-methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*R*)-4-(2-chloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- 20 (*R*)-4-(2-methoxy-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*R*)-4-(2'-chloro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- (*R*)-4-(3'-fluoro-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- 25 4-(3-methyl-4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- 4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one;
- 4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxolan-2-one;
- 30 6-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one;
- 4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-oxazinan-2-one;
- 4-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)-1,3-dioxan-2-one;
- 5-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)pyrrolidin-2-one;
- 5-(4'-(2-((*R*)-2-methylpyrrolidin-1-yl)ethyl)biphenyl-4-yl)morpholin-3-one;
- 35 (*S*)-4-(2'-methyl-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one;
- and
- (*S*)-4-(2'-methoxy-4'-(2-(pyrrolidin-1-yl)ethyl)biphenyl-4-yl)oxazolidin-2-one.

27. A pharmaceutical composition comprising a compound according to any one of claims 1 to 26 and a pharmaceutically acceptable carrier.
- 5 28. A method for treating a histamine H3-receptor associated disorder 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 26 or a pharmaceutical composition according to claim 27.
- 10 29. A method according to claim 28, wherein said histamine H3-receptor associated disorder is selected from a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea and the like, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, 15 allergic rhinitis, nasal congestion, dementia, Alzheimer's disease and pain.
30. A method according to claim 28, wherein said histamine H3-receptor associated disorder is a disorder of sleep and wakefulness.
- 20 31. A method according to claim 28, wherein said histamine H3-receptor associated disorder is a cognitive disorder.
32. A method according to claim 28, wherein said histamine H3-receptor associated disorder is cataplexy. 25
33. A method of inducing wakefulness 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 26 or a pharmaceutical composition according to claim 27.
- 30 34. A method for treating pain 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 26 or a pharmaceutical composition according to claim 27.
- 35 35. Use of a compound according to any one of claims 1 to 26 in the manufacture of a medicament for the treatment of a histamine H3-receptor associated disorder.

36. Use of a compound according to any one of claims 1 to 26 in the manufacture of a medicament for the treatment of a disorder selected from a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea and the like,
5 attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease and pain.
37. Use of a compound according to any one of claims 1 to 26 in the manufacture of a
10 medicament for the treatment of a disorder of sleep and wakefulness.
38. Use of a compound according to any one of claims 1 to 26 in the manufacture of a medicament for the treatment of a cognitive disorder.
39. Use of a compound according to any one of claims 1 to 26 in the manufacture of a
15 medicament for the treatment of cataplexy.
40. Use of a compound according to any one of claims 1 to 26 in the manufacture of a
20 medicament for inducing wakefulness.
41. Use of a compound according to any one of claims 1 to 26 in the manufacture of a medicament for the treatment of pain.
42. A compound according to any one of claims 1 to 26 for use in a method of treatment of
25 the human or animal body by therapy.
43. A compound according to any one of claims 1 to 26 for use in a method for the treatment of a histamine H3-receptor associated disorder.
44. A compound according to any one of claims 1 to 26 for use in a method for the
30 treatment of a histamine H3-receptor associated disorder selected from a cognitive disorder, epilepsy, brain trauma, depression, obesity, disorders of sleep and wakefulness, narcolepsy, cataplexy, hypersomnia, somnolence syndrome, jet lag, sleep apnea, attention deficit hyperactivity disorder (ADHD), schizophrenia, allergies, allergic
35 responses in the upper airway, allergic rhinitis, nasal congestion, dementia, Alzheimer's disease and pain.

45. A compound according to any one of claims 1 to 26 for use in a method for the treatment of a disorder of sleep and wakefulness.
- 5 46. A compound according to any one of claims 1 to 26 for use in a method for the treatment of a cognitive disorder.
47. A compound according to any one of claims 1 to 26 for use in a method for the treatment of cataplexy.
- 10 48. A compound according to any one of claims 1 to 26 for use in a method of inducing wakefulness.
49. A compound according to any one of claims 1 to 26 for use in a method of treating pain.
- 15 50. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 26 and a pharmaceutically acceptable carrier.

