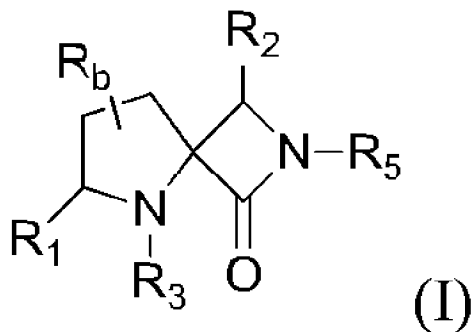




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(54) Titre : MODULATEURS SPIROLACTAMES D'UN RECEPTEUR NMDA ET LEURS UTILISATIONS  
(54) Title: SPIRO-LACTAM NMDA RECEPTOR MODULATORS AND USES THEREOF



(57) **Abrégé/Abstract:**

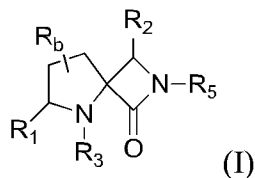
Disclosed are compounds having enhanced potency in the modulation of NMDA receptor activity. Such compounds are contemplated for use in the treatment of conditions such as depression and related disorders. Orally available formulations and other pharmaceutically acceptable delivery forms of the compounds, including intravenous formulations, are also disclosed. Such compounds include compounds of the Formula (I):

(see formula I)

or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

## ABSTRACT

Disclosed are compounds having enhanced potency in the modulation of NMDA receptor activity. Such compounds are contemplated for use in the treatment of conditions such as depression and related disorders. Orally available formulations and other pharmaceutically acceptable delivery forms of the compounds, including intravenous formulations, are also disclosed. Such compounds include compounds of the Formula (I):



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

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**SPIRO-LACTAM NMDA RECEPTOR MODULATORS AND USES THEREOF****CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of United States Provisional Application No. 61/757,920, filed on January 29, 2013.

**BACKGROUND**

[0002] An N-methyl-d-aspartate (NMDA) receptor is a postsynaptic, ionotropic receptor that is responsive to, *inter alia*, the excitatory amino acids glutamate and glycine and the  
5 synthetic compound NMDA. The NMDA receptor controls the flow of both divalent and monovalent ions into the postsynaptic neural cell through a receptor associated channel (Foster *et al.*, Nature 1987, 329:395-396; Mayer *et al.*, Trends in Pharmacol. Sci. 1990, 11:254-260). The NMDA receptor has been implicated during development in specifying neuronal architecture and synaptic connectivity, and may be involved in experience-dependent synaptic  
10 modifications. In addition, NMDA receptors are also thought to be involved in long term potentiation and central nervous system disorders.

[0003] The NMDA receptor plays a major role in the synaptic plasticity that underlies many higher cognitive functions, such as memory acquisition, retention and learning, as well as in certain cognitive pathways and in the perception of pain (Collingridge *et al.*, The NMDA  
15 Receptor, Oxford University Press, 1994). In addition, certain properties of NMDA receptors suggest that they may be involved in the information-processing in the brain that underlies consciousness itself.

[0004] The NMDA receptor has drawn particular interest since it appears to be involved in a broad spectrum of CNS disorders. For instance, during brain ischemia caused by stroke or  
20 traumatic injury, excessive amounts of the excitatory amino acid glutamate are released from damaged or oxygen deprived neurons. This excess glutamate binds to the NMDA receptors which opens their ligand-gated ion channels; in turn the calcium influx produces a high level of intracellular calcium which activates a biochemical cascade resulting in protein degradation and cell death. This phenomenon, known as excitotoxicity, is also thought to be responsible for

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the neurological damage associated with other disorders ranging from hypoglycemia and cardiac arrest to epilepsy. In addition, there are preliminary reports indicating similar involvement in the chronic neurodegeneration of Huntington's, Parkinson's, and Alzheimer's diseases. Activation of the NMDA receptor has been shown to be responsible for post-stroke  
5 convulsions, and, in certain models of epilepsy, activation of the NMDA receptor has been shown to be necessary for the generation of seizures. Neuropsychiatric involvement of the NMDA receptor has also been recognized since blockage of the NMDA receptor  $\text{Ca}^{++}$  channel by the animal anesthetic PCP (phencyclidine) produces a psychotic state in humans similar to schizophrenia (reviewed in Johnson, K. and Jones, S., 1990). Further, NMDA receptors have  
10 also been implicated in certain types of spatial learning.

[0005] The NMDA receptor is believed to consist of several protein chains embedded in the postsynaptic membrane. The first two types of subunits discovered so far form a large extracellular region, which probably contains most of the allosteric binding sites, several transmembrane regions looped and folded so as to form a pore or channel, which is permeable  
15 to  $\text{Ca}^{++}$ , and a carboxyl terminal region. The opening and closing of the channel is regulated by the binding of various ligands to domains (allosteric sites) of the protein residing on the extracellular surface. The binding of the ligands is thought to affect a conformational change in the overall structure of the protein which is ultimately reflected in the channel opening, partially opening, partially closing, or closing.

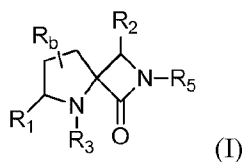
20 [0006] NMDA receptor compounds may exert dual (agonist/antagonist) effect on the NMDA receptor through the allosteric sites. These compounds are typically termed "partial agonists". In the presence of the principal site ligand, a partial agonist will displace some of the ligand and thus decrease  $\text{Ca}^{++}$  flow through the receptor. In the absence of or lowered level of the principal site ligand, the partial agonist acts to increase  $\text{Ca}^{++}$  flow through the receptor  
25 channel.

[0007] A need continues to exist in the art for novel and more specific/potent compounds that are capable of binding the glycine binding site of NMDA receptors, and provide pharmaceutical benefits. In addition, a need continues to exist in the medical arts for orally deliverable forms of such compounds.

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## SUMMARY

[0008] Provided herein, at least in part, are compounds that are NMDA modulators, for example, partial agonists of NMDA. For example, disclosed herein are compounds represented by the formula:



5 and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of phenyl, a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, or a 4- to 6-membered heterocyclyl ring having 1, 2, or 3 heteroatoms selected from O, S, or

15 N, and wherein X is optionally substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy;

or, in other embodiments, the variables set forth in formula (I) are defined as follows:

R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl;

20 R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;


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R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of:

(i) phenyl;

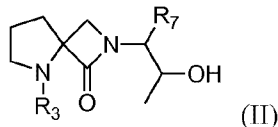
(ii) heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and S; and

5 (iii) heterocyclyl including from 3 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and S;

wherein R<sub>5</sub> is optionally substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

10 [0009] Also disclosed herein are compounds represented by the formula:

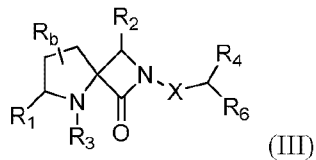


and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>alkyl and a nitrogen protecting group; and

15 R<sub>7</sub> is a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted on a free carbon by a substituent selected from the group consisting of: halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, hydroxyl, cyano, and phenyl.

[0010] Also provided herein are compounds represented by the formula:



and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

20 R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;


R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;

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R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

X is selected from the group consisting of phenyl, a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, or a 4- to 6-membered heterocyclyl ring having 1,

2, or 3 heteroatoms selected from O, S, or N, wherein  is present on a free carbon of X;

5 and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

[0011] Also provided herein are pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. For example, such  
10 compositions may be suitable for oral or intravenous administration to a patient.

[0012] In another aspect, a method of treating a condition selected from the group consisting of autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder, phobia, post-traumatic stress  
15 syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder, a sleep disorder, a memory disorder, a learning disorder, urinary incontinence, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivio-ponto-cerebellar atrophy, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS dementia,  
20 Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy, spinal cord injury, peripheral neuropathy, acute neuropathic pain, and chronic neuropathic, in a patient in need thereof is provided. Such methods may comprise administering to the patient a pharmaceutically effective amount of a disclosed compound or  
25 pharmaceutically acceptable salts, stereoisomers, N-oxides, and hydrates thereof.

[0013] In some embodiments, a contemplated method includes treating depression. For example, depression may include one or more of major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, seasonal affective disorder, bipolar disorder, mood disorder, or depression caused by a chronic medical condition. In other  
30 embodiments, a contemplated method may treat schizophrenia. Such schizophrenia may be,

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for example, paranoid type schizophrenia, disorganized type schizophrenia, catatonic type schizophrenia, undifferentiated type schizophrenia, residual type schizophrenia, post-schizophrenic depression, or simple schizophrenia.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **Figure 1** shows the potentiation of [<sup>3</sup>H]MK-801 binding in the presence of  
5 Compound Y.

#### DETAILED DESCRIPTION

[0015] This disclosure is generally directed to compounds that are capable of modulating NMDA, e.g., NMDA antagonists or partial agonists, and compositions and/or methods of using the disclosed compounds.

#### Definitions

10 [0016] “Treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0017] The term “alkenyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein for example as C<sub>2</sub>-C<sub>6</sub> alkenyl, and C<sub>3</sub>-C<sub>4</sub>  
15 alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[0018] The term “alkoxy” as used herein refers to a straight or branched alkyl group attached to an oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxys of 1-6 or 2-6 carbon atoms, referred to herein as C<sub>1</sub>-C<sub>6</sub> alkoxy, and C<sub>2</sub>-C<sub>6</sub> alkoxy,  
20 respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[0019] The term “alkenyloxy” used herein refers to a straight or branched alkenyl group attached to an oxygen (alkenyl-O). Exemplary alkenyloxy groups include, but are not limited to, groups with an alkenyl group of 3-6 carbon atoms, (also e.g. referred to as C<sub>3</sub>-C<sub>6</sub> alkenyloxy).  
25 Exemplary “alkenyloxy” groups include, but are not limited to allyloxy, butenyloxy, etc.

[0020] The term “alkynyloxy” used herein refers to a straight or branched alkynyl group attached to an oxygen (alkynyl-O)). Exemplary alkynyloxy groups include, but are not limited to, C<sub>3</sub>-C<sub>6</sub> alkynyloxy, e.g., propynyloxy.



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[0021] The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>3</sub> alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc. The term “haloalkyl” as used herein refers to a saturated straight or branched alkyl groups, in which one or more hydrogen atoms of the alkyl group are replaced with one or more independently selected halogens. The term “haloalkyl” encompasses alkyl groups in which all of hydrogen atoms of the alkyl group are replaced independently selected halogens (sometimes referred to as “perhalo” alkyl groups. Exemplary haloalkyl groups include, but are not limited to, CH<sub>2</sub>F, CH<sub>2</sub>CH<sub>2</sub>Cl, CF<sub>3</sub>, CHFCH<sub>2</sub>Cl.

[0022] The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-6, or 3-6 carbon atoms, referred to herein as C<sub>2</sub>-C<sub>6</sub> alkynyl, and C<sub>3</sub>-C<sub>6</sub> alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[0023] The term “bridged cycloalkyl”, as used herein, is defined as a monocyclic 4- to 7-membered cycloalkyl group in which two non-adjacent atoms are linked by a CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub> group. A “bridged cycloalkyl” may be fused to one or more phenyl, partially unsaturated, or saturated rings. Examples of bridged carbocyclic groups include but are not limited to bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[2.2.2]octene etc.

[0024] The term “carbonyl” as used herein refers to the radical -C(O)-. The term “cyano” as used herein refers to the radical -CN. The term “nitro” refers to the radical -NO<sub>2</sub>. The term “H” refers to hydrogen.

[0025] The term “cycloalkoxy” as used herein refers to a cycloalkyl group attached to an oxygen (cycloalkyl-O-).

[0026] The term “cycloalkyl” as used herein refers to a monocyclic saturated or partially unsaturated hydrocarbon group of for example 3-6, or 4-6 carbons, referred to herein, e.g., as “C<sub>3-6</sub> cycloalkyl” or “C<sub>4-6</sub> cycloalkyl,” and derived from a cycloalkane. Exemplary cycloalkyl

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groups include, but are not limited to, cyclohexyl, cyclohexenyl, cyclopentyl, cyclobutyl, cyclopropyl or cyclopentyl.

[0027] The terms “halo” or “halogen” as used herein refer to F, Cl, Br, or I.

[0028] The terms “heteroaryl” as used herein refers to a monocyclic aromatic 4-6  
5 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, said heteroaryl ring may be linked to the adjacent radical through carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, imidazolyl, pyrazolyl, triazolyl, oxadiazolyl (e.g., 1,2,4- oxadiazolyl or 1,3,4- oxadiazolyl),  
10 pyridyl, and pyrimidinyl.

[0029] The terms “heterocyclyl” or “heterocyclic group” are art-recognized and refer to saturated or partially unsaturated 4- to 7-membered ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. A heterocycle may be fused to one or more phenyl, partially unsaturated, or saturated rings. Examples of heterocyclyl  
15 groups include but are not limited to pyrrolidinyl, piperidinyl, morpholino, thiomorpholino, and piperazinyl.

[0030] The term “heterocyclylalkoxy” as used herein refers to a heterocyclyl- alkyl-O- group.

[0031] The term “heterocyclylalkoxyalkyl” refers to a heterocyclyl-O-alkyl- group.

20 [0032] The term “heterocycloxy” refers to a heterocyclyl-O- group. The term “cycloalkoxy” refers to a cycloalkyl-O- group.

[0033] The term “heteroaryloxy” refers to a heteroaryl-O- group.

[0034] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.

[0035] The term “oxo” as used herein refers to the radical =O.

25 [0036] The term “nitrogen protecting group” or “amino protecting group” is art-recognized and as used herein refers to a chemical moiety that is covalently linked to a nitrogen atom of an amino (primary or secondary) group and that temporarily blocks the reactivity of the amino group during a synthetic step and is selectively removed once the synthetic step is complete. Nitrogen protecting groups include, for example, 9-Fluorenylmethyloxycarbonyl (Fmoc), tert-  
30 butoxycarbonyl (Boc), carbobenzyloxycarbonyl (Cbz), p-methoxybenzyloxycarbonyl, acetyl,

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- trifluoroacetyl, benzoyl, phthalimido, benzyl (Bn), p-methoxybenzyl, p-methoxyphenyl, 3,4-dimethoxybenzyl, triphenylmethyl, benzylidene, and p-toluenesulfonyl (Ts). In some embodiments, the nitrogen protecting group can have one of the following formulas: – C(O)OR<sub>31</sub> or –C(O)R<sub>32</sub> as defined herein. In certain embodiments, R<sub>31</sub> is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl, wherein the C<sub>3</sub>-C<sub>10</sub> cycloalkyl is optionally substituted with from 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkyl; –CH<sub>2</sub>-C<sub>3</sub>-C<sub>10</sub> cycloalkyl wherein the C<sub>3</sub>-C<sub>10</sub> cycloalkyl is optionally substituted with from 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkyl; –CH<sub>2</sub>-phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy, nitro, halo, SO<sub>2</sub>Me, cyano, and –OC(O)CH<sub>3</sub>; and –CH<sub>2</sub>-pyridyl. In certain embodiments, R<sub>32</sub> is selected from the group consisting of: H; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> haloalkyl; phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy, nitro, halo, SO<sub>2</sub>Me, cyano, and –OC(O)CH<sub>3</sub>; and pyridyl.
- 15 **[0037]** As used in the present disclosure, the term “partial NMDA receptor agonist” generally refers to a compound that is capable of binding to a glycine binding site of an NMDA receptor; at low concentrations a NMDA receptor agonist acts substantially as agonist and at high concentrations it acts substantially as an antagonist. These concentrations are experimentally determined for each and every “partial agonist.”
- 20 **[0038]** “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.
- 25 **[0039]** The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing
- 30 supplemental, additional, or enhanced therapeutic functions.

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[0040] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[0041] “Individual,” “patient,” or “subject” are used interchangeably and include any  
5 animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and  
10 laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). The mammal treated in the methods of the invention is desirably a mammal in which treatment *e.g.*, of pain or depression is desired. “Modulation” includes antagonism (*e.g.*, inhibition), agonism, partial antagonism and/or partial agonism.


[0042] In the present specification, the term “therapeutically effective amount” means the  
15 amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the invention are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an  
20 amount which results in lessening a symptom of depression.

[0043] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to  
25 prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate,  
30 glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature

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are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[0044] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term “stereoisomers” when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0045] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as geometric isomers, enantiomers or diastereomers. The enantiomer and diastereomers may be designated by the symbols “(+),” “(-).” “R” or “S,” depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocyclic ring, can also exist in the compounds of the present invention. The symbol  denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as “cis” or “trans.” The term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring.

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Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0046] The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. The present invention encompasses various stereoisomers of these compounds and mixtures thereof.

[0047] Individual enantiomers and diastereomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[0048] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[0049] The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the

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invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

**[0050]** Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with  $^3\text{H}$  and  $^{14}\text{C}$ ) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*,  $^3\text{H}$ ) and carbon-14 (*i.e.*,  $^{14}\text{C}$ ) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the *e.g.*, Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

**[0051]** The term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound.

The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al*, Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>12</sub>)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>2</sub>-C<sub>3</sub>)alkyl (such as  $\beta$ -dimethylaminoethyl), carbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl, N,N-di(C<sub>1</sub>-C<sub>2</sub>)alkylcarbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl and piperidino-, pyrrolidino- or morpholino(C<sub>2</sub>-C<sub>3</sub>)alkyl.