**Figure 1**

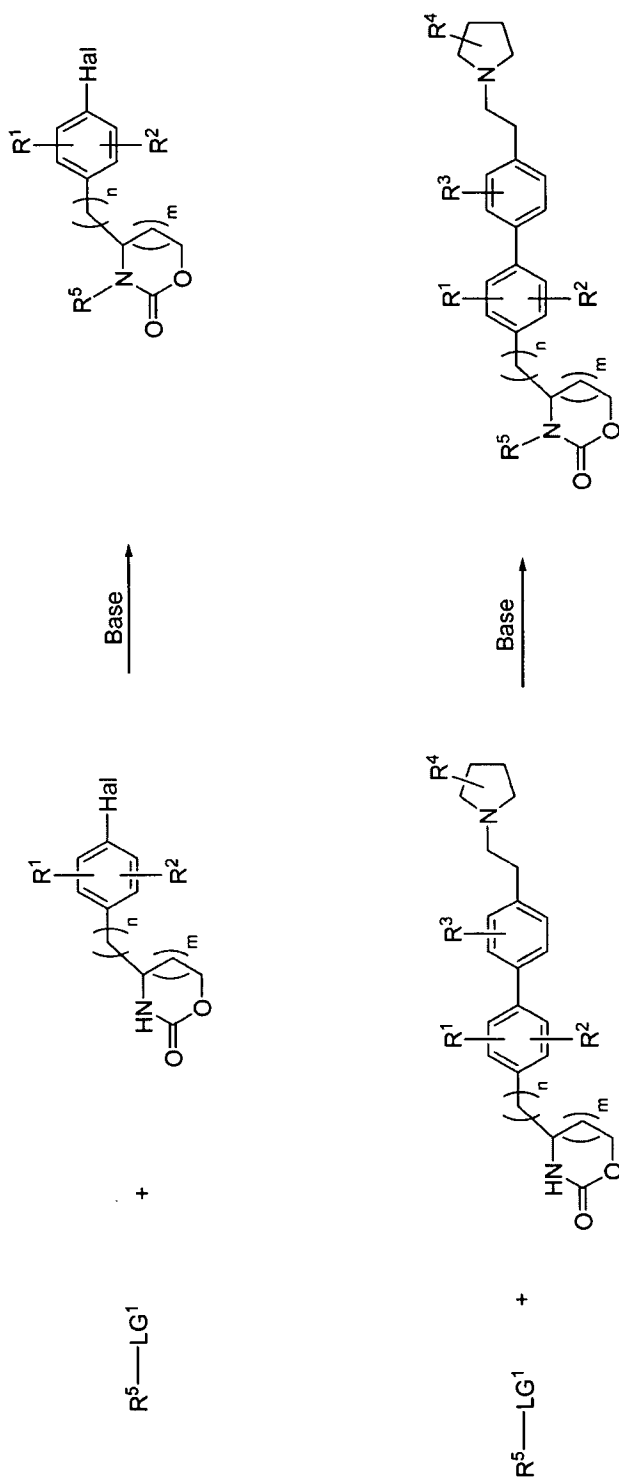
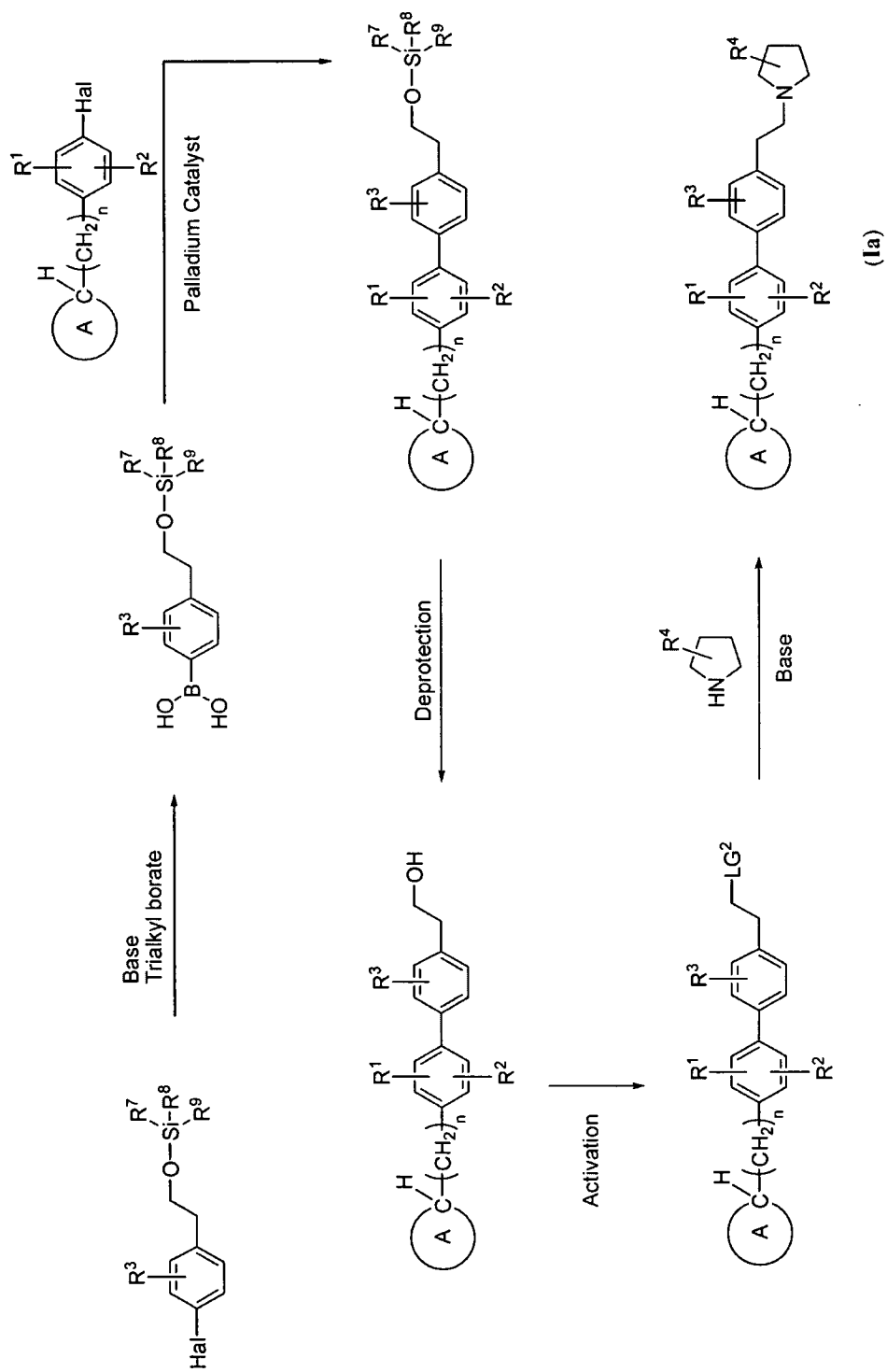


Figure 2



R^7 , R^8 and R^9 are each independently C_1 - C_6 alkyl or aryl.
 Hal = halogen
 LG^2 = for example, halide, sulfonate ester and the like.