**[0052]** Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a

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group such as (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxymethyl, 1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl, 1-methyl-1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyloxymethyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonylaminomethyl, succinoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl,  $\alpha$ -amino(C<sub>1</sub>-C<sub>4</sub>)alkanoyl, arylacyl and  $\alpha$ -aminoacyl, or  $\alpha$ -aminoacyl- $\alpha$ -aminoacyl, where each  $\alpha$ -aminoacyl group is

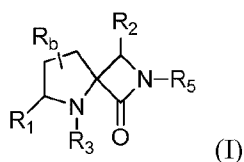
5 independently selected from the naturally occurring L-amino acids, P(O)(OH)<sub>2</sub>, -P(O)(O(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub> or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0053] If a compound of the invention incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-acyloxyakyl

10 derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simplicio, *et al.*, *Molecules* 2008, 13, 519 and references therein.

## 15 Compounds

[0054] Disclosed compounds include those represented by formula I:




and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

- R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl;
- 20 R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;
- R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;
- R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;
- 25 R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of phenyl, a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from



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O, S, or N, or a 4- to 6-membered heterocyclyl ring having 1, 2, or 3 heteroatoms

selected from O, S, or N, and wherein R<sub>5</sub> is optionally substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy;

5 or, in other embodiments, the variables set forth in formula (I) are defined as follows:

R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., H);

R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;


R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of:

(i) phenyl;

15 (ii) heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and S; and

(iii) heterocyclyl including from 3 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and

20 S; wherein R<sub>5</sub> is optionally substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

[0055] In certain embodiments, R<sub>1</sub> is H.

[0056] In certain embodiments, R<sub>2</sub> is H.

25 [0057] In certain embodiments, R<sub>3</sub> is H.

[0058] In other embodiments, R<sub>3</sub> is a nitrogen protecting group. In certain embodiments, R<sub>3</sub> has formula -C(O)OR<sub>31</sub>, wherein R<sub>31</sub> is selected from the group consisting of: C<sub>1</sub>-C<sub>6</sub> alkyl;

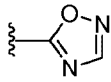
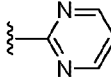
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
C<sub>1</sub>-C<sub>6</sub> haloalkyl; C<sub>2</sub>-C<sub>6</sub> alkenyl; C<sub>2</sub>-C<sub>6</sub> alkynyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl, wherein the C<sub>3</sub>-C<sub>10</sub> cycloalkyl is optionally substituted with from 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkyl; -CH<sub>2</sub>-C<sub>3</sub>-C<sub>10</sub> cycloalkyl wherein the C<sub>3</sub>-C<sub>10</sub> cycloalkyl is optionally substituted with from 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkyl; -CH<sub>2</sub>-phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>3</sub> haloalkyl; C<sub>1</sub>-C<sub>3</sub> alkoxy; C<sub>1</sub>-C<sub>3</sub> haloalkoxy; nitro; halo; SO<sub>2</sub>Me, cyano; and -OC(O)CH<sub>3</sub>; and -CH<sub>2</sub>-pyridyl. In certain embodiments, R<sub>31</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., *tert*-butyl). In other embodiments, R<sub>3</sub> has formula -C(O)R<sub>32</sub>, wherein R<sub>32</sub> is selected from the group consisting of: H; C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> haloalkyl; phenyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>3</sub> haloalkyl; C<sub>1</sub>-C<sub>3</sub> alkoxy; C<sub>1</sub>-C<sub>3</sub> haloalkoxy; nitro; halo; SO<sub>2</sub>Me, cyano; and -OC(O)CH<sub>3</sub>; and pyridyl. In certain embodiments, R<sub>32</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., -CH<sub>3</sub> or *iso*-propyl).

[0059] In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments, R<sub>4</sub> is methyl.

[0060] In certain embodiments, R<sub>b</sub> is H.

[0061] In certain embodiments, R<sub>5</sub> is X, and wherein X is a 5- to 6-membered heteroaryl ring selected from the group consisting of azetidine, pyrrolidine, pyrazolidine, pyridine, pyrimidine, isooxazolidine, imidazolidine, oxazolidine, thiazolidine, and isothiazolidine. In

other embodiments, R<sub>5</sub> is  or . In certain other embodiments, R<sub>5</sub> is X, and

wherein X is optionally substituted with  (sometimes referred to herein as “-

CH(R<sub>4</sub>)(R<sub>6</sub>)”).

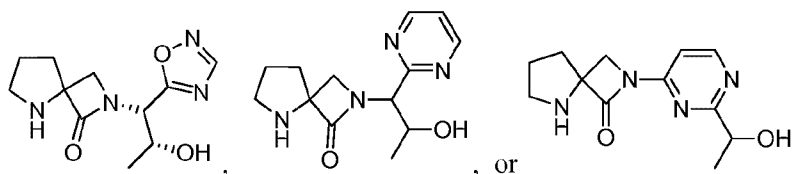
[0062] In some embodiments, R<sub>5</sub> is X. In certain embodiments, X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and S. For example, X can be selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, and pyrimidinyl. In certain embodiments, R<sub>5</sub> (here, X as defined anywhere herein) is substituted with -CH(R<sub>4</sub>)(R<sub>6</sub>). In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., R<sub>4</sub> is methyl). In certain embodiments, R<sub>6</sub> is selected from the group consisting of hydroxyl, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy (e.g., R<sub>6</sub> is hydroxyl). Embodiments in which R<sub>5</sub> is X can include one or more of the following features: R<sub>1</sub> is H or methyl; R<sub>2</sub> is H or methyl; R<sub>3</sub> is H, -C(O)OR<sub>31</sub>, or -C(O)R<sub>32</sub>; when present, R<sub>4</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., R<sub>4</sub> is methyl), and R<sub>6</sub> is selected from the group consisting of hydroxyl, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy (e.g., R<sub>6</sub> is hydroxyl); R<sub>b</sub> is H.

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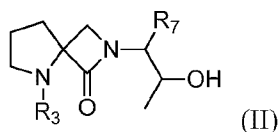
[0063] In some embodiments,  $R_5$  is  $-C_1-C_6$  alkylene-X (e.g.,  $-C_1-C_2$  alkylene-X or  $-C_1$  alkylene-X). In certain embodiments, X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N( $C_1-C_3$  alkyl), O, and S. For example, X can be selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, and pyrimidinyl. In certain embodiments,  $R_5$  is substituted on either the X portion or the alkylene chain portion with  $-CH(R_4)(R_6)$ . In certain of these embodiments,  $R_5$  is substituted on the alkylene portion with  $-CH(R_4)(R_6)$ , and  $R_5$  can have, for example, the formula  $-CH(CHR_4R_6)-X$ . In certain embodiments,  $R_4$  is  $C_1-C_6$  alkyl (e.g.,  $R_4$  is methyl). In certain embodiments,  $R_6$  is selected from the group consisting of hydroxyl,  $-O-C(O)-C_1-C_6$  alkyl, and  $C_1-C_6$  alkoxy (e.g.,  $R_6$  is hydroxyl). Embodiments in which  $R_5$  is  $-C_1-C_6$  alkylene-X can include one or more of the following features:  $R_1$  is H or methyl;  $R_2$  is H or methyl;  $R_3$  is H,  $-C(O)OR_{31}$ , or  $-C(O)R_{32}$ ; when present,  $R_4$  is  $C_1-C_6$  alkyl (e.g.,  $R_4$  is methyl), and  $R_6$  is selected from the group consisting of hydroxyl,  $-O-C(O)-C_1-C_6$  alkyl, and  $C_1-C_6$  alkoxy (e.g.,  $R_6$  is hydroxyl);  $R_b$  is H.

[0064] In certain embodiments,  $R_6$  is hydroxyl.

[0065] In some embodiments, a disclosed compound includes those delineated in Table 1 and/or the Examples, e.g., one having the formula:



[0066] Disclosed compounds also include compounds represented by formula II:



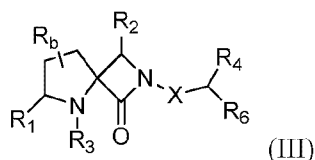
and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

$R_3$  is selected from the group consisting of H,  $C_1-C_6$ alkyl and a nitrogen protecting group; and

$R_7$  is a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted on a free carbon by a substituent selected from the group consisting of: halogen,  $C_1-C_6$ alkyl, hydroxyl, cyano, and phenyl.

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[0067] Also disclosed are compounds represented by formula III:



and pharmaceutically acceptable salts, stereoisomers, and N-oxides thereof, wherein

R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano or C<sub>1</sub>-C<sub>6</sub> alkyl;

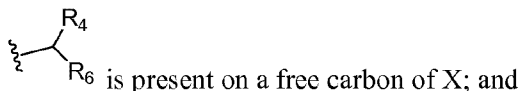
5 R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

10 X is selected from the group consisting of phenyl, a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, or a 4- to 6-membered heterocyclyl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, wherein



R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy.

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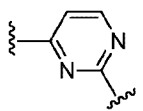
[0068] In certain embodiments, R<sub>1</sub> is H.

[0069] In certain embodiments, R<sub>2</sub> is H.

[0070] In some embodiments, R<sub>3</sub> is H.

[0071] In certain embodiments, R<sub>4</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl. In other embodiments, R<sub>4</sub> is methyl.

20 [0072] In some embodiments, R<sub>b</sub> is H.



[0073] In certain embodiments, X is

[0074] In some embodiments, R<sub>6</sub> is hydroxyl.

[0075] The compounds of the present disclosure and formulations thereof may have a plurality of chiral centers. Each chiral center may be independently *R*, *S*, or any mixture of *R* and *S*. For example, in some embodiments, a chiral center may have an *R*:*S* ratio of between

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about 100:0 and about 50:50, between about 100:0 and about 75:25, between about 100:0 and about 85:15, between about 100:0 and about 90:10, between about 100:0 and about 95:5, between about 100:0 and about 98:2, between about 100:0 and about 99:1, between about 0:100 and 50:50, between about 0:100 and about 25:75, between about 0:100 and about 15:85, between about 0:100 and about 10:90, between about 0:100 and about 5:95, between about 0:100 and about 2:98, between about 0:100 and about 1:99, between about 75:25 and 25:75, and about 50:50. Formulations of the disclosed compounds comprising a greater ratio of one or more isomers (i.e., *R* and/or *S*) may possess enhanced therapeutic characteristic relative to racemic formulations of a disclosed compounds or mixture of compounds. In some instances, chemical formulas contain the descriptor “-(R)-” or “-(S)-” that is further attached to solid wedge or dashed wedge. This descriptor is intended to show a methine carbon (CH) that is attached to three other substituents and has either the indicated R or S configuration (see, e.g., Table 1).

**[0076]** Disclosed compounds may provide for efficient cation channel opening at the NMDA receptor, e.g. may bind or associate with the glutamate site of the NMDA receptor to assist in opening the cation channel. The disclosed compounds may be used to regulate (turn on or turn off) the NMDA receptor through action as an agonist.

**[0077]** The compounds as described herein may be glycine site NMDA receptor partial agonists. A partial agonist as used in this context will be understood to mean that at a low concentration, the analog acts as an agonist and at a high concentration, the analog acts as an antagonist. Glycine binding is not inhibited by glutamate or by competitive inhibitors of glutamate, and also does not bind at the same site as glutamate on the NMDA receptor. A second and separate binding site for glycine exists at the NMDA receptor. The ligand-gated ion channel of the NMDA receptor is, thus, under the control of at least these two distinct allosteric sites. Disclosed compounds may be capable of binding or associating with the glycine binding site of the NMDA receptor. In some embodiments, disclosed compounds may possess a potency that is 10-fold or greater than the activity of existing NMDA receptor glycine site partial agonists.

**[0078]** The disclosed compounds may exhibit a high therapeutic index. The therapeutic index, as used herein, refers to the ratio of the dose that produces a toxicity in 50% of the population (i.e.,  $TD_{50}$ ) to the minimum effective dose for 50% of the population (i.e.,  $ED_{50}$ ). Thus, the therapeutic index =  $(TD_{50})/(ED_{50})$ . In some embodiments, a disclosed compound

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may have a therapeutic index of at least about 10:1, at least about 50:1, at least about 100:1, at least about 200:1, at least about 500:1, or at least about 1000:1.

#### Compositions

[0079] In other aspects, formulations and compositions comprising the disclosed  
5 compounds and optionally a pharmaceutically acceptable excipient are provided. In some  
embodiments, a contemplated formulation comprises a racemic mixture of one or more of the  
disclosed compounds.

[0080] Contemplated formulations may be prepared in any of a variety of forms for use.  
By way of example, and not limitation, the compounds may be prepared in a formulation  
10 suitable for oral administration, subcutaneous injection, or other methods for administering an  
active agent to an animal known in the pharmaceutical arts.

[0081] Amounts of a disclosed compound as described herein in a formulation may vary  
according to factors such as the disease state, age, sex, and weight of the individual. Dosage  
regimens may be adjusted to provide the optimum therapeutic response. For example, a single  
15 bolus may be administered, several divided doses may be administered over time or the dose  
may be proportionally reduced or increased as indicated by the exigencies of the therapeutic  
situation. It is especially advantageous to formulate parenteral compositions in dosage unit  
form for ease of administration and uniformity of dosage. Dosage unit form as used herein  
refers to physically discrete units suited as unitary dosages for the mammalian subjects to be  
20 treated; each unit containing a predetermined quantity of active compound calculated to  
produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0082] The specification for the dosage unit forms of the invention are dictated by and  
directly dependent on (a) the unique characteristics of the compound selected and the particular  
therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding  
25 such an active compound for the treatment of sensitivity in individuals.

[0083] Therapeutic compositions typically must be sterile and stable under the conditions  
of manufacture and storage. The composition can be formulated as a solution, microemulsion,  
liposome, or other ordered structure suitable to high drug concentration. The carrier can be a  
solvent or dispersion medium containing, for example, water, ethanol, polyol (for example,  
30 glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures  
thereof. The proper fluidity can be maintained, for example, by the use of a coating such as  
lecithin, by the maintenance of the required particle size in the case of dispersion and by the use  
of surfactants. In many cases, it will be preferable to include isotonic agents, for example,

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sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition.

Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin.

[0084] The compounds can be administered in a time release formulation, for example in a composition which includes a slow release polymer. The compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are generally known to those skilled in the art.

[0085] Sterile injectable solutions can be prepared by incorporating the compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0086] In accordance with an alternative aspect of the invention, a compound may be formulated with one or more additional compounds that enhance the solubility of the compound.

#### Methods

[0087] Methods for treating a condition in a patient in need thereof by administering a therapeutically effective dose of a compound described herein are provided. In some embodiments, the condition may be a mental condition. For example, a mental illness may be treated. In another aspect, a nervous system condition may be treated. For example, a condition that affects the central nervous system, the peripheral nervous system, and/or the eye may be treated. In some embodiments, neurodegenerative diseases may be treated.

[0088] In some embodiments, the methods include administering a compound to treat patients suffering from autism, anxiety, depression, bipolar disorder, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, a psychotic disorder, a psychotic symptom, social withdrawal, obsessive-compulsive disorder (OCD), phobia, post-

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traumatic stress syndrome, a behavior disorder, an impulse control disorder, a substance abuse disorder (e.g., a withdrawal symptom, opiate addiction, nicotine addiction, and ethanol addition), a sleep disorder, a memory disorder (e.g., a deficit, loss, or reduced ability to make new memories), a learning disorder, urinary incontinence, multiple system atrophy, progressive  
 5 supra-nuclear palsy, Friedrich's ataxia, Down's syndrome, fragile X syndrome, tuberous sclerosis, olivio-ponto-cerebellar atrophy, cerebral palsy, drug-induced optic neuritis, ischemic retinopathy, diabetic retinopathy, glaucoma, dementia, AIDS dementia, Alzheimer's disease, Huntington's chorea, spasticity, myoclonus, muscle spasm, Tourette's syndrome, epilepsy, cerebral ischemia, stroke, a brain tumor, traumatic brain injury, cardiac arrest, myelopathy,  
 10 spinal cord injury, peripheral neuropathy, acute neuropathic pain, and chronic neuropathic pain.

[0089] In some embodiments, methods of treating a memory disorder associated with aging, schizophrenia, special learning disorders, seizures, post-stroke convulsions, brain ischemia, hypoglycemia, cardiac arrest, epilepsy, migraine, AIDS dementia, Huntington's chorea, Parkinson's disease, early stage Alzheimer's disease, and Alzheimer's disease are  
 15 contemplated.

[0090] In certain embodiments, methods for treating schizophrenia are provided. For example, paranoid type schizophrenia, disorganized type schizophrenia (i.e., hebephrenic schizophrenia), catatonic type schizophrenia, undifferentiated type schizophrenia, residual type schizophrenia, post-schizophrenic depression, and simple schizophrenia may be treated using  
 20 the methods and compositions contemplated herein. Psychotic disorders such as schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders, and psychotic disorders with delusions or hallucinations may also be treated using the compositions contemplated herein.