Figure 3

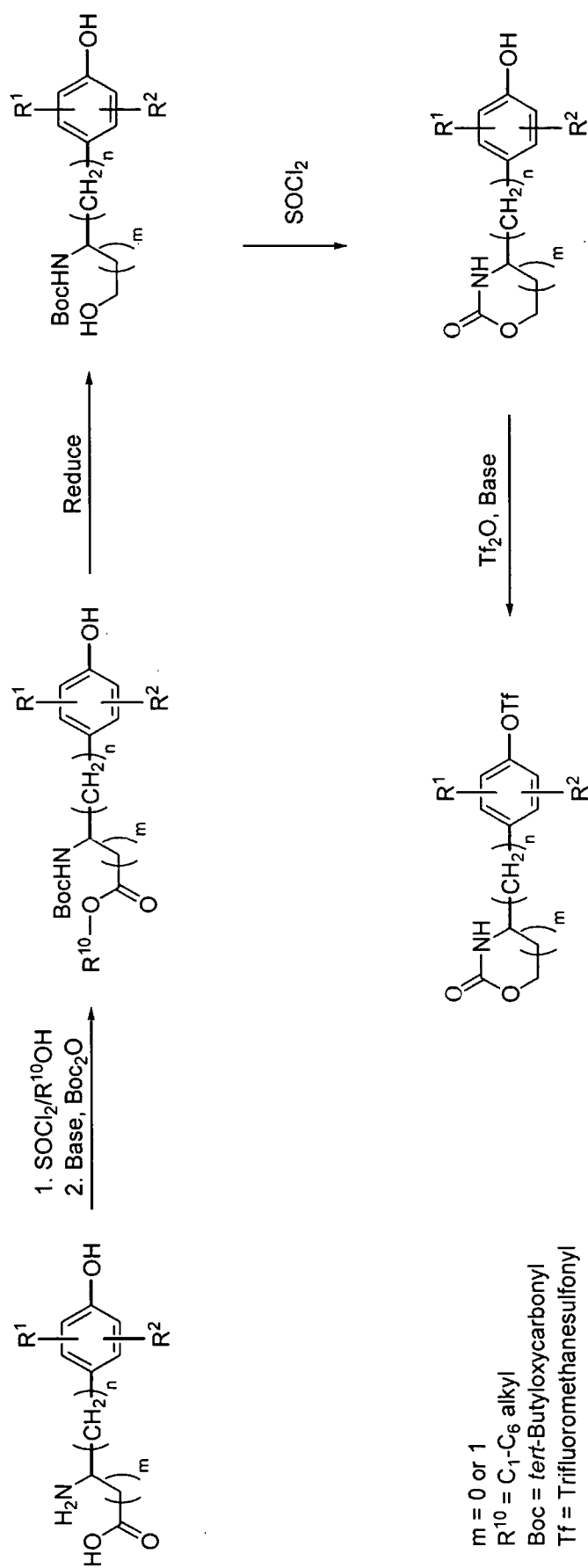


Figure 4

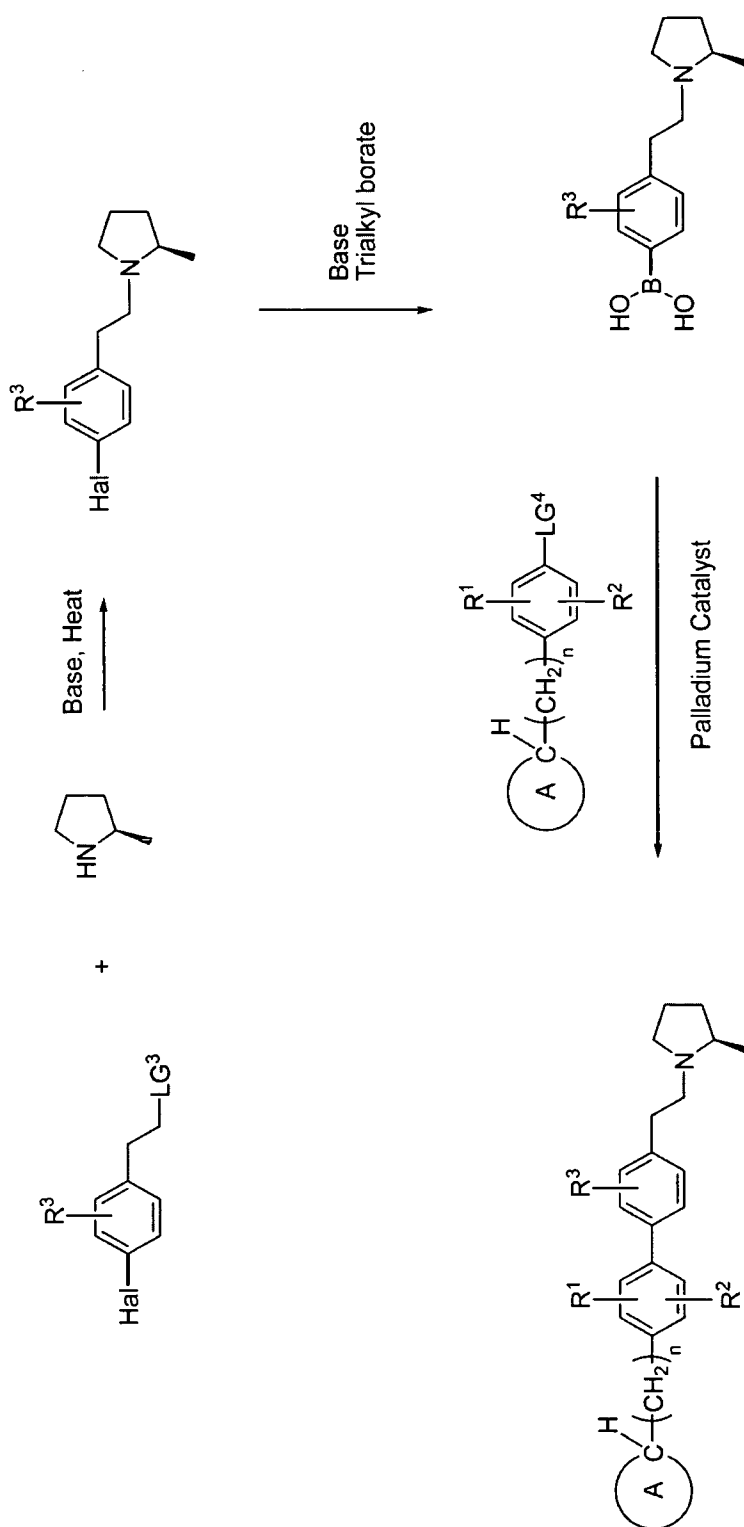


Figure 5