[0091] Paranoid schizophrenia may be characterized where delusions or auditory  
 25 hallucinations are present, but thought disorder, disorganized behavior, or affective flattening are not. Delusions may be persecutory and/or grandiose, but in addition to these, other themes such as jealousy, religiosity, or somatization may also be present. Disorganized type schizophrenia may be characterized where thought disorder and flat affect are present together. Catatonic type schizophrenia may be characterized where the patient may be almost immobile  
 30 or exhibit agitated, purposeless movement. Symptoms can include catatonic stupor and waxy flexibility. Undifferentiated type schizophrenia may be characterized where psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. Residual type schizophrenia may be characterized where positive symptoms are



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present at a low intensity only. Post-schizophrenic depression may be characterized where a depressive episode arises in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present. Simple schizophrenia may be characterized by insidious and progressive development of prominent negative symptoms with no history of psychotic episodes.

[0092] In some embodiments, methods are provided for treating psychotic symptoms that may be present in other mental disorders, including, but not limited to, bipolar disorder, borderline personality disorder, drug intoxication, and drug-induced psychosis. In another embodiment, methods for treating delusions (e.g., "non-bizarre") that may be present in, for example, delusional disorder are provided.

[0093] Also provided are methods for treating social withdrawal in conditions including, but not limited to, social anxiety disorder, avoidant personality disorder, and schizotypal personality disorder.

[0094] In some embodiments, methods are provided for treating neuropathic pain. The neuropathic pain may be acute or chronic. In some cases, the neuropathic pain may be associated with a condition such as herpes, HIV, traumatic nerve injury, stroke, post-ischemia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, and cancer chemotherapeutic-induced neuropathic pain. Methods for enhancing pain relief and for providing analgesia to a patient are also contemplated.

[0095] Further contemplated methods include a method of treating autism and/or an autism spectrum disorder in a patient need thereof, comprising administering an effective amount of a compound to the patient. In an embodiment, a method for reducing the symptoms of autism in a patient in need thereof is contemplated, comprising administering an effective amount of a disclosed compound to the patient. For example, upon administration, the compound may decrease the incidence of one or more symptoms of autism such as eye contact avoidance, failure to socialize, attention deficit, poor mood, hyperactivity, abnormal sound sensitivity, inappropriate speech, disrupted sleep, and perseveration. Such decreased incidence may be measured relative to the incidence in the untreated individual or an untreated individual(s).

[0096] Also provided herein is a method of modulating an autism target gene expression in a cell comprising contacting a cell with an effective amount of a compound described herein. The autism gene expression may be for example, selected from ABAT, APOE, CHRNA4, GABRA5, GFAP, GRIN2A, PDYN, and PENK. In another embodiment, a method of

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modulating synaptic plasticity in a patient suffering from a synaptic plasticity related disorder is provided, comprising administering to the patient an effective amount of a compound.

[0097] In another embodiment, a method of treating Alzheimer's disease, or e.g., treatment of memory loss that e.g., accompanies early stage Alzheimer's disease, in a patient in need thereof is provided, comprising administering a compound. Also provided herein is a method of modulating an Alzheimer's amyloid protein (e.g., beta amyloid peptide, e.g. the isoform  $A\beta_{1-42}$ ), in-vitro or in-vivo (e.g. in a cell) comprising contacting the protein with an effective amount of a compound is disclosed. For example, in some embodiments, a compound may block the ability of such amyloid protein to inhibit long-term potentiation in hippocampal slices as well as apoptotic neuronal cell death. In some embodiments, a disclosed compound may provide neuroprotective properties to a Alzheimer's patient in need thereof, for example, may provide a therapeutic effect on later stage Alzheimer's -associated neuronal cell death.

[0098] In a further embodiment, a method of treating depression comprising administering a compound described herein is provided. In some embodiments, the treatment may relieve depression or a symptom of depression without affecting behavior or motor coordination and without inducing or promoting seizure activity. Exemplary depression conditions that are expected to be treated according to this aspect of the invention include, but are not limited to, major depressive disorder, dysthymic disorder, psychotic depression, postpartum depression, premenstrual syndrome, premenstrual dysphoric disorder, seasonal affective disorder (SAD), bipolar disorder (or manic depressive disorder), mood disorder, and depressions caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress, and post traumatic stress disorders. In addition, patients suffering from any form of depression often experience anxiety. Various symptoms associated with anxiety include fear, panic, heart palpitations, shortness of breath, fatigue, nausea, and headaches among others. Anxiety or any of the symptoms thereof may be treated by administering a compound as described herein.

[0099] Also provided herein are methods of treating a condition in treatment-resistant patients, e.g., patients suffering from a mental or central nervous system condition that does not, and/or has not, responded to adequate courses of at least one, or at least two, other compounds or therapeutics. For example, provided herein is a method of treating depression in a treatment resistant patient, comprising a) optionally identifying the patient as treatment resistant and b) administering an effective dose of a compound to said patient.

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**[00100]** In some embodiments, a compound described herein may be used for acute care of a patient. For example, a compound may be administered to a patient to treat a particular episode (e.g., a severe episode) of a condition contemplated herein.

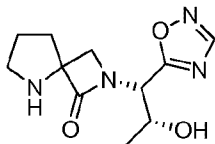
**[00101]** Also contemplated herein are combination therapies comprising a compound in combination with one or more other active agents. For example, a compound may be combined with one or more antidepressants, such as tricyclic antidepressants, MAO-I's, SSRI's, and double and triple uptake inhibitors and/or anxiolytic drugs. Exemplary drugs that may be used in combination with a compound include Anafranil, Adapin, Aventyl, Elavil, Norpramin, Pamelor, Pertofrane, Sinequan, Surmontil, Tofranil, Vivactil, Parnate, Nardil, Marplan, Celexa, Lexapro, Luvox, Paxil, Prozac, Zoloft, Wellbutrin, Effexor, Remeron, Cymbalta, Desyrel (trazodone), and Ludiomill. In another example, a compound may be combined with an antipsychotic medication. Non-limiting examples of antipsychotics include butyrophenones, phenothiazines, thioxanthenes, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, paliperidone, iloperidone, zotepine, sertindole, lurasidone, and aripiprazole. It should be understood that combinations of a compound and one or more of the above therapeutics may be used for treatment of any suitable condition and are not limited to use as antidepressants or antipsychotics.

#### EXAMPLES

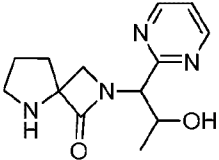
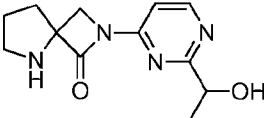
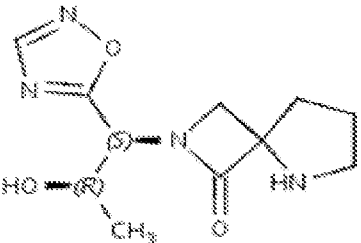
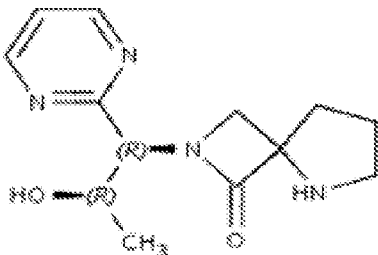
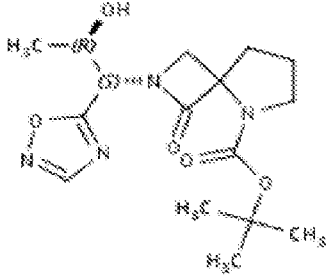
**[00102]** The following examples are provided for illustrative purposes only, and are not intended to limit the scope of the disclosure.

**[00103]** Table 1 below shows some exemplary compounds of the disclosure and provides physiochemical characteristics of the compounds.

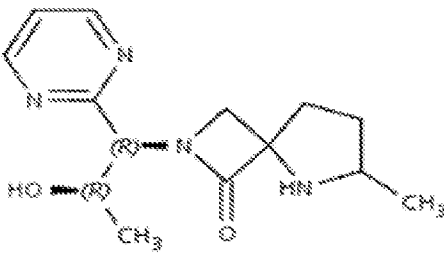
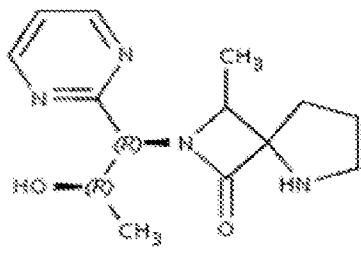
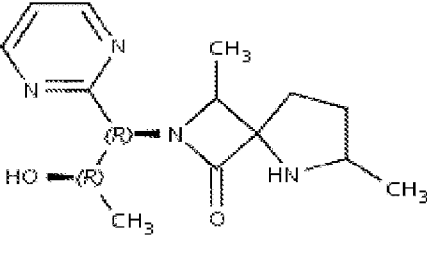
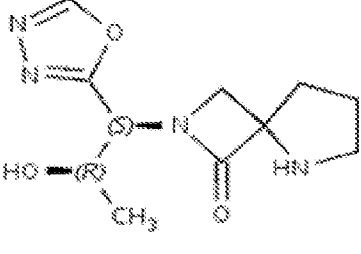
**Table 1.**

Compound	Structure	Molecular Weight (Da)	cLogP	tPSA
Compound X		252	-1.14	91.5

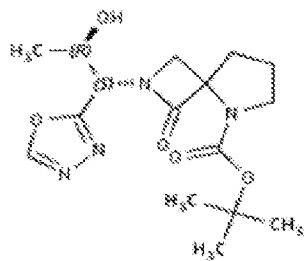
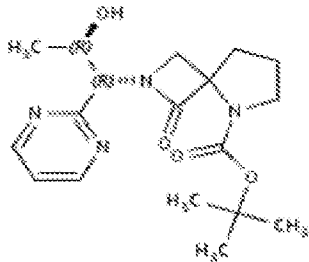
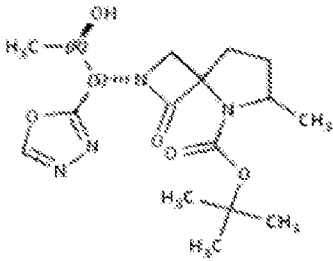
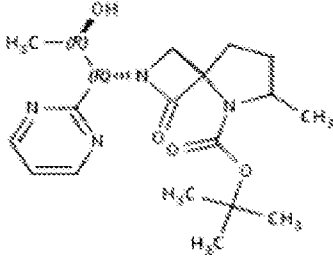
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Compound Y		262	-0.57	78.35
Compound Z		248	-0.15	78.35
C-16		252.2697	-1.1382	91.49
C-4		262.3076	-0.57075	78.35
C-15		352.3856	0.144989	109

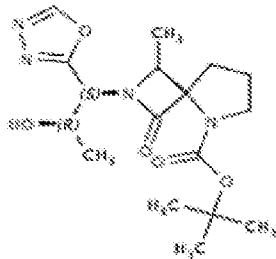
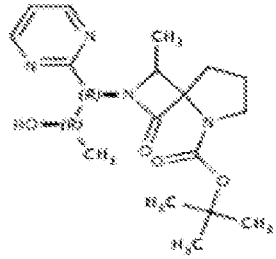
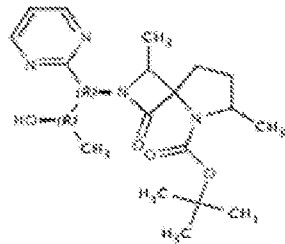
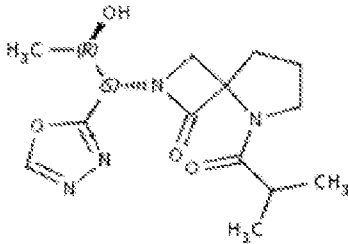
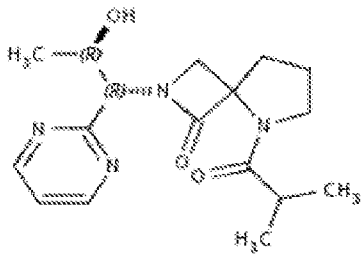
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C-20		276.3342	- 0.160256	78.35
C-36		276.3342	- 0.160256	78.35
C-33		290.3608	0.250239	78.35
C-10		252.2697	-1.83479	91.49

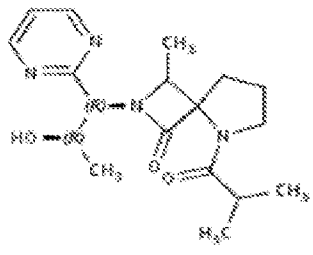
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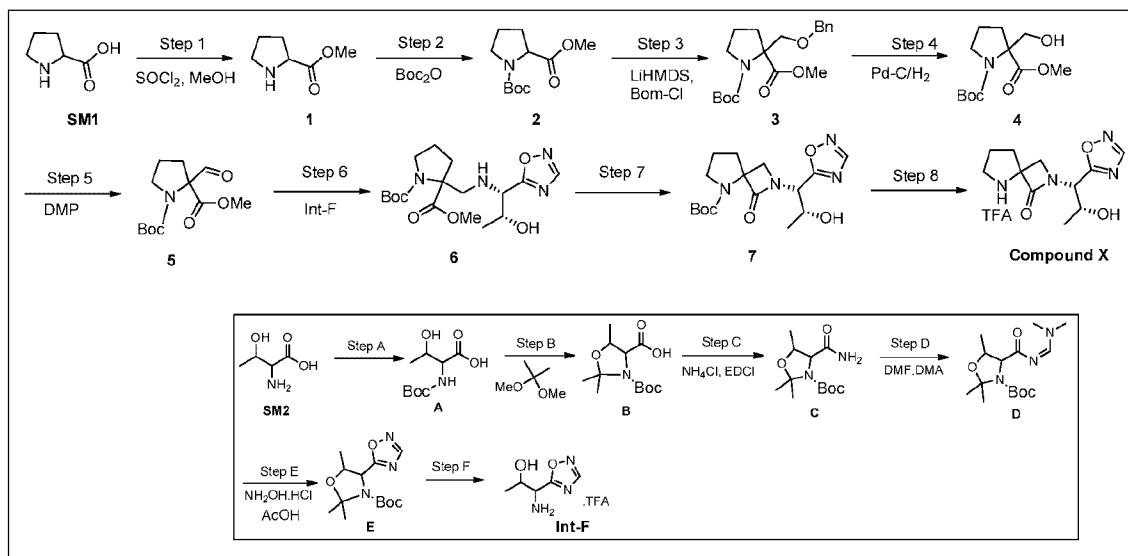
C-9		352.3856	- 0.551597	109
C-3		362.4234	0.672806	95.86
C-23		366.4121	- 0.135022	109
C-19		376.45	1.0833	95.86

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C-26		366.4121	- 0.135022	109
C-29		376.45	1.0833	95.86
C-32		390.4766	1.4938	95.86
C-11		322.3596	- 0.981326	99.77
C-5		332.3975	0.335914	86.63

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C-37		346.424	0.746408	86.63
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Example 1 – Synthesis of Compound XScheme 1.

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Synthesis of 2-((tert-butoxycarbonyl) amino)-3-hydroxybutanoic acid (A)

[00104] To a stirring solution of 2-amino-3-hydroxybutanoic acid (SM2) (10 g, 83.9 mmol) in 1,4-dioxane/water (100 mL, 1: 1)) was added NaHCO<sub>3</sub> (21.1 g, 0.25 mol) followed by Boc-anhydride (21.9 mL, 0.101 mol) at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water and washed with EtOAc. The aqueous layer was acidified using citric acid solution (pH~3-4) and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 150 mL). The separated organic extracts were dried over



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anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to afford **A** (15 g, crude). This material was directly used for the next step without further purification.

**Synthesis of 3-(*tert*-butoxycarbonyl)-2, 2, 5-trimethyloxazolidine-4-carboxylic acid (B)**

[00105] To a stirring solution of **A** (15 g, 59.28 mmol) in THF (150 mL) was added PPTS (1.47 g, 5.92 mmol) followed by 2,2-dimethoxy propane (21.79 mL, 0.17 mol) at 0°C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at RT for 16 h. The reaction mixture was again heated to reflux for 6 h. The reaction mixture was diluted with aqueous NaHCO<sub>3</sub> solution and washed with EtOAc. The aqueous layer was acidified using citric acid solution (pH~2) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 mL). The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to afford **B** (18 g, crude).

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 13.25 (br s, 1H), 4.11-4.05 (m, 1H), 3.79 (d, 1H), 1.50 (s, 3H), 1.67 (s, 3H), 1.45 (s, 9H), 1.29 (d, 3H).

**Synthesis of *tert*-butyl 4-carbamoyl-2, 2, 5-trimethyloxazolidine-3-carboxylate (C)**

[00106] To a stirring solution of **B** (18 g, 69.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (180 mL) was added HOBt (14.16 g, 0.104 mol), EDCI.HCl (19.88 g, 0.104 mol) followed by NH<sub>4</sub>Cl (5.56 g, 0.104 mol) and DIPEA (31.9 mL, 0.173 mol) at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with aqueous citric acid, NaHCO<sub>3</sub> followed by brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **C** (13 g, 72.5%).

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.51 (br s, 1H), 7.14 (br s, 1H), 3.97-3.95 (m, 1H), 3.71 (d, 1H), 1.51 (d, 6H), 1.34 (s, 9H), 1.24 (d, 3H).

LCMS (ESI): 159.1[(M<sup>+</sup>+1)-Boc]

**Synthesis of (Z)-*tert*-butyl 4-(((dimethylamino) methylene) carbamoyl)-2, 2, 5-trimethyloxazolidine-3-carboxylate (D)**

[00107] A solution of **C** (13 g, 50.3 mmol) in DMF.DMA (130 mL) was stirred at reflux temperature for 3 h under N<sub>2</sub> atmosphere. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **D** (15.7 g, crude). This crude material was directly taken for the next step without further purification.

**Synthesis of *tert*-butyl 2, 2, 5-trimethyl-4-(1, 2, 4-oxadiazol-5-yl) oxazolidine-3-carboxylate (E)**

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[00108] To a stirring solution of **D** (15.7 g, 50.09 mmol) in ethanol (157 mL) was added hydroxylamine hydrochloride (6.96 g, 0.10 mol) under N<sub>2</sub> atmosphere. The reaction mixture was heated to reflux and stirred for 2 h. After consumption of the starting material (by TLC), acetic acid (28.6 mL, 0.50 mol) was added to the reaction mixture and then refluxed for 16 h.

5 Solvents from the reaction mixture were evaporated under vacuum. The resulting crude material was purified by silica gel column chromatography eluting with 10% EtOAc/Hexane to afford **E** (4.5 g, 32%).

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.35 (s, 2H), 4.61 (d, 1H), 4.22-4.15 (m, 1H), 1.55 (s, 6H), 1.37 (s, 2H), 1.25 (d, 3H), 1.21 (s, 6H).

10 LCMS (ESI): 284 [M<sup>+</sup>+1]

Mass (m/z): 283 [M<sup>+</sup>]

#### Synthesis of 1-amino-1-(1, 2, 4-oxadiazol-5-yl) propan-2-ol (Int-F)

[00109] To a stirring solution of **E** (5 g, 17.6 mmol) in water (25 mL) was added trifluoroacetic acid (25 mL). The reaction mixture was stirred at RT for 5 h. After consumption  
15 of the starting material (by TLC), the reaction mixture was concentrated under vacuum. The residue was dissolved in water and neutralized with aqueous NaHCO<sub>3</sub>. The solvents from the reaction mixture were evaporated under vacuum and extracted with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (4x 150 mL). The organic layer was concentrated under reduced pressure to afford **Int-F** (2.5 g, crude).

<sup>1</sup>H-NMR: (400 MHz, D<sub>2</sub>O): δ 8.84 (s, 1H), 4.05 (d, 1H), 3.98-3.95 (m, 1H), 3.67 (s, 1H), 3.58  
20 (d, 1H), 1.15 (d, 3H), 1.12 (d, 3H).

LCMS (ESI): 144.1 [M<sup>+</sup>+1]

#### Synthesis of methyl pyrrolidine-2-carboxylate (1)

[00110] To a stirring solution of pyrrolidine-2-carboxylic acid (**SM1**) (100 g, 0.87 mol) in methanol (800 mL) was added thionyl chloride (76.9 mL, 1.04 mol) slowly drop wise at 0°C.

25 The reaction mixture was heated to reflux for 12 h. After consumption of the starting material (by TLC), the reaction was concentrated under vacuum. Obtained residue was washed with *n*-Hexane and distilled off the solvent to afford **1** (143.9 g, HCl salt).

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) (Rotamers): δ 3.89 (s, 3H), 3.68-3.62 (m, 2H), 3.59-3.47 (m, 2H), 2.49-2.37 (m, 1H), 2.27-2.05 (m, 3H).

30 LCMS (ESI): 166 [M<sup>+</sup>+1]

#### Synthesis of 1-*tert*-butyl 2-methyl pyrrolidine-1,2-dicarboxylate (2)

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[00111] To a stirring solution of **1** (35 g, 0.22 mol) in CH<sub>2</sub>Cl<sub>2</sub> (175 mL) were added Et<sub>3</sub>N (90 mL, 0.65 mol) followed by Boc-anhydride (56.9 mL, 0.26 mol) at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 mL). The organic layer was washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Obtained crude material was purified by silica gel column chromatography eluting with 30% EtOAc/Hexane to afford **2** (41 g, 95%).

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>) (Rotamers): δ 4.25-4.21 (m, 1H), 3.75 (s, 3H), 3.57-3.26 (m, 2H), 2.29-2.10 (m, 1H), 1.99-1.75 (m, 3H), 1.45 (s, 9H).

10 LCMS (ESI): 130 [(M<sup>+</sup>+1)-Boc]

**Synthesis of 1-tert-butyl 2-methyl 2-((benzyloxy) methyl) pyrrolidine-1, 2-dicarboxylate (3)**

[00112] To a stirring solution of **2** (100 g, 0.43 mol) in THF (800 mL) was added LiHMDS (873 mL, 0.87 mol) at -78°C and stirred for 1 h. To this BOM-chloride (93.2 mL, 0.65 mol) was added drop wise at -78°C and stirred for 2 h at -20 °C. After consumption of the starting material (by TLC), the reaction was quenched with NH<sub>4</sub>Cl at 0 °C. The separated organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford **3** (180 g, crude). This material was directly taken for the next step without further purification.

LCMS (ESI): 250 [(M<sup>+</sup>+1)-Boc]

20 **Synthesis of 1-tert-butyl 2-methyl 2-(hydroxymethyl)pyrrolidine-1, 2-dicarboxylate (4)**

[00113] To a stirring solution of **3** (74 g, 0.21 mol) in methanol (740 mL) was added 10% Pd/C (50% wet, 14.8 g) under N<sub>2</sub> atmosphere and stirred for 6 h under H<sub>2</sub> atmosphere (balloon pressure). The reaction mixture was filtered through celite pad and concentrated under reduced pressure to afford **4** (45 g, 82%) as crude.

25 **Synthesis of 1-tert-butyl 2-methyl 2-formylpyrrolidine-1, 2-dicarboxylate (5)**

[00114] To a stirring solution of **4** (10 g, 38.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added Dess-martin periodinane (19.6 g, 46.27 mmol) at 0°C under N<sub>2</sub> atmosphere and stirred for 3 h. After consumption of the starting material (determined by TLC), the reaction was quenched with aqueous NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The resulting crude material

30

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was purified by column chromatography eluting with 10% EtOAc/Hexane to afford **5** (7 g, 70.5%).

**Synthesis of 1-*tert*-butyl 2-methyl 2-((((1*S*, 2*R*)-2-hydroxy-1-(1, 2, 4-oxadiazol-5-yl) propyl) amino) methyl) pyrrolidine-1, 2-dicarboxylate (**6**)**

- 5 **[00115]** To a stirring solution of **5** (3 g, 11.6 mmol) in MeOH (30 mL) was added sodium acetate (1.91 g, 23.3 mmol) followed by **Int-F** (3.6 g, 13.9 mmol). The reaction mixture was heated to reflux for 1 h. The reaction mixture was slowly cooled to RT-0°C, to this sodium cyanoborohydride (1.465 g, 23.3 mmol) was added, and stirring was continued for another 6 h at RT. After consumption of the starting material (determined by TCL), methanol from the  
 10 reaction was evaporated under reduced pressure and the residue was diluted with water and extracted with EtOAc (2x 50 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography eluting with 40% EtOAc/Hexane to afford **6** (2.5 g, 56%).  
**LCMS *m/z*: 385 [M<sup>+</sup>+1]**

- 15 **Synthesis of *tert*-butyl 2-((((1*S*, 2*R*)-2-hydroxy-1-(1, 2, 4-oxadiazol-5-yl) propyl)-1-oxo-2, 5-diazaspiro[3.4] octane-5-carboxylate (**7**)**

- [00116]** To a stirring solution of **6** (1.5 g, 3.90 mmol) in THF (30 mL) was cooled to 0 °C and added *t*-BuMgCl (1M in THF, 15.6 mL, 15.6 mmol) and stirred for 15 min. After consumption of the starting material (by TLC), the reaction mixture was quenched with  
 20 aqueous NH<sub>4</sub>Cl solution and diluted with water. Aqueous layer was extracted with EtOAc (2x 25 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography eluting with 150% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to afford **7** (0.15 g, 11%).  
**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.02 (s, 1H), 5.15 (s, 1H), 4.37-4.32 (m, 1H), 3.95 (d, 1H),  
 25 3.66-3.60 (m, 1H), 3.36-3.30 (m, 1H), 2.29-2.09 (m, 2H), 1.87-1.82 (m, 2H), 1.55 (s, 9H), 1.27 (d, 3H).

**LCMS (ESI) *m/z*: 351 [M<sup>+</sup>-1]**

**UPLC Purity: 96%**

- Synthesis of 2-((((1*S*, 2*R*)-2-hydroxy-1-(1, 2, 4-oxadiazol-5-yl) propyl)-2, 5-diazaspiro [3.4] octan-1-one (Compound X)**  
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[00117] To a stirring solution of **7** (0.4 g, 1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added TFA (0.43 mL) at 0°C and stirred at RT for 30 min. The reaction mixture was concentrated under vacuum. The resulting crude material was purified by prep-HPLC to afford **Compound X** (65 mg) as TFA salt.

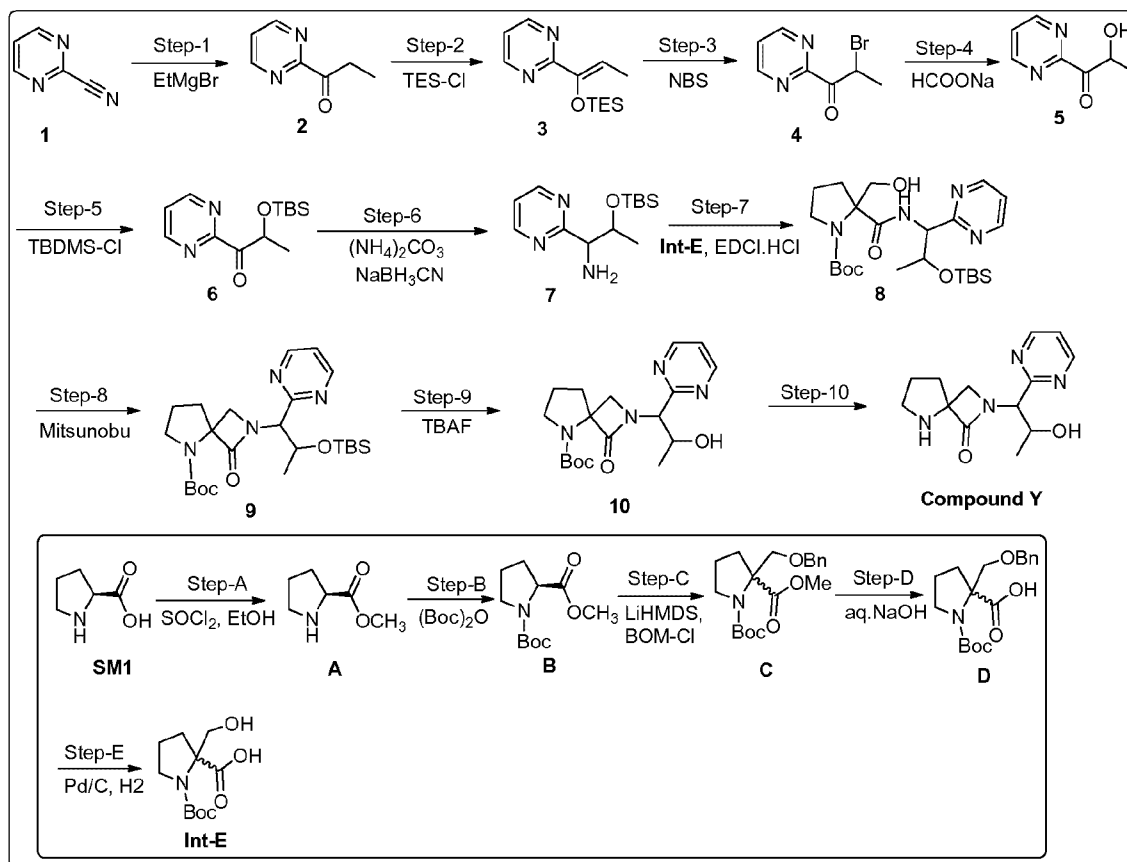
- 5 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-d<sub>6</sub>): δ 9.89 (br s, 1H), 9.08 (s, 1H), 5.46 (d, 1H), 5.31 (s, 1H), 4.37-4.35 (m, 1H), 3.99 (d, 1H), 3.81 (d, 1H), 3.42-3.35 (m, 2H), 2.35-2.18 (m, 2H), 2.10-2.03 (m, 2H), 1.24 (d, 3H).

**LCMS (ESI) *m/z*:** 253.4 [M<sup>+</sup>+1]

**Prep-HPLC Purity:** 95%

# 10 Example 2 - Synthesis of Compound Y

## *Scheme 2.*



## Synthesis of (S)-methyl pyrrolidine-2-carboxylate (A)

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[00118] To a stirring solution of L-proline (**SM1**) (100 g, 0.87 mol) in methanol (800 mL) was slowly added thionyl chloride (76.9 mL, 1.04 mol) at 0°C. The reaction mixture was slowly warmed to RT and heated to reflux for 12 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure to afford **A** (143.9 g, HCl salt).

5 <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 3.89 (s, 3H), 3.68-3.62 (m, 2H), 3.59-3.47 (m, 2H), 2.49-2.37 (m, 1H), 2.27-2.05 (m, 3H).

LCMS (m/z): 166 [M<sup>+</sup>+1]

**Synthesis of (S)-1-tert-butyl 2-methyl pyrrolidine-1,2-dicarboxylate (B)**

[00119] To a stirring solution of **A** (35 g, 0.22 mol) in CH<sub>2</sub>Cl<sub>2</sub> (175 mL) were added Et<sub>3</sub>N (90 mL, 0.65 mol) followed by Boc-anhydride (56.9 mL, 0.26 mol) at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 mL). The organic layer was washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The resulting crude material was purified by silica gel column chromatography eluting with 30% EtOAc/Hexane to afford **B** (41 g, 95%).

15 <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 4.25-4.21 (m, 1H), 3.75 (s, 3H), 3.57-3.26 (m, 2H), 2.29-2.10 (m, 1H), 1.99-1.75 (m, 3H), 1.45 (s, 9H).

LCMS (m/z): 130 [(M<sup>+</sup>+1)-Boc]

**Synthesis of 1-tert-butyl 2-methyl 2-((benzyloxy) methyl) pyrrolidine-1, 2-dicarboxylate (C)**

[00120] To a stirring solution of **B** (100 g, 0.43 mol) in THF (800 mL) was added LiHMDS (873 mL, 0.87 mol) at -78°C and stirred for 1 h. To this BOM-chloride (93.2 mL, 0.65 mol) was added drop wise at -78°C and stirred for 2 h at -20°C. After consumption of the starting material (by TLC), the reaction was quenched with sat.NH<sub>4</sub>Cl solution at 0°C. The separated organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford **C** (180 g, crude). This material was directly taken for the next step without further purification.

25 LCMS (m/z): 250 [(M<sup>+</sup>+1)-Boc]

**Synthesis of 2-((benzyloxy) methyl)-1-(tert-butoxycarbonyl) pyrrolidine-2-carboxylic acid (D)**

30 [00121] To a stirring solution of **C** (100 g, 0.28 mol) in methanol (200 mL) was added 2N NaOH solution (300 mL) at RT. The reaction mixture was heated to reflux for 4 h. After

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consumption of the starting material (by TLC), the solvent from the reaction was evaporated under reduced pressure and diluted with EtOAc (100 mL). The aqueous layer was acidified using citric acid solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 250 mL). The separated organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford **D** (60 g, 63%).

- 5 **<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>): δ 7.37-7.32 (m, 5H), 4.61 (s, 2H), 4.05-3.88 (m, 2H), 3.65-3.42 (m, 2H), 2.54-2.46 (m, 2H), 1.95 (br s, 2H), 1.57 (s, 9H).

**LCMS (m/z):** 334 [M<sup>+</sup>-1]

**Synthesis of 1-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine-2-carboxylic acid (Int-E)**

- 10 **[00122]** To a stirring solution of **D** (10 g, 29.81 mmol) in methanol (300 mL) was added 50% wet 10% Pd/C (5 g) at RT and stirred for 24 h under H<sub>2</sub> atmosphere (balloon pressure). After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to afford **Int-E** (6 g, 82%).
- 15 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.55 (br m, 1H), 3.99 (d, 1H), 3.88 (d, 1H), 7.65-7.60 (m, 1H), 3.51-3.45 (m, 1H), 3.39-3.34 (m, 1H), 2.32-2.14 (m, 1H), 1.98-1.69 (m, 3H), 1.39 (s, 9H).

**Synthesis of 1-(pyrimidin-2-yl)propan-1-one (2)**

- [00123]** To a stirring solution of **1** (15 g, 0.14 mol) in THF (150 mL) was added ethylmagnesium bromide (1M in THF) (171.4 mL, 0.17 mol) at 0°C under nitrogen atmosphere
- 20 slowly over a period of 15 min. After being stirred for 30 min, the reaction mixture was quenched with aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with EtOAc. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 50% EtOAc/hexane to afford **2** (8.5 g, 44%).
- 25 **<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>): δ 8.95 (d, 2H), 7.47 (t, 1H), 3.26 (q, 2H), 1.25 (t, 3H).