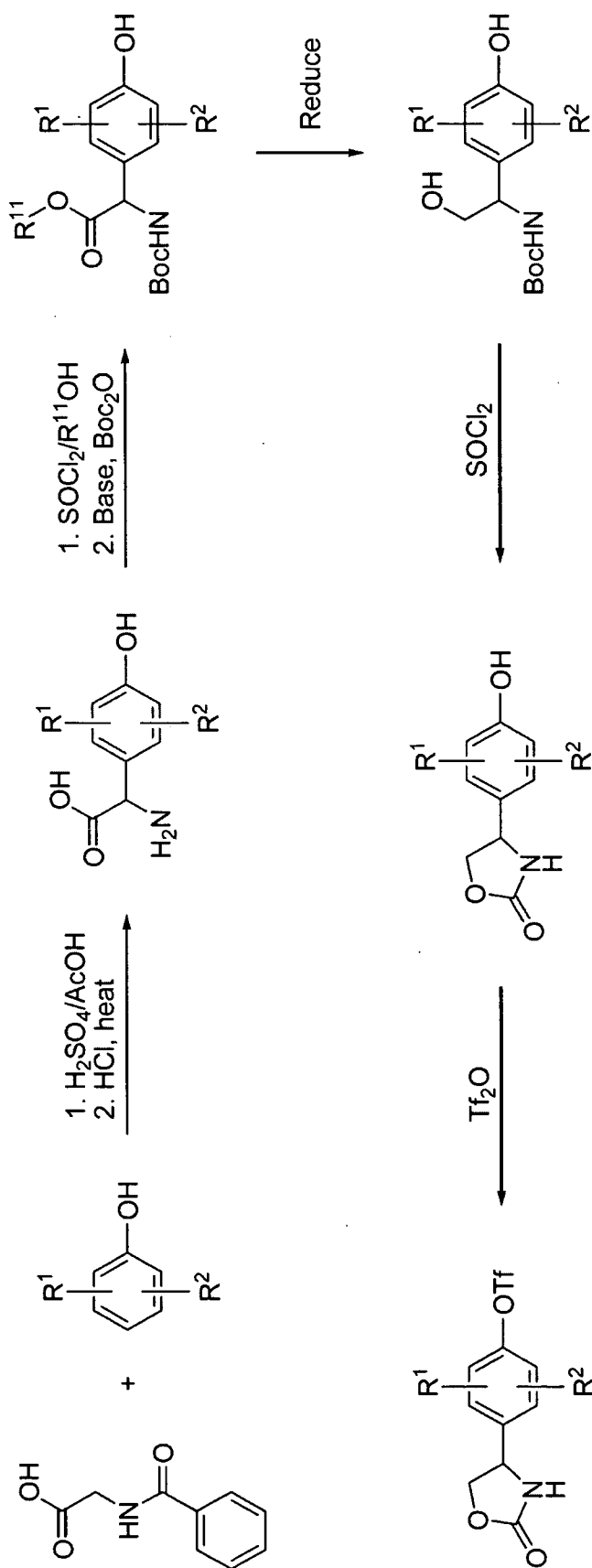


Figure 6

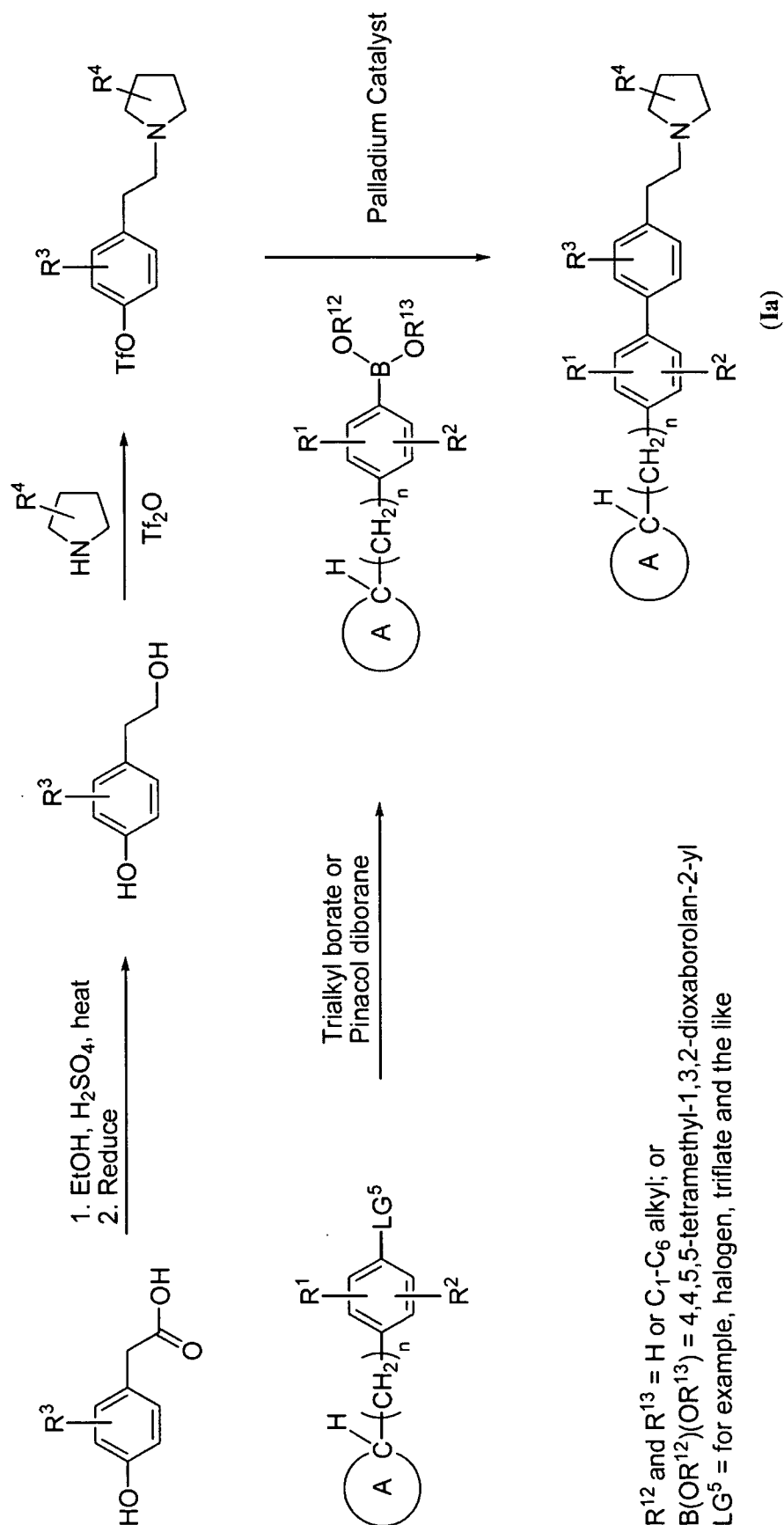
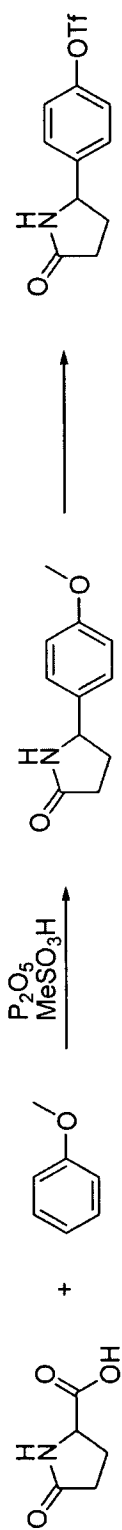
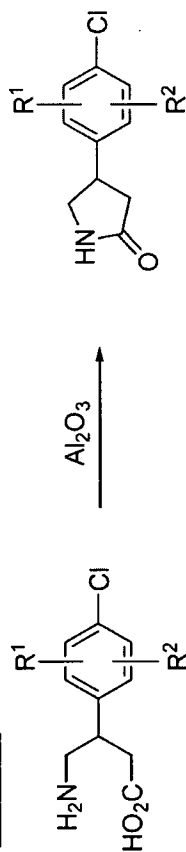
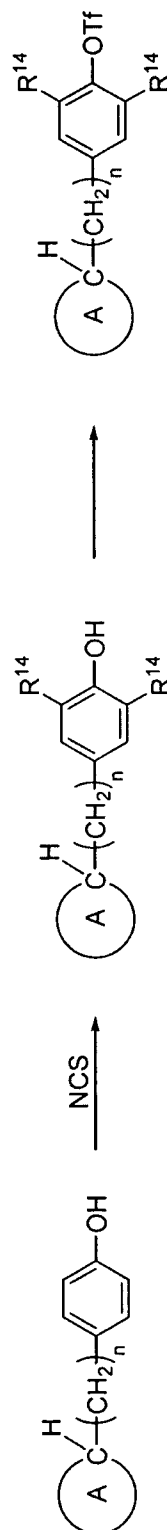
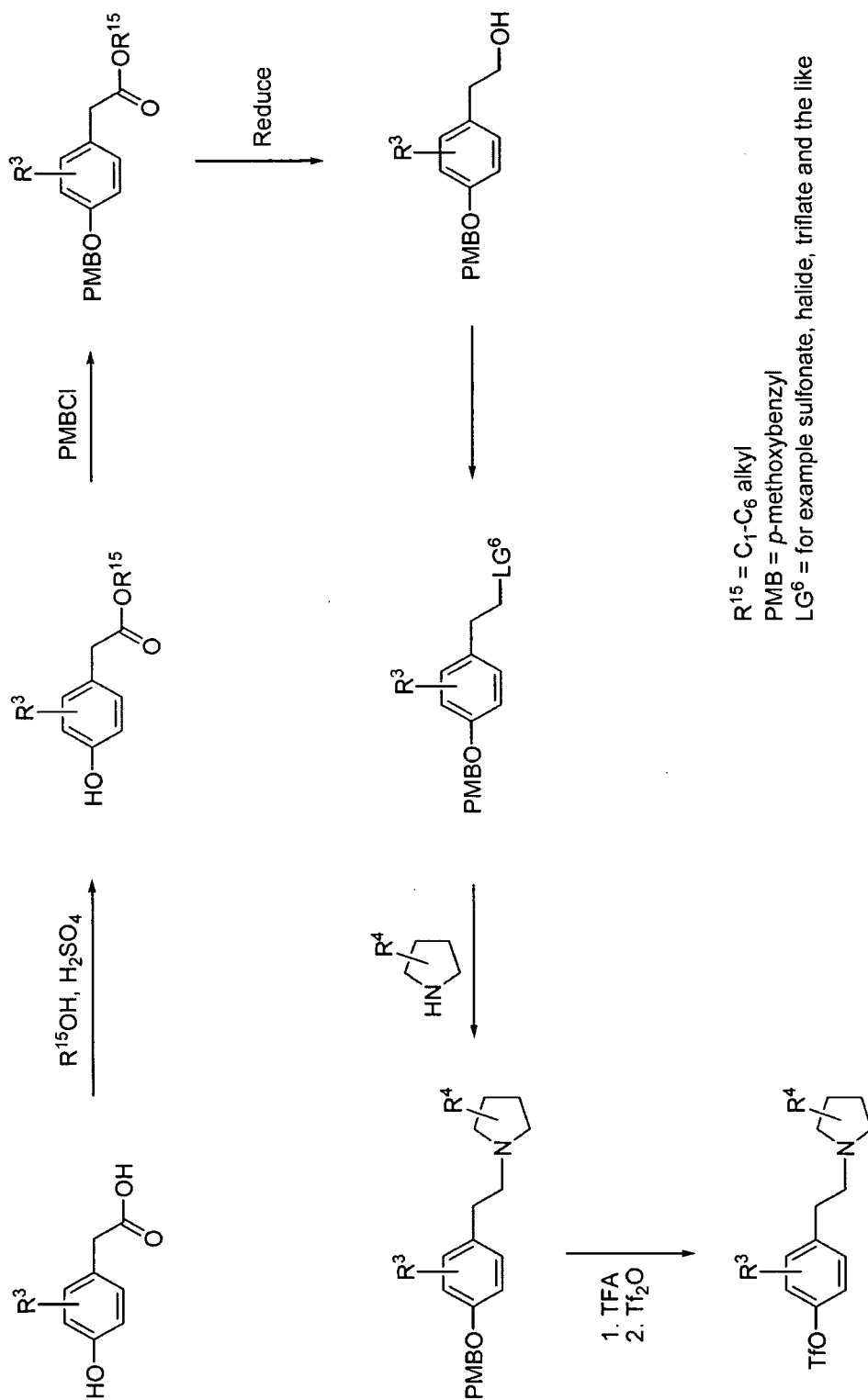