**Synthesis of (Z)-2-(1-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)pyrimidine (3)**

- [00124]** To a stirring solution of **2** (8.5 g, 62.5 mmol) in THF (170 mL) was added LiHMDS (1M in THF) (93.7 mL, 93.7 mmol) and stirred for 1 h. To this was added TES-Cl (12.5 mL, 75 mmol) at 0°C under N<sub>2</sub> atmosphere and further stirred for 1 h. After consumption of the starting
- 30 material (by TLC), the reaction was quenched with aqueous NH<sub>4</sub>Cl solution and extracted with EtOAc. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and

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concentrated under reduced pressure to afford **3** (10 g, 64%). The resulting crude material was directly used for the next step without further purification.

**Synthesis of 2-bromo-1-(pyrimidin-2-yl) propan-1-one (4)**

[00125] To a stirring solution of **3** (10 g, 0.04 mol) in THF: H<sub>2</sub>O (100 mL, 4:1) was added  
5 NBS (5.6 g, 0.05 mol) at RT and stirred for 1 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure and obtained residue was diluted with EtOAc and washed with water. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 30% EtOAc/hexane to  
10 afford **4** (6.5 g, 75.5%).

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 8.97 (d, 2H), 7.52 (t, 1H), 5.92 (q, 1H), 2.79 (s, 1H), 1.99 (d, 3H).

**Synthesis of 2-hydroxy-1-(pyrimidin-2-yl) propan-1-one (5)**

[00126] To a stirring solution of **4** (6.5 g, 0.03 mol) in MeOH (65 mL) was added sodium  
15 formate (10.28 g, 0.15 mol) and heated to reflux for 8 h. After consumption of the starting material (by TLC), the reaction mixture was cooled to RT and solvent was removed under reduced pressure. The resulting crude material was purified by silica gel column chromatography eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **5** (3.5 g, 76%).

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 9.01 (d, 2H), 7.52 (t, 1H), 5.92 (q, 1H), 3.73 (br s, 1H), 3.41  
20 (s, 1H), 2.78 (s, 2H), 1.55 (d, 3H).

**Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propan-1-one (6)**

[00127] To a stirring solution of **5** (3.5 g, 23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (70 mL) was added  
imidazole (3.91 g, 57 mmol) followed by DMAP (281 mg, 2.30 mmol) at RT. The reaction  
mixture was cooled to 0°C, to which TBS-Cl (5.18 g, 0.03 mol) was added and stirred at RT  
25 for 4 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain a crude product, which was purified by silica gel column chromatography eluting with 20% EtOAc/hexane to afford **6** (3 g, 49%).

30 <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 8.93 (d, 2H), 7.45 (t, 1H), 5.59 (q, 1H), 1.52 (d, 3H), 0.89 (s, 9H), 0.09 (s, 6H).



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**Synthesis of 2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propan-1-amine (7)**

[00128] To a stirring solution of **6** (3.0 g, 11.27 mmol) in MeOH (60 mL) was added sodium acetate (1.84 g, 22.55 mmol) followed by ammonium carbonate (8.85 g, 56.3 mmol) and acetic acid (0.64 mL, 11.27 mmol) at RT. The reaction mixture was heated to reflux for 1 h, added  
 5 NaCNBH<sub>3</sub> (1.41 g, 22.5 mmol) and continued reflux for another 6 h. After consumption of the starting material (by TLC), the reaction mixture was cooled to RT and volatiles were evaporated. Obtained residue was diluted with water and extracted with EtOAc. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to get crude product, which was purified by silica gel column chromatography eluting  
 10 with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **7** (2 g, 66.4%).

<sup>1</sup>H-NMR: (400 MHz, DMSO-d<sub>6</sub>): δ 8.91 (d, 1H), 8.85 (d, 1H), 7.48 (t, 1H), 5.71 (br m, 2H), 4.24 (t, 1H), 4.05 (d, 1H), 1.29 (d, 1H), 1.12 (d, 2H), 0.74 (s, 9H), 0.03 (s, 3H), 0.02 (s, 2H), 0.01 (s, 1H).

LCMS (m/z): 268 [M<sup>+</sup>+1]

15 **Synthesis of *tert*-butyl 2-((2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)carbamoyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (8)**

[00129] To a stirring solution of Int-E (2 g, 8.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added compound **7** (2.39 g, 8.97 mmol), EDCI. HCl (2.33 g, 12.2 mmol) followed by HOBt (1.66 g, 12.24 mmol) and DIPEA (4.5 mL, 24.4 mmol) at 0°C. The reaction mixture was warmed to RT  
 20 and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The separated organic layer was washed with aqueous NaHCO<sub>3</sub> solution followed by aqueous NH<sub>4</sub>Cl. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to get crude product, which was purified by silica gel column chromatography eluting with 70% EtOAc/hexane to afford **8** (2.3 g, 57.5%).  
 25 <sup>1</sup>H-NMR: (400 MHz, DMSO-d<sub>6</sub>): δ 8.91 (d, 1H), 8.68 (d, 2H), 7.41 (br s, 1H), 5.74 (br t, 1H), 5.07-4.89 (m, 1H), 4.15-4.10 (m, 1H), 3.97-3.92 (m, 1H), 3.45-3.41 (m, 1H), 1.79-1.74 (m, 2H), 1.43-1.39 (m, 4H), 1.29-1.21 (m, 6H), 1.12 (d, 5H), 0.71 (s, 9H), 0.12 (t, 1H), 0.09 (s, 2H), 0.08 (s, 1H), 0.04 (s, 2H).

LCMS (m/z): 495.5 [M<sup>+</sup>+1]

30 **Mass:** 495.5 [M<sup>+</sup>+1]

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**Synthesis of *tert*-butyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (9)**

[00130] To a stirring solution of **8** (2.3 g, 4.65 mmol) in THF (23 mL) was added TPP (1.34 g, 5.12 mmol) followed by DTAD (1.6 g, 6.98 mmol) at 0°C. The reaction mixture was  
 5 warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to get crude product, which was purified by silica gel column chromatography eluting with 25% EtOAc/hexane to afford **9** (1.2 g, 54.2%).

LCMS (m/z): 477.4 [M<sup>+</sup>+1]

10 <sup>1</sup>H-NMR: (400 MHz, DMSO-d<sub>6</sub>): δ 8.82 (d, 2H), 7.49 (t, 1H), 4.72 (d, 1H), 4.31 (q, 1H), 3.62 (br s, 2H), 3.25-3.19 (m, 1H), 2.24-2.05 (m, 2H), 1.85-1.81 (m, 2H), 1.42 (br s, 1H), 1.25 (t, 3H), 0.92 (s, 8H), 0.75 (s, 9H), 0.02 (s, 3H).

**Synthesis of *tert*-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (10)**

15 [00131] To a stirring solution of **9** (1.0 g, 2.10 mmol) in THF (20 mL) was added TBAF (1M in THF) (6.3 mL, 6.30 mmol) at 0°C under N<sub>2</sub> atmosphere and stirred for 1 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with ice water and extracted with EtOAc. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain crude product, which was  
 20 purified by silica gel column chromatography eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **10** (0.35 g, 46%).

<sup>1</sup>H-NMR: (400 MHz, DMSO-d<sub>6</sub>): δ 8.81 (d, 2H), 7.49 (t, 1H), 4.81 (d, 1H), 4.65 (d, 1H), 4.25-4.20 (m, 1H), 3.64-3.51 (m, 2H), 3.34 (s, 1H), 3.25-3.20 (m, 1H), 2.25-2.20 (m, 2H), 1.87-1.82 (m, 2H), 1.19 (d, 3H), 0.97 (s, 9H).

25 LCMS (m/z): 363.3 [M<sup>+</sup>+1]

**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-2,5-diazaspiro[3.4]octan-1-one (Compound Y)**

[00132] To a stirring solution of **10** (0.3 g, 0.82 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was added molecular sieves (0.3 g) followed by BF<sub>3</sub>-etherate (0.31 mL, 2.48 mmol) at 0 °C and stirred at  
 30 RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was filtered and obtained residue was dissolved in MeOH and washed with CH<sub>2</sub>Cl<sub>2</sub>. The volatiles

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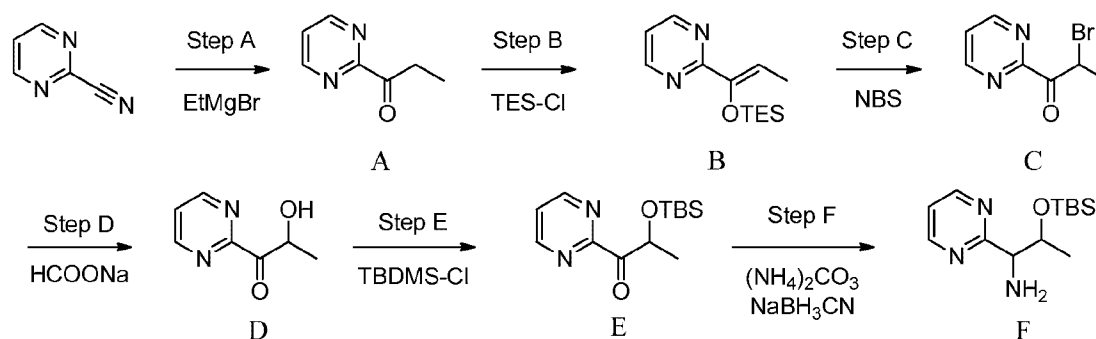
were evaporated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **Compound Y** (0.12 g, 55%).

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (d, 2H), 7.49 (t, 1H), 4.81 (d, 1H), 4.65 (d, 1H), 4.25-4.20 (m, 1H), 3.64-3.51 (m, 2H), 3.12-3.01 (m, 2H), 2.15-2.10 (m, 2H), 1.87-1.82 (m, 2H), 1.19 (d, 3H).

**LCMS (m/z):** 263.1 [M<sup>+</sup>+1]

**Preparation of key intermediates, schemes I-1 to I-7:**

**Scheme I-1**



**Synthesis of 1-(pyrimidin-2-yl)propan-1-one, A:**

**[00133]** Referring to Scheme I-1, to a stirring solution of pyrimidine-2-carbonitrile (25 g, 238 mmol) in THF (180 mL) was added ethyl magnesium bromide (1M in THF, 37.9 g, 285 mmol) at 0 °C and stirred for 2 h at RT. After completion of starting material (by TLC), the reaction mixture was diluted with saturated ammonium chloride solution and EtOAc (150 mL). The separated organic layer was washed with brine solution (2 x 100 mL). The extracted organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **A** (18.3 g, 57%) as an off-white solid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.00 (d, *J* = 5.2 Hz, 2H), 7.70 (t, *J* = 4.8 Hz, 1H), 3.20-3.15 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H).

**LCMS m/z:** 137 [M<sup>+</sup>+1].

**Synthesis of (Z)-2-(1-((triethylsilyl)oxy)prop-1-en-1-yl)pyrimidine (B):**

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[00134] To a stirring solution of **A** (14 g, 103 mmol) in dry THF (140 mL) was added LiHMDS (1M in THF, 206 mL, 206 mmol) slowly at 0 °C and stirred for 30 min. After added chloro triethylsilane (24.8 g, 165 mmol) in THF (50 mL) dropwise at 0 °C and stirred 1 h. After completion of starting material (by TLC), the reaction mixture was diluted with saturated ammonium chloride solution (100 mL) and EtOAc (150 mL). The separated organic layer was washed with brine solution (2 x 100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 20% EtOAc/hexane to afford **B** (23 g, 89.4%) as yellow thick syrup.

10 <sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.75 (d, *J* = 4.8 Hz, 2H), 7.32 (t, *J* = 4.8 Hz, 1H), 6.36-6.31 (m, 1H), 1.77 (d, *J* = 7.2 Hz, 3H), 0.95-0.87 (m, 9H), 0.71-0.65 (m, 6H).

**Synthesis of 2-bromo-1-(pyrimidin-2-yl) propan-1-one (C):**

[00135] To a stirring solution of **B** (23 g, 92 mmol) in THF/H<sub>2</sub>O (184 mL/46 mL) were added N-bromosuccinamide (18 g, 101 mmol) slowly at 0 °C and stirred for 3 h at RT. After completion of starting material (by TLC), the reaction mixture was diluted with H<sub>2</sub>O and EtOAc (100 mL/150 mL). The separated organic layer was washed with hypo solution (2 x 100 mL) followed by brine solution (2 x 100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 15% EtOAc/hexane to afford **C** (11.5 g, 58%) as yellow thick syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.06 (d, *J* = 4.8 Hz, 2H), 7.75 (t, *J* = 4.8 Hz, 1H), 5.97-5.92 (m, 1H), 1.83 (d, *J* = 6.4 Hz, 3H).

25 **Synthesis of 2-hydroxy-1-(pyrimidin-2-yl) propan-1-one (D):**

[00136] To a stirring solution of **C** (11.5 g, 53.4 mmol) in MeOH (80 mL) was added sodium formate (14.5 g, 214 mmol) and stirred the reaction mass at 80 °C for 6 h. After completion of reaction (by TLC), the reaction mixture was evaporated under reduced pressure to give crude product, which was purified by column chromatography eluting 50% EtOAc/*n*-hexane to afford **D** (5.0 g, 61.6%) as colorless liquid.

30 <sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.73 (d, *J* = 5.2 Hz, 2H), 7.55 (t, *J* = 4.8 Hz, 1H), 5.28-5.26 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H)

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**Synthesis of (2-((tert-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propan-1-one (E):**

[00137] To a stirring solution of **D** (5 g, 32.8 mmol) in DCM (50 mL) were added imidazole (5.5 g, 82.2 mmol), DMAP (800 mg, 0.65 mmol) at 0 °C and stirred for 10 min.  
5 After added TBDMS-Cl (7.38 g, 49.2 mmol) at 0 °C and stirred at RT for 12 h. After completion of starting material (by TLC), diluted the reaction mass with H<sub>2</sub>O (50 mL). The separated organic layer was washed with brine solution (2 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 20% EtOAc/hexane to afford **E**  
10 (6 g, 68.8%) as an off-white solid.

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>): δ 9.00 (d, *J* = 5.2 Hz, 2H), 7.71 (t, *J* = 4.8 Hz, 1H), 5.47-5.42 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 9H), 0.05 (s, 6H).

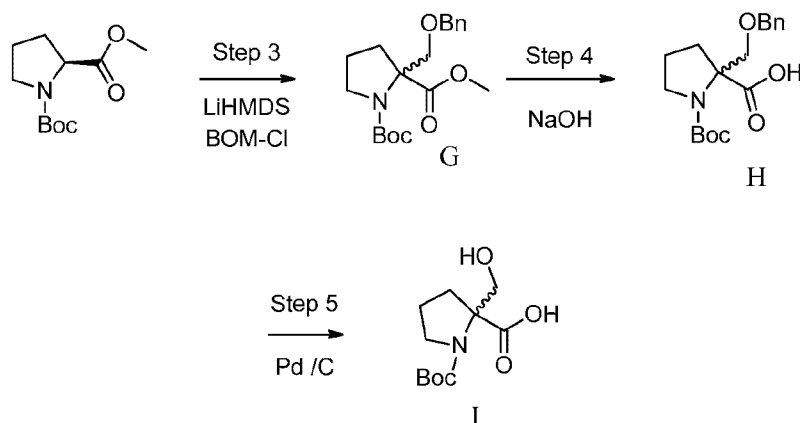
**Synthesis of (2-((tert-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propan-1-amine (F):**

15 [00138] To a stirring solution of **E** (6 g, 22.5 mmol) in MeOH (50 mL) were added sodium acetate (3.69 g, 45.1 mmol), ammonium carbonate (21 g, 135 mmol), AcOH (1.28 mL, 22.5 mmol) at RT and stirred the reaction mixture at 90 °C for 2 h. The temperature of the reaction was cooled to RT and added sodium cyanoborohydride (2.84 g, 45.1 mmol) slowly and stirred at 90 °C for 6 h. After completion of reaction (by TLC), evaporated MeOH under  
20 reduced pressure. The crude residue was diluted with water (20 mL) and extracted with DCM (2 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 5% MeOH/DCM to afford **F** (4.2 g, 69.6%) as semi solid.

25 **<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>): δ 8.83 (d, *J* = 4.8 Hz, 2H), 7.40 (t, *J* = 5.2 Hz, 1H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.90 (d, *J* = 6.4 Hz, 2H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.70 (s, 9H), 0.02 (s, 6H).

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Scheme I-2



**Synthesis of 1-tert-butyl 2-methyl 2-((benzyloxy) methyl) pyrrolidine-1, 2-dicarboxylate**

5 **(G):**

[00139] To a stirring solution of t-BOC proline methyl ester (25 g, 109 mmol) in THF (250 mL) was added LiHMDS (240 mL, 240 mmol) at -20 °C and stirred for 2 h. To this BOM-chloride (23 mL, 163 mmol) was added drop wise at -30 °C and stirred for 2 h. After consumption of the starting material (by TLC), the reaction was quenched with aqueous NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with water (2 x 150 mL) followed by brine solution (2 x 100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to obtain crude compound which was purified by column chromatography by eluting 10% EtOAc/*n*-hexane to afford compound G (30 g, 79%) as thick syrup.