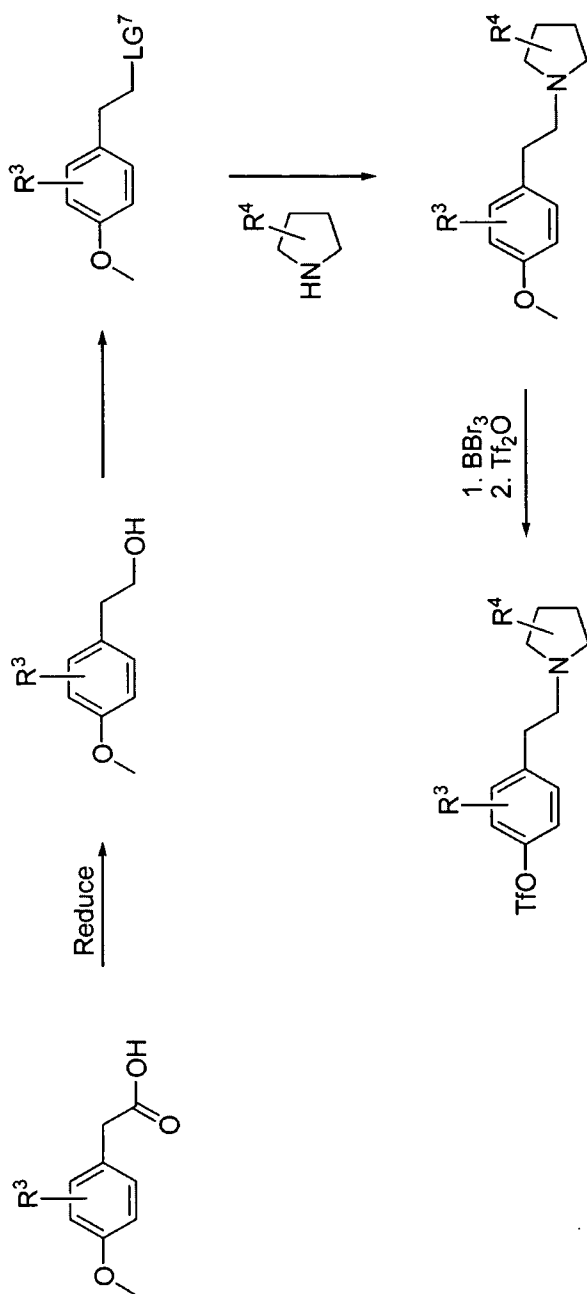
Figure 7

Method 1**Method 2****Method 3**

each R^{14} is independently selected from H and Cl

Figure 8

**Figure 9**



LG^7 = for example