15 **<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.36-7.22 (m, 5H), 4.59-4.48 (m, 2H), 4.02-3.88 (m, 1H), 3.63 (s, 3H), 3.49-3.35 (m, 2H), 3.34-3.30 (m, 1H), 2.31-2.23 (m, 1H), 2.04-1.89 (m, 2H), 1.82-1.78 (m, 1H).

**LCMS** (*m/z*): 249.4 [(M<sup>+</sup>+1)-Boc].

**Synthesis of 2-((benzyloxy) methyl)-1-(tert-butoxycarbonyl) pyrrolidine-2-carboxylic acid**

20 **(H):**

[00140] To a stirring solution of compound G (30 g, 86 mmol) in methanol (70 mL) was added NaOH solution (6.88 g in 70 mL H<sub>2</sub>O) at RT. The reaction mixture was heated to 70 °C for 16 h. After consumption of the starting material (by TLC), the solvent from the reaction was evaporated under reduced pressure and diluted with EtOAc (2 x 200 mL). The separated

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aqueous layer was acidified using citric acid solution (pH~3) and extracted with EtOAc (2 x 250 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford crude which was triturated with n-hexane to obtain compound **H** (25 g, 86.8%) as off-white solid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.35 (br s, 1H), 7.37-7.29 (m, 5H), 4.56-4.48 (m, 2H), 4.06-4.00 (m, 1H), 3.92-3.89 (m, 1H), 3.66-3.45 (m, 1H), 3.37-3.28 (m, 1H), 2.31-2.20 (m, 1H), 2.05-1.97 (m, 1H), 1.87-1.75 (m, 2H), 1.38 (s, 9H).

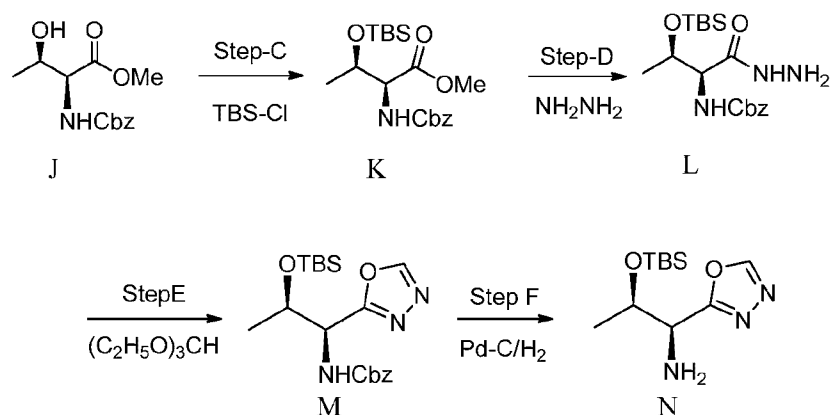
**LCMS** (*m/z*): 335.3 [M<sup>+</sup>+1].

**Synthesis of 1-(tert-butoxycarbonyl)-2-(hydroxymethyl) pyrrolidine-2-carboxylic acid (I):**

**[00141]** To a stirring solution of compound **H** (25 g, 74 mmol) in methanol (150 mL) was added 50% wet 10% Pd/C (7 g) at RT and stirred for 10 h under H<sub>2</sub> atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the pad was washed with methanol (100 mL). Obtained filtrate was concentrated under reduced pressure to afford compound **I** (15 g, 82.8%) as white solid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 4.66 (br s, 1H), 3.96-3.83 (m, 1H), 3.63-3.59 (m, 1H), 3.49-3.41 (m, 1H), 3.34-3.25 (m, 1H), 2.30-2.17 (m, 1H), 1.95-1.72 (m, 3H), 1.38 (s, 9H).

**Scheme I-3**



**Synthesis of (2S, 3R)-methyl 2-(((benzyloxy) carbonyl) amino)-3-((tert-butyldimethylsilyl) oxy) butanoate (K):**

**[00142]** Referring to Scheme I-3, to a stirring solution of **J** (50 g, 187 mmol) in DMF (400 mL) were added DIPEA (86 mL, 468 mmol) TBDMS-Cl (33.66 mL, 224 mmol) at 0 °C and stirred at RT for 12 h. After completion of starting material (by TLC), diluted the reaction

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mass with EtOAc (500 ml). The separated organic layer was washed with (2x200 mL) of Water followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 10% EtOAc/hexane to afford **K** (50 g, 70.1%) as colorless syrup.

**<sup>1</sup>H-NMR:** (400 MHz, CDCl<sub>3</sub>): δ 7.39-7.32 (m, 5H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.14 (s, 2H), 4.45-4.43 (m, 1H), 4.29-4.26 (m, 1H), 3.72 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 0.83 (s, 9H), 0.09 (s, 6H).

LCMS *m/z*: 382.2[M<sup>+</sup>+1].

**Synthesis of benzyl ((2*S*, 3*R*)-3-((tert-butyldimethylsilyl) oxy)-1-hydrazinyl-1-oxobutan-2-yl) carbamate (L):**

[00143] A solution of **K** (50 g, 131 mmol) in EtOH (400 mL) was added hydrazine hydrate (32.8 g, 656 mmol), at RT and after stirred at 90 °C for 24 h. After completion of starting material (by TLC), evaporated ethanol under reduced pressure. The crude residue was diluted with water (100 mL) and EtOAc (500 mL). After the separated organic layer was washed with (2x100 mL) of water followed by brine solution (1x100 mL). Dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 20% EtOAc/hexane to afford **L** (25 g, 50%) as colorless thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.10 (s, 1H), 7.36-7.30 (m, 5H), 6.83 (d, *J* = 9.6 Hz, 1H), 5.02 (s, 2H), 4.19 (s, 2H), 4.05-4.02 (m, 1H), 3.97-3.93 (m, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 6H).

**Synthesis of benzyl ((1*S*, 2*R*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamate (M):**

[00144] A solution of **L** (25 g, 65.6 mmol) in triethyl orthoformate (250 mL) was added *p*-TSA (catalytic, 250 mg) at RT and after stirred at 80 °C for 3 h. After completion of starting material (by TLC), evaporated triethyl orthoformate under reduced pressure. The crude residue was purified by column chromatography eluting 10% EtOAc/hexane to afford **M** (15 g, 58%) as thick syrup.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.22 (s, 1H), 7.85 (d, *J* = 9.5 Hz, 1H), 7.36-7.31 (m, 5H), 5.05 (s, 2H), 4.96-4.93 (m, 1H), 4.25 (t, *J* = 6.0 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.80 (s, 9H), 0.10 (s, 6H).



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LCMS  $m/z$ : 392.4 $[M^+ + 1]$ .

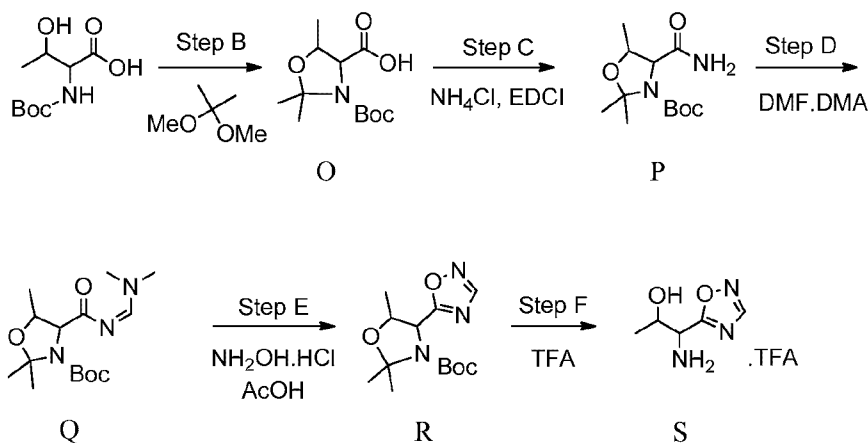
**Synthesis of (1*S*, 2*R*)-2-(((tert-butyl)dimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propan-1-amine (N):**

5 [00145] To a stirring solution of **M** (15 g, 38.3 mmol) in methanol (200 mL) was added 50% wet 10% Pd/C (5 g) and stirred under H<sub>2</sub> atmosphere (balloon pressure) for 4 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (100 mL). The filtrate was concentrated under reduced pressure to afford **N** (10 g, crude) as thick syrup.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.15 (s, 1H), 4.11 (t, *J* = 5.0 Hz, 1H), 4.03 (d, *J* = 2.0 Hz, 1H), 2.05 (br s, 2H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.76 (s, 9H), 0.02 (s, 6H).

LCMS  $m/z$ : 258.3  $[M^+ + 1]$ .

**Scheme I-4**



**Synthesis of 3-(tert-butoxycarbonyl)-2, 2, 5-trimethyloxazolidine-4-carboxylic acid (O)**

[00146] To a stirring solution of N-BOC threonine (15 g, 59.28 mmol) in THF (150 mL) was added PPTS (1.47 g, 5.92 mmol) followed by 2,2-dimethoxy propane (21.79 mL, 0.17 mol) at 0 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at RT for 16 h. The reaction mixture was again heated to reflux for 6 h. The reaction mixture was diluted with aqueous NaHCO<sub>3</sub> solution and washed with EtOAc (1x100 mL). Aqueous layer was acidified using citric acid solution (pH~2) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x100 mL). The organic layer was

20

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washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to afford compound **O** (18 g, crude).

<sup>1</sup>H-NMR: (400 MHz, DMSO-d<sub>6</sub>): δ 13.25 (br s, 1H), 4.11-4.05 (m, 1H), 3.79 (d, 1H), 1.50 (s, 3H), 1.67 (s, 3H), 1.45 (s, 9H), 1.29 (d, 3H).

5 **Synthesis of *tert*-butyl 4-carbamoyl-2, 2, 5-trimethyloxazolidine-3-carboxylate (P):**

[00147] To a stirring solution of compound **O** (18 g, 69.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (180 mL) was added HOBT (14.16 g, 0.104 mol), EDCI.HCl (19.88 g, 0.104 mol) followed by NH<sub>4</sub>Cl (5.56 g, 0.104 mol) and DIPEA (31.9 mL, 0.173 mol) at 0 °C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with aqueous citric acid, NaHCO<sub>3</sub> followed by brine. Organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give crude; which was purified by silica gel column chromatography eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford compound **P** (13 g, 72.5%).

10 <sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.51 (br s, 1H), 7.14 (br s, 1H), 3.97-3.95 (m, 1H), 3.71 (d, 1H), 1.51 (d, 6H), 1.34 (s, 9H), 1.24 (d, 3H).

LCMS (ESI): 159.1[(M<sup>+</sup>+1)-Boc]

**Synthesis of (Z)-*tert*-butyl 4-(((dimethylamino) methylene) carbamoyl)-2, 2, 5-trimethyloxazolidine-3-carboxylate (Q):**

20 [00148] A solution of compound **P** (13 g, 50.3 mmol) in DMF.DMA (130 mL) was stirred at reflux temperature for 3 h under N<sub>2</sub> atmosphere. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford compound **Q** (15.7 g, crude). This crude material was directly taken for the next step without further purification.

25

**Synthesis of *tert*-butyl 2, 2, 5-trimethyl-4-(1, 2, 4-oxadiazol-5-yl) oxazolidine-3-carboxylate (R):**

[00149] To a stirring solution of compound **Q** (15.7 g, 50.09 mmol) in ethanol (157 mL) was added hydroxylamine hydrochloride (6.96 g, 0.10 mol) under N<sub>2</sub> atmosphere. The reaction mixture was heated to reflux and stirred for 2 h. After consumption of the starting material (by

30

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TLC), acetic acid (28.6 mL, 0.50 mol) was added to the reaction mixture and then refluxed for 16 h. The solvents from the reaction mixture was evaporated under vacuum to give crude; which was purified by silica gel column chromatography eluting with 10% EtOAc/Hexane to afford compound **R** (4.5 g, 32%).

- 5 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.35 (s, 2H), 4.61 (d, 1H), 4.22-4.15 (m, 1H), 1.55 (s, 6H), 1.37 (s, 2H), 1.25 (d, 3H), 1.21 (s, 6H).

**LCMS (ESI):** 284 [ $M^+ + 1$ ]

**Mass (m/z):** 283 [ $M^+$ ]

**Synthesis of 1-amino-1-(1, 2, 4-oxadiazol-5-yl) propan-2-ol (S):**

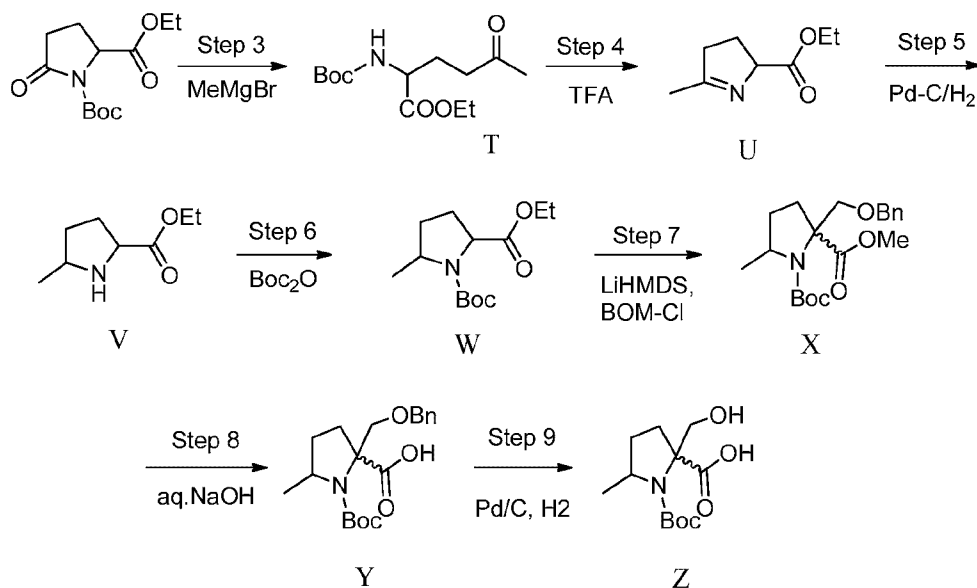
- 10 **[00150]** To a stirring solution of compound **R** (5 g, 17.6 mmol) in water (25 mL) was added trifluoroacetic acid (25 mL). The reaction mixture was stirred at RT for 5 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under vacuum. The residue was dissolved in water and neutralized with aqueous NaHCO<sub>3</sub>. The solvent from the reaction mixture was evaporated under vacuum and extracted with 5%  
15 MeOH/CH<sub>2</sub>Cl<sub>2</sub> (3x 100 mL). The organic layer was concentrated under reduced pressure to afford compound **S** (2.5 g, crude).

**<sup>1</sup>H-NMR:** (400 MHz, D<sub>2</sub>O): δ 8.84 (s, 1H), 4.05 (d, 1H), 3.98-3.95 (m, 1H), 3.67 (s, 1H), 3.58 (d, 1H), 1.15 (d, 3H), 1.12 (d, 3H).

**LCMS (ESI):** 144.1 [ $M^+ + 1$ ]

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Scheme I-5

**Synthesis of ethyl 2-((tert-butoxycarbonyl) amino)-5-oxohexanoate (T):**

- 5 [00151] To a stirring solution of 1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (12 g, 46.6 mmol) in THF (120 mL) under inert atmosphere was added MeMgBr (3M in ether) (20.2 mL, 60.6 mmol) at 0 °C and stirred for 2 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue obtained was purified by silica gel column chromatography eluting with 20% EtOAc/Hexane to afford compound **T** (10 g, 79%).

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 5.14 (br s, 1H), 4.23 (q, 2H), 2.62-2.47 (m, 2H), 2.17 (s, 4H), 1.91-1.82 (m, 1H), 1.45 (s, 10H), 1.26 (t, 3H).

15 **Synthesis of ethyl 5-methylpyrrolidine-2-carboxylate (V):**

[00152] To a stirring solution of compound **T** (10 g, 36.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added TFA (14.89 mL, 194.6 mmol) at 0 °C. After being stirred for 2 h at RT, the reaction mixture was concentrated under reduced pressure to get compound **U**. Obtained material was dissolved in ethanol (100 mL) and 10% Pd/C (50% wet, 3 g) under N<sub>2</sub> atmosphere. The reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon pressure) for 16 h. The reaction

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mixture was filtered through a pad of celite and filtrate was concentrated under reduced pressure to afford compound **V** (15 g, crude). This material was directly taken for the next step without further purification.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): 4.4 (m, 1H), 4.2 (m, 2H), 3.6 (m, 1H), 2.3 (m, 1H), 2.1 (m, 2H), 1.6 (m, 1H), 1.3 (d, 3H), 1.2 (t, 3H).

**LCMS *m/z*:** 158.1 [ $M^+$ +1].

**Synthesis of 1-tert-butyl 2-ethyl 5-methylpyrrolidine-1, 2-dicarboxylate (W):**

**[00153]** To a stirring solution of compound **V** (30 g, 191 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added DMAP (23.3 g, 191 mmol) followed by Et<sub>3</sub>N (79.8 mL, 573 mmol) and Boc-anhydride (104 mL, 477 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with water (2x150 mL) followed by brine. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. Obtained crude material was purified by column chromatography eluting with 6% EtOAc/Hexane to afford compound **W** (12 g, 82%) as pale yellow liquid.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 4.13-3.86 (m, 4H), 2.15 (d, *J* = 3.5 Hz, 1H), 1.99-1.82 (m, 2H), 1.52 (t, *J* = 4.5 Hz, 1H), 1.38 (s, 9H), 1.24 (t, *J* = 5.5 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H)  
**LCMS (*m/z*):** 258 [ $M^+$ +1].