sulfonate, halide, triflate and the like

Figure 10

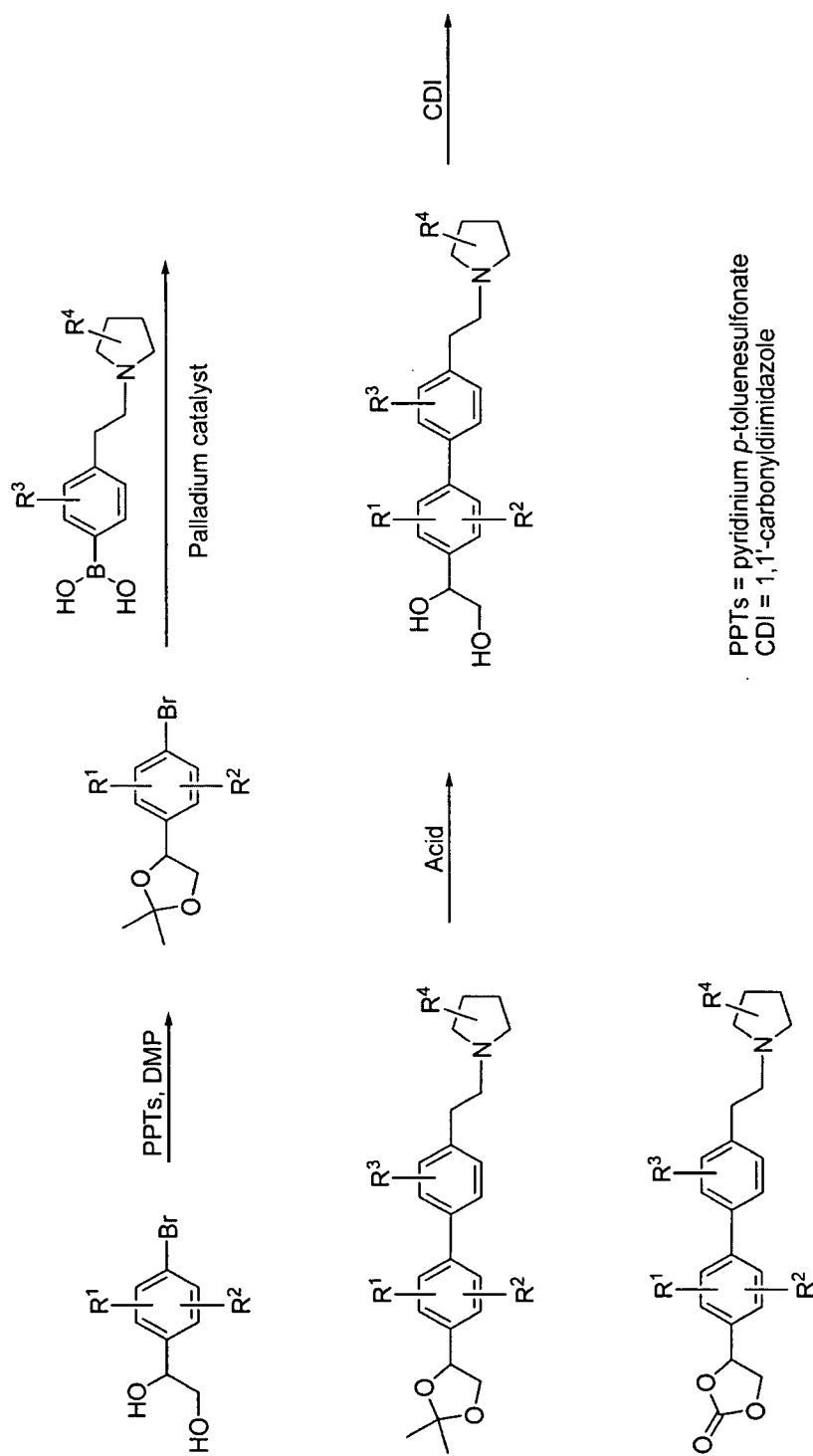
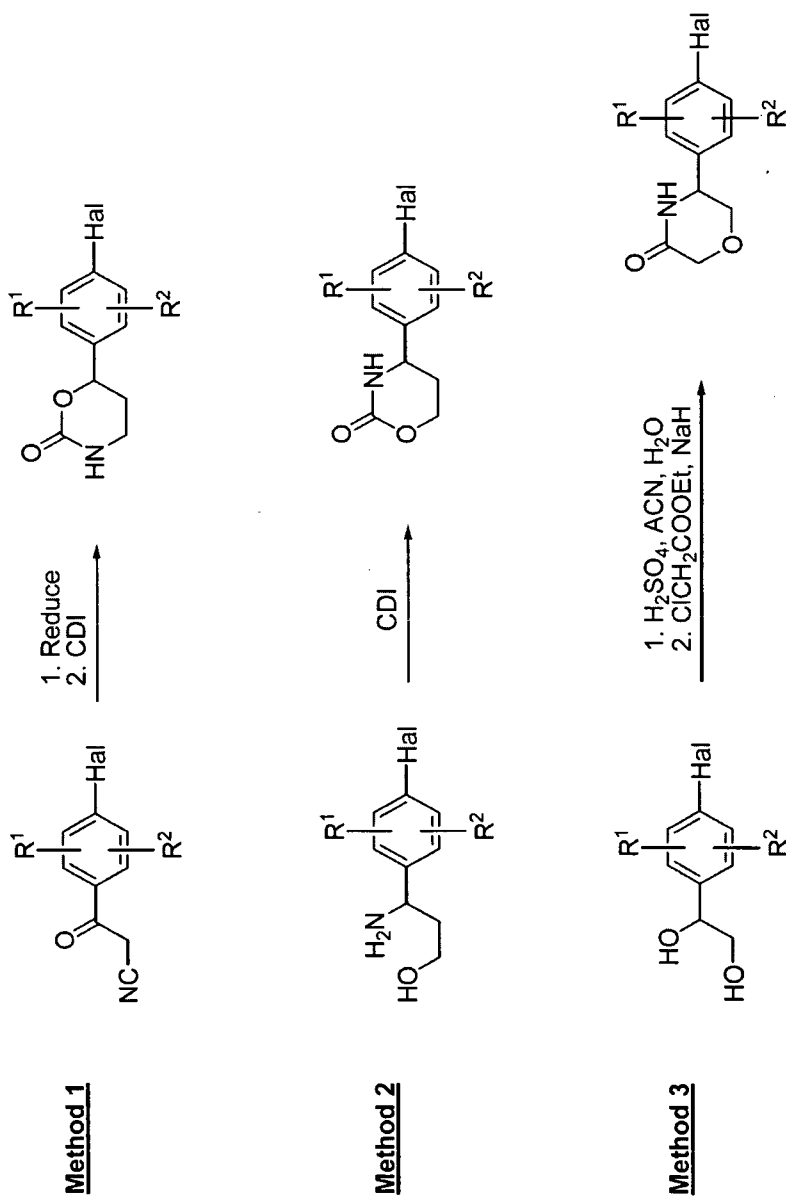
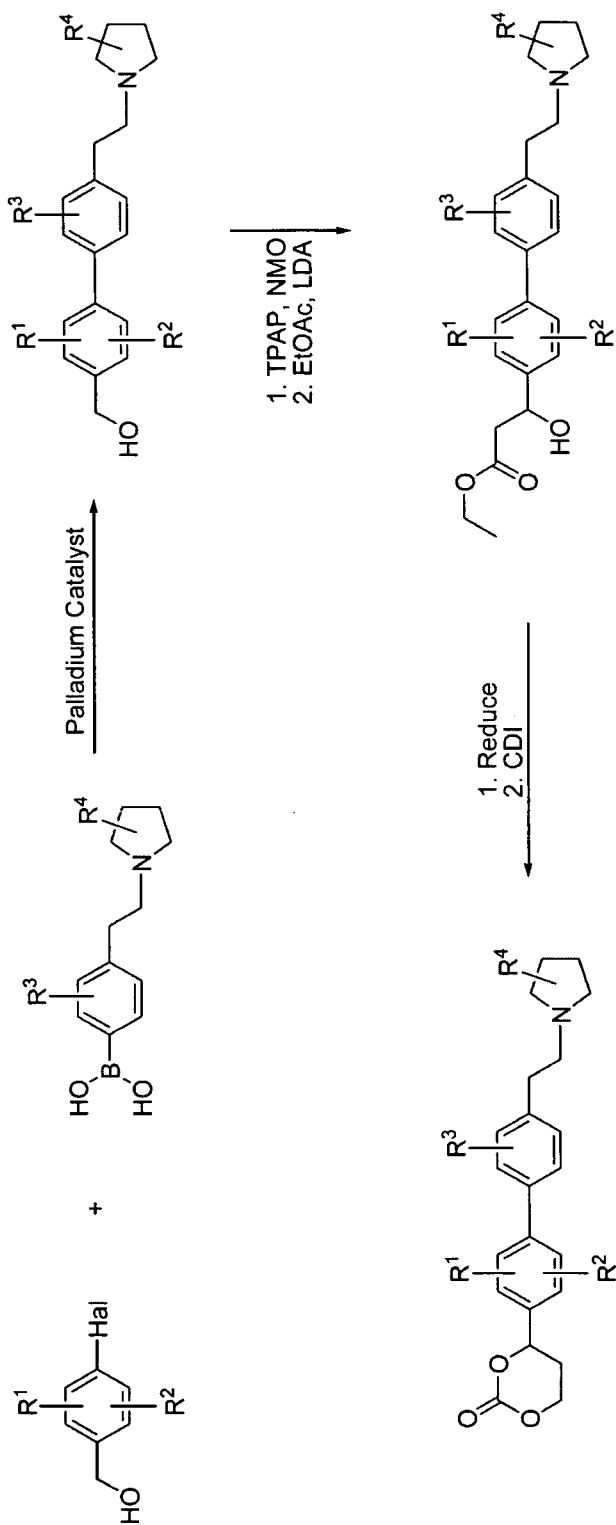