**Synthesis of 1-tert-butyl 2-ethyl 2-((benzyloxy) methyl)-5-methylpyrrolidine-1, 2-dicarboxylate (X):**

**[00154]** To a stirring solution of compound **W** (8.0 g, 31.12 mmol) in THF (70 mL) was added LiHMDS (59 mL, 41.72 mmol) at -78 °C and stirred for 2 h. To this BOM-chloride (6.56 mL, 41.72 mmol) was added drop wise and stirred for 2 h at -30 °C. After consumption of the starting material (by TLC), the reaction was quenched with aqueous NH<sub>4</sub>Cl solution (20 mL) and extracted with DCM (30 mL). The separated organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford crude material was purified by column chromatography eluting with 10% EtOAc/Hexane to afford compound **X** (11 g, 94.2%) as pale yellow liquid.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.33-7.25 (m, 5H), 4.38 (d, *J* = 10.5 Hz, 2H), 4.08-3.98 (m, 1H), 3.88 (d, *J* = 9.5 Hz, 2H), 2.20-2.08 (m, 2H), 1.38 (s, 9H), 1.37-1.29 (m, 4H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.14-1.10 (m, 3H).

**LCMS (*m/z*):** 378 ( $M^+$ +1).

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**Synthesis of 2-((benzyloxy) methyl)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (Y):**

[00155] To a stirring solution of compound X (11 g, 29.17 mmol) in CH<sub>3</sub>OH/THF (22 mL/20 mL) were added 2N NaOH solution (33 mL) at RT. The reaction mixture was heated to 65 °C for 8 h. After consumption of the starting material (by TLC), the solvent from the reaction was evaporated under reduced pressure and diluted with EtOAc (50 mL). The aqueous layer was acidified using citric acid solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The separated organic layer was washed with water (1 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford compound Y (8 g, 80%).

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.58 (s, 1H), 7.34-7.28 (m, 5H), 4.54-4.47 (m, 2H), 4.05-3.87 (m, 2H), 3.70-3.62 (m, 1H), 2.28-2.08 (m, 3H), 1.46-1.37 (m, 1H), 1.28 (s, 9H).

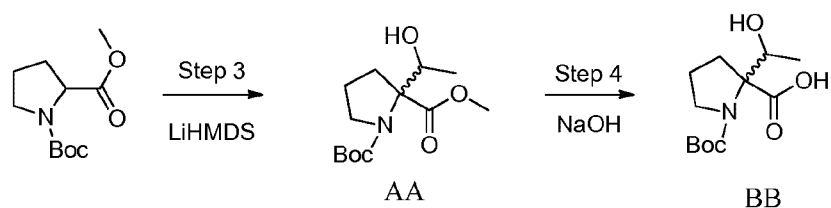
LCMS (m/z): 350 [M<sup>+</sup>+1].

**Synthesis of 1-(tert-butoxycarbonyl)-2-(hydroxymethyl)-5-methylpyrrolidine-2-carboxylic acid (Z):**

[00156] To a stirring solution of compound Y (8 g, 1.45 mmol) in methanol (40 mL) was added 50% wet Pd/C (4 g) under N<sub>2</sub> atmosphere. The reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon pressure) at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the pad was washed with methanol. Obtained filtrate was concentrated under reduced pressure to afford crude compound which was triturated with n-pentane to obtained compound Z (4.5 g, 75.2%) as white solid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 12.37 (br s, 1H), 4.61 (br s, 1H), 3.95-3.85 (m, 3H), 2.18-2.06 (m, 3H), 1.44-1.41 (m, 1H), 1.38 (s, 9H), 1.09 (d, *J* = 6.0 Hz, 3H); LCMS (ESI): 260 [M<sup>+</sup>+1]

**Scheme 1-6**



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**Synthesis of 1-(tert-butyl) 2-methyl 2-(1-hydroxyethyl) pyrrolidine-1, 2-dicarboxylate (AA):**

[00157] To a stirring solution of N-BOC proline methyl ester (30 g, 131 mmol) in THF (100 mL) was added LiHMDS (323 mL, 327 mmol) at -20 °C and stirred for 30 min. To this  
 5 acetaldehyde (12.3 mL, 196 mmol) was added drop wise at -20 °C and stirred for 2 h. After consumption of the starting material (by TLC), the reaction was quenched with aqueous NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with brine solution (2 x 150 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to obtain crude compound which was purified by column chromatography by  
 10 eluting 10% EtOAc/*n*-hexane to afford compound **AA** (30 g, 83.8%) as thick syrup.

<sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 5.82 (d, *J* = 10.0 Hz, 1H), 4.71-4.11 (m, 1H), 3.76 (s, 3H), 3.66-3.57 (m, 1H), 3.45-3.36 (m, 1H), 2.51-2.46 (m, 1H), 2.33-2.24 (m, 1H), 2.04-1.97 (m, 1H), 1.95-1.83 (m, 1H), 1.49 (s, 9H), 1.20-1.11 (m, 3H).

LCMS (*m/z*): 274.3 [M<sup>+</sup>+1].

15 **Synthesis of 1-(tert-butoxycarbonyl)-2-(1-hydroxyethyl) pyrrolidine-2-carboxylic acid (BB):**

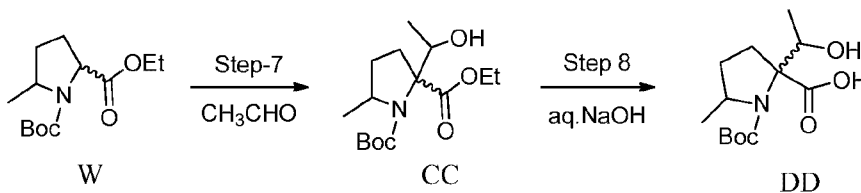
[00158] To a stirring solution of compound **AA** (30 g, 109 mmol) in methanol (50 mL) was added NaOH solution (8.72 g in 10 mL H<sub>2</sub>O, 218 mmol) at RT. The reaction mixture was heated to 70 °C for 12 h. After consumption of the starting material (by TLC), the solvent from  
 20 the reaction was evaporated under reduced pressure and diluted with DCM (200 mL). The separated aqueous layer was acidified using citric acid solution (pH~3) and extracted with DCM (2 x 250 mL). The combined organic layer was washed with brine solution (1 x 100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford compound **BB** (9.5 g, 33.6%) as brown solid.

25 <sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 4.53-4.45 (m, 1H), 3.59-3.48 (m, 1H), 3.25-3.19 (m, 1H), 2.33-2.16 (m, 1H), 1.90-1.78 (m, 3H), 1.38 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H).

LCMS (*m/z*): 258.2 [M<sup>-</sup>-1].

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Scheme I-7



5 **Synthesis of 1-tert-butyl 2-ethyl 2-(1-hydroxyethyl)-5-methylpyrrolidine-1, 2-dicarboxylate (CC):**

[00159] To a stirring solution of compound **W** (18.0 g, 70 mmol) in THF (200 mL) was added LiHMDS (84 mL, 84 mmol) drop wise at  $-20\text{ }^{\circ}\text{C}$  and stirred for 30 min. To this acetaldehyde (4.2 mL, 77 mmol) was added drop wise and stirred for 45 min at  $-20\text{ }^{\circ}\text{C}$ . After consumption of the starting material (by TLC), the reaction was quenched with aqueous  $\text{NH}_4\text{Cl}$  solution (100 mL) and extracted with EtOAc (2 x 150 mL). The separated organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated to afford crude material was purified by column chromatography eluting with 30% EtOAc/Hexane to afford compound **CC** (15 g, 71.4%) as colorless syrup.

15

$^1\text{H-NMR}$ : (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.33-7.25 (m, 5H), 4.38 (d,  $J = 10.5\text{ Hz}$ , 2H), 4.08-3.98 (m, 1H), 3.88 (d,  $J = 9.5\text{ Hz}$ , 2H), 2.20-2.08 (m, 2H), 1.38 (s, 9H), 1.37-1.29 (m, 4H), 1.19 (t,  $J = 7.5\text{ Hz}$ , 3H), 1.14-1.10 (m, 3H);

LCMS ( $m/z$ ): 378 ( $\text{M}^+ + 1$ )

20

**Synthesis of 1-(tert-butoxycarbonyl)-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxylic acid (DD):**

[00160] To a stirring solution of compound **CC** (15 g, 49 mmol) in  $\text{CH}_3\text{OH}/\text{THF}$  (10 mL/40 mL) were added NaOH (3.98 g, 99 mmol) in water (10 mL) at RT. The reaction mixture was heated to  $70\text{ }^{\circ}\text{C}$  for 16 h. After consumption of the starting material (by TLC), the solvent from the reaction was evaporated under reduced pressure and acidified by using citric acid (pH~4). The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated to obtained crude compound, which was purified by column chromatography eluting 40% EtOAc to afford compound **DD** (4 g, 29.4%) as brown syrup.

30

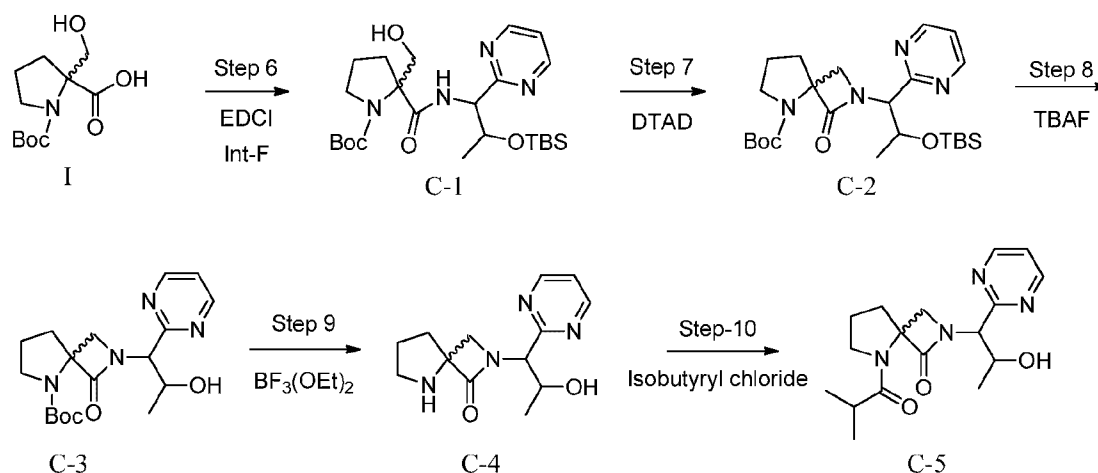


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**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 12.15 (br s, 2H), 4.54-4.50 (m, 1H), 4.03-4.02 (m, 1H), 2.17-1.77 (m, 3H), 1.41(s, 9H), 1.39-1.09 (m, 3H), 0.99-0.94 (m, 3H).

**LCMS** (*m/z*): 272.4 [*M*<sup>-</sup>1].

## 5 Scheme 1



### Synthesis of *tert*-butyl2-((2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl) carbamoyl)-2-(hydroxymethyl) pyrrolidine-1-carboxylate(C-1):

10 **[00161]** Referring to Scheme 1, to a stirring solution of I (2 g, 8.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added intermediate F (2.39 g, 8.97 mmol), EDCI. HCl (2.33 g, 12.2 mmol) followed by HOBT (1.66 g, 12.24 mmol) and DIPEA (4.5 mL, 24.4 mmol) at 0°C. The reaction mixture was warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC),  
 15 the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The separated organic layer was washed with aqueous NaHCO<sub>3</sub> solution followed by aqueous NH<sub>4</sub>Cl. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to get crude product, which was purified by silica gel column chromatography eluting with 70% EtOAc/hexane to afford compound **C-1** (2.3 g, 57.5%).

20 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.91 (d, 1H), 8.68 (d, 2H), 7.41 (br s, 1H), 5.74 (br t, 1H), 5.07-4.89 (m, 1H), 4.15-4.10 (m, 1H), 3.97-3.92 (m, 1H), 3.45-3.41 (m, 1H), 1.79-1.74 (m, 2H), 1.43-1.39 (m, 4H), 1.29-1.21 (m, 6H), 1.12 (d, 5H), 0.71 (s, 9H), 0.12 (t, 1H), 0.09 (s, 2H), 0.08 (s, 1H), 0.04 (s, 2H).

**LCMS** (*m/z*): 495.5 [*M*<sup>+</sup>+1].

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**Synthesis of *tert*-butyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate(C-2):**

[00162] To a stirring solution of compound C-1 (2.3 g, 4.65mmol) in THF (23 mL) was added TPP (1.34 g, 5.12 mmol) followed by DTAD (1.6 g, 6.98 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to get crude product, which was purified by silica gel column chromatography eluting with 25% EtOAc/hexane to afford compound C-2 (1.2 g, 54.2%)

10 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ8.82 (d, 2H), 7.49 (t, 1H), 4.72 (d, 1H), 4.31 (q, 1H), 3.62 (br s, 2H), 3.25-3.19 (m, 1H), 2.24-2.05 (m, 2H), 1.85-1.81 (m, 2H), 1.42 (br s, 1H), 1.25 (t, 3H), 0.92 (s, 8H), 0.75 (s, 9H), 0.02 (s, 3H).

LCMS (*m/z*): 477.4 [*M*<sup>+</sup>+1].

**Synthesis of *tert*-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-1-oxo-2,5 diazaspiro [3.4]octane-5-carboxylate (C-3):**

15 [00163] To a stirring solution of compound C-2 (1.0 g, 2.10 mmol) in THF (20 mL) was added TBAF (1M in THF) (6.3 mL, 6.30 mmol) at 0 °C under N<sub>2</sub> atmosphere and stirred for 1 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with ice water and extracted with EtOAc. The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford compound C-3 (0.35 g, 46%).

25 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ8.81 (d, 2H), 7.49 (t, 1H), 4.81 (d, 1H), 4.65 (d, 1H), 4.25-4.20 (m, 1H), 3.64-3.51 (m, 2H), 3.34 (s, 1H), 3.25-3.20 (m, 1H), 2.25-2.20 (m, 2H), 1.87-1.82 (m, 2H), 1.19 (d, 3H), 0.97 (s, 9H).

LCMS (*m/z*): 363.3 [*M*<sup>+</sup>+1].

**Synthesis of *tert*-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-1-oxo-2, 5-diazaspiro [3.4]octane-5-carboxylate (C-4)**

30 [00164] To a stirring solution of compound C-3 (200 mg, 0.42 mmol) in THF (5 mL) was added TBAF (1M in THF) (0.84 mL, 0.84 mmol) at 0 °C under N<sub>2</sub> atmosphere and stirred for 2 h. After consumption of the starting material (by TLC), the reaction mixture was

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concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford **C-4** (125 mg, 82.2%).

**<sup>1</sup>H-NMR:** (400 MHz, CD<sub>3</sub>OD): 8.78 (t, *J* = 3.2 Hz, 2H), 7.42-7.38 (m, 1H), 4.92-4.87 (m, 1H), 4.79-4.56 (m, 1H), 4.43-4.38 (m, 1H), 4.33-3.97 (m, 1H), 3.88-3.80 (m, 1H), 3.48-3.44 (m, 1H), 3.40-3.30 (m, 1H), 2.31-2.12 (m, 2H), 1.96-1.84 (m, 2H), 1.42 (s, 9H), 1.32-1.28 (m, 3H);

**LCMS** (*m/z*): 363.3 [*M*<sup>+</sup>+1].

**HPLC:** 94.5%.

**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-2,5-diazaspiro[3.4]octan-1-one (C-5):**

10 **[00165]** To a stirring solution of compound C-4 (0.3 g, 0.82 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was added molecular sieves (0.3 g) followed by BF<sub>3</sub>-etherate (0.31 mL, 2.48 mmol) at 0 °C and stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was filtered and obtained residue was dissolved in MeOH and washed with CH<sub>2</sub>Cl<sub>2</sub>. The volatiles were evaporated under reduced pressure to obtain crude product, which was purified  
15 by silica gel column chromatography eluting with 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford C-5 (0.12 g, 55%).

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (d, 2H), 7.49 (t, 1H), 4.81 (d, 1H), 4.65 (d, 1H), 4.25-4.20 (m, 1H), 3.64-3.51 (m, 2H), 3.12-3.01 (m, 2H), 2.15-2.10 (m, 2H), 1.87-1.82 (m, 2H), 1.19 (d, 3H).

20 **LCMS** (*m/z*): 263.1 [*M*<sup>+</sup>+1].