Figure 11

**Figure 12**



Hal = Halogen
CDI = 1,1'-carbonyldiimidazole

Figure 13

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/012272

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/10 C07D405/10 C07D413/10 A61K31/422 A61K31/4025
 A61K31/5355 A61P37/08

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 practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/245543 A1 (HOWARD HARRY R [US] ET AL) 3 November 2005 (2005-11-03) abstract; examples 1-9,20,24,25,38,70-79 -----	1-50
A	WO 2006/011042 A (PFIZER PROD INC [US]; HOWARD HARRY RALPH JR [US]; WLODECKI BISHOP [US]) 2 February 2006 (2006-02-02) abstract; examples 13,14 -----	1-50
A	MORINI G ET AL: "Dibasic non-imidazole histamine H3 receptor antagonists with a rigid biphenyl scaffold" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 16, no. 15, 1 August 2006 (2006-08-01), pages 4063-4067, XP025107130 ISSN: 0960-894X [retrieved on 2006-08-01] abstract; compound 17 -----	1-50



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

21 January 2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/012272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005245543 A1	03-11-2005	NONE	
WO 2006011042 A	02-02-2006	BR PI0513486 A CA 2574361 A1 EP 1771438 A1 JP 2008506765 T	06-05-2008 02-02-2006 11-04-2007 06-03-2008