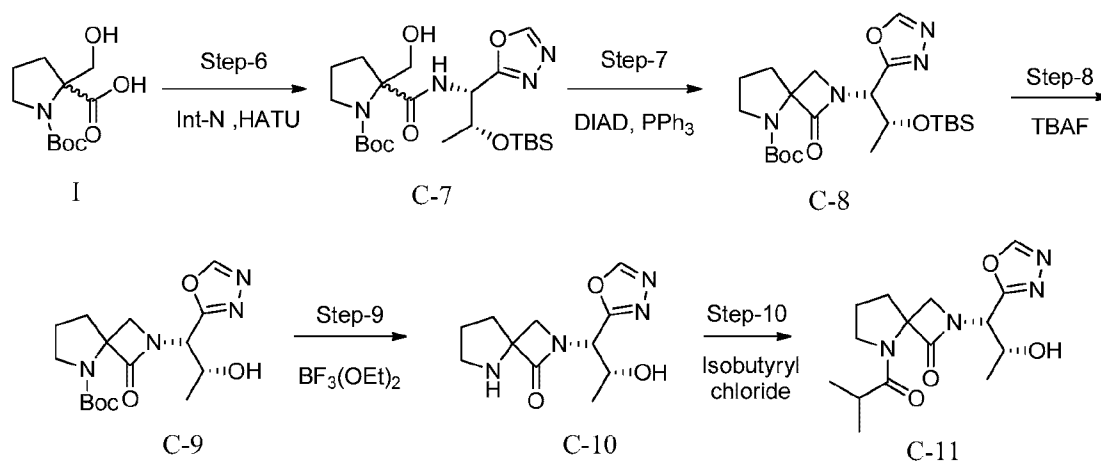
**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-5-isobutyryl-2, 5-diazaspiro [3.4] octan-1-one (C-6):**

**[00166]** To a stirring solution of compound **C-5** (500 mg, 1.9 mmol) in DCM (10 mL)  
25 was added TEA (0.79 mL, 5.72 mmol) followed by isobutyryl chloride (241 mg, 2.28 mmol) at 0 °C under N<sub>2</sub> atmosphere and stirred for 2 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 mL). The combined organic layer was washed with citric acid solution (1 x 20 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under  
30 reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 2% MeOH/DCM to afford **C-6** (85 mg, 13.4%) as white solid.

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**<sup>1</sup>H-NMR:** (400 MHz, CD<sub>3</sub>OD): δ 4.91-4.75 (m, 1H), 4.46-4.40 (m, 1H), 3.99-3.85 (m, 1H), 3.70-3.64 (m, 1H), 3.60-3.45 (m, 3H), 2.80-2.69 (m, 1H), 2.29-2.22 (m, 2H), 2.07-1.96 (m, 2H), 1.45-1.33 (m, 3H), 1.16-1.10 (m, 3H), 1.06-1.01 (m, 3H) .

## 5 Scheme 2



10

### Synthesis of tert-butyl 2-(((1*R*, 2*S*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamoyl)-2-(hydroxymethyl) pyrrolidine-1-carboxylate (C-7):

[00167] To a stirring solution of compound I (2.1 g, 8.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added DIPEA (3.81 mL, 21.4 mmol), intermediate F (2.64 g, 10.28 mmol), HATU (3.90 g, 10.28 mmol) at 0 °C and stirred to RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL). The organic layer was washed with citric acid (1 x 50 mL) followed by brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 50% EtOAc/*n*-hexane to afford compound C-7 (3.5 g, 85.15%) as yellow thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.24 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 5.82-5.54 (m, 1H), 4.36-4.28 (m, 1H), 4.12-4.00 (m, 1H), 3.93-3.66 (m, 1H), 3.43-3.39 (m, 1H), 2.69-2.66 (m, 2H), 2.02-1.94 (m, 2H), 1.78-1.68 (m, 2H), 1.40 (s, 9H), 1.23-1.15 (m, 3H), 0.75 (s, 9H), -0.08 (s, 6H);

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Mass (ESI):  $m/z$  484.7 [ $M^+ + 1$ ]

**Synthesis of tert-butyl 2-(((1*R*, 2*S*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamoyl)-2-(hydroxymethyl) pyrrolidine-1-carboxylate (C-8):**

[00168] To a stirring solution of triphenylphosphine (4.05 g, 15.4 mmol) in THF (30 mL) was added DIAD (3.03 g, 15.4 mmol) at RT and stirred for 15 min. After added compound C-7 (3 g, 6.19 mmol) in (20 mL) THF slowly and reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was triturated with 30% Ether/*n*-hexane (2 x 50 mL). The filtered organic solvent was concentrated and crude residue was purified by column chromatography by eluting 30% EtOAc/*n*-hexane to afford compound C-8 (2 g, 69.4%) as thick syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  9.28 (s, 1H), 5.30-5.21 (m, 1H), 4.84-4.81 (m, 1H), 4.49-4.29 (m, 1H), 4.05-3.91 (m, 1H), 3.65-3.61 (m, 1H), 3.39-3.24 (m, 1H), 2.23-2.12 (m, 2H), 1.81-1.76 (m, 2H), 1.41 (s, 9H), 1.20-1.14 (m, 3H), 0.75 (s, 9H), -0.22 (s, 6H);

Mass (ESI):  $m/z$  467.6 [ $M^+ + 1$ ]

**Synthesis of tert-butyl 2-(((1*R*, 2*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-9):**

[00169] To a stirring solution of compound C-8 (2 g, 4.29 mmol) in THF (20 mL) was added TBAF (4.3 mL, 6.43 mmol) slowly at 0° C and stirred at RT for 30 min. After completion of reaction (by TLC), the reaction mixture was evaporated under reduced pressure. The crude residue was purified by column chromatography by eluting 70% EtOAc/*n*-hexane to afford C-9 (400 mg, 26.5%) as white solid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): 9.29 (s, 1H), 5.30-5.21 (m, 1H), 5.08-4.95 (m, 1H), 4.08-4.03 (m, 1H), 3.91-3.71 (m, 1H), 3.75-3.71 (m, 1H), 3.65-3.52 (m, 1H), 3.36-3.22 (m, 1H), 2.22-2.09 (m, 2H), 1.83-1.77 (m, 2H), 1.41 (s, 9H), 1.10-1.04 (m, 3H);

LCMS: 353.4;

HPLC: 99.82%.

**Synthesis of 2-(((1*R*, 2*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl)propyl)-2, 5-diazaspiro [3.4] octan-1-one (C-10):**

[00170] To a stirring solution of compound C-9 (500 mg, 1.07 mmol) in DCM (5 mL) was added BF<sub>3</sub>(OEt)<sub>2</sub> (0.26 mL, 2.14 mmol) slowly at 0 °C and stirred at RT for 30 min. After completion of reaction (by TLC), the reaction mixture was evaporated under reduced pressure.

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The crude residue was triturated with di ethylether/*n*-pentane (5 mL/5 mL) to obtain solid, **C-10**, which was taken into the next step without further purification.

**Synthesis of 2-((1*R*, 2*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-5-isobutyryl-2, 5-diazaspiro [3.4] octan-1-one (C-11):**

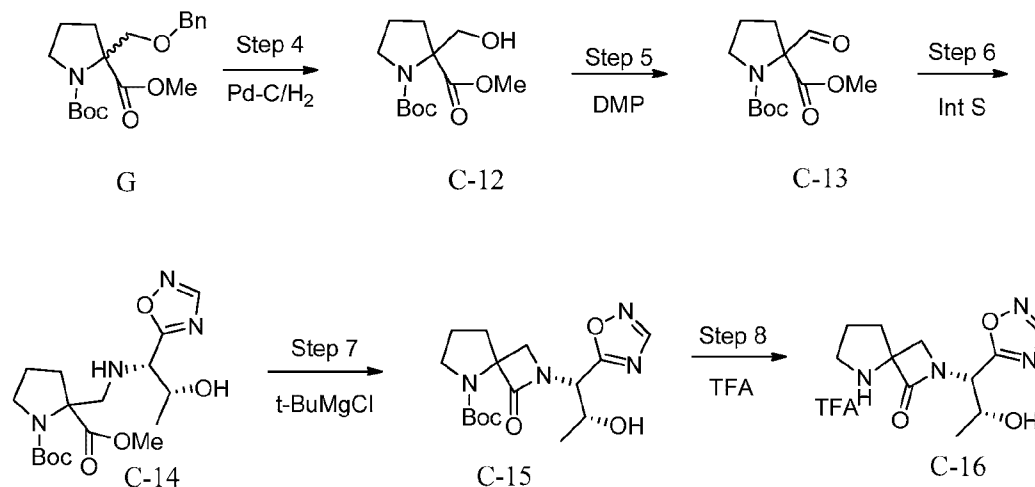
- 5 **[00171]** To a stirring solution of compound **C-10** (700 mg, 2.77 mmol) in DCM (10 mL) was added TEA (0.94 mL, 6.92 mmol), SM-3 (440 mg, 4.15 mmol) at 0 °C and stirred to RT for 1 h. After completion of reaction (by TLC), diluted with water (20 mL). The organic layer was washed with brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was purified by  
10 column chromatography followed by preparative HPLC purification to afford **C-11** (150 mg, 16.8%) as white solid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): 9.26 (s, 1H), 5.24-5.04 (m, 1H), 5.03-4.93 (m, 1H), 4.27-3.91 (m, 1H), 3.90-3.64 (m, 1H), 3.49-3.45 (m, 3H), 2.73-2.61 (m, 1H), 2.17-2.14 (m, 2H), 2.10-2.06 (m, 2H), 1.25-1.07 (m, 3H), 0.95-0.93 (m, 6H).

15 **LCMS** *m/z*: 323.3.

**HPLC**: 97.89%.

Scheme 3



20 **Synthesis of 1-*tert*-butyl 2-methyl 2-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate(C-12):**

**[00172]** To a stirring solution of compound **G** (74 g, 0.21 mol) in methanol (740 mL) was added 10% Pd/C (50% wet, 14.8 g) under N<sub>2</sub> atmosphere and stirred for 6 h under H<sub>2</sub>

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atmosphere (balloon pressure). The reaction mixture was filtered through celite pad and concentrated under reduced pressure to afford compound **C-12** (45 g, 82%) as crude.

**Synthesis of 1-tert-butyl 2-methyl 2-formylpyrrolidine-1,2-dicarboxylate(C-13):**

- 5   **[00173]**       To a stirring solution of compound **C-12** (10 g, 38.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added Dess-Martin periodinane (19.6 g, 46.27 mmol) at 0 °C under N<sub>2</sub> atmosphere and stirred for 3 h. After consumption of the starting material (by TLC), the reaction was quenched with aqueous NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude was purified by  
10 column chromatography eluting with 10% EtOAc/Hexane to afford compound **C-13** (7 g, 70.5%).

**Synthesis of 1-tert-butyl 2-methyl 2-(((1S,2R)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl) propyl) amino) methyl)pyrrolidine-1,2-dicarboxylate (C-14):**

- 15   **[00174]**       To a stirring solution of compound **C-13** (3 g, 11.6 mmol) in MeOH (30 mL) was added sodium acetate (1.91 g, 23.3 mmol) followed by intermediate **S** (3.6 g, 13.9 mmol). The reaction mixture was heated to reflux for 1 h. The reaction mixture was slowly cooled to RT-0 °C, to this sodium cyanoborohydride (1.465 g, 23.3 mmol) and stirring was continued for  
20 another 6 h at RT. After consumption of the starting material (by TLC), methanol from the reaction was evaporated under reduced pressure and the residue was diluted with water and extracted with EtOAc (2x 50 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give crude; which was purified by silica gel column chromatography eluting with 40% EtOAc/Hexane to afford compound **C-14** (2.5 g, 56%).  
25   **LCMS** *m/z*: 385 [M<sup>+</sup>+1].

**Synthesis of tert-butyl 2-(((1S,2R)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl) propyl)-1-oxo-2,5-diazaspiro [3.4] octane-5-carboxylate (C-15):**

- 30   **[00175]**       To a stirring solution of compound **C-14** (1.5 g, 3.90 mmol) in THF (30 mL) was cooled to 0 °C and added *t*-BuMgCl (1M in THF, 15.6 mL, 15.6 mmol) and stirred for 15 min. After consumption of the starting material (by TLC), the reaction mixture was quenched with aqueous NH<sub>4</sub>Cl solution and diluted with water. Aqueous layer was extracted with EtOAc (2x 25 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated

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under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 150% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to afford **C-15** (0.15 g, 11%).

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-d<sub>6</sub>): δ 9.02 (s, 1H), 5.15 (s, 1H), 4.37-4.32 (m, 1H), 3.95 (d, 1H), 3.66-3.60 (m, 1H), 3.36-3.30 (m, 1H), 2.29-2.09 (m, 2H), 1.87-1.82 (m, 2H), 1.55 (s, 9H), 1.27 (d, 3H).

**LCMS (ESI) *m/z*:** 351 [M<sup>+</sup>-1].

**HPLC Purity:** 96%.

**Synthesis of 2-((1*S*,2*R*)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl)propyl)-2,5-diazaspiro[3.4]octan-1-one (C-16):**

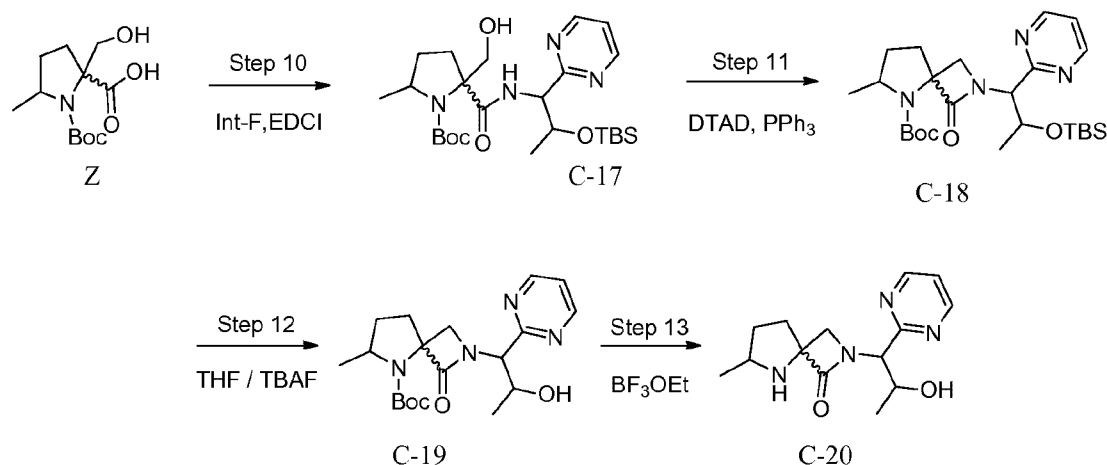
**[00176]** To a stirring solution of C-15 (0.4 g, 1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added TFA (0.43 mL) at 0 °C and stirred at RT for 30 min. The reaction mixture was concentrated under vacuum. Obtained crude material was purified by prep-HPLC to afford C-16 (65mg) as TFA salt.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-d<sub>6</sub>): δ 9.89 (br s, 1H), 9.08 (s, 1H), 5.46 (d, 1H), 5.31 (s, 1H), 4.37-4.35 (m, 1H), 3.99 (d, 1H), 3.81 (d, 1H), 3.42-3.35 (m, 2H), 2.35-2.18 (m, 2H), 2.10-2.03 (m, 2H), 1.24 (d, 3H).

**LCMS (ESI) *m/z*:** 253.4 [M<sup>+</sup>+1].

**HPLC Purity:** 95%.

Scheme 4



**Synthesis of *tert*-butyl 2-((2-((*tert*-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) carbamoyl)-2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate (C-17):**



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[00177] To a stirring solution of compound **Z** (500 mg, 1.93 mmol) in DCM (10 mL) were added *N,N*-diisopropylethylamine (1.0 mL, 5.79 mmol), intermediate **F** (566mg, 2.12mmol), followed by EDCI (737mg, 3.86 mmol), HOBT (521mg, 3.86mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL). The separated organic layer was washed with saturated brine solution (1x30 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography to obtained compound **C-17** (300 mg, 30.6%) as pale yellow liquid. <sup>1</sup>H-NMR: (500 MHz, CDCl<sub>3</sub>): δ 8.73-8.68 (m, 3H), 5.30 (s, 2H), 4.40-4.15 (m, 1H), 3.76-3.61 (m, 1H), 3.18-3.13 (m, 1H), 2.18-2.13 (m, 4H), 1.46 (s, 9H), 1.32 (d, *J* = 5.5 Hz, 3H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 1H), 0.79 (s, 9H), 0.74 (t, *J* = 10.5 Hz, 1H), 0.12 (s, 6H)

**Synthesis of *tert*-butyl 2-(2-((*tert*-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)-6-methyl-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-18):**

[00178] To a stirring solution of triphenylphosphine (380 mg, 1.47 mmol) in dry THF (10 mL) was added DTAD (339 mg, 1.47 mmol) at RT and stirred for 10 min. After added compound **C-17** (300 mg, 0.59 mmol) and the reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 30% EtOAc/hexane to afford compound **C-18** (80 mg, 27.5%) as yellow liquid. <sup>1</sup>H-NMR: (400 MHz, CDCl<sub>3</sub>): δ 7.73-7.64 (m, 3H), 5.26 (s, 2H), 4.30 (dd, *J* = 4.4 Hz, 4.4 Hz, 1H), 4.17-4.12 (m, 1H), 2.76 (t, *J* = 6.8 Hz, 1H), 2.32-2.28 (m, 2H), 2.05-2.00 (m, 2H), 1.49 (s, 9H), 1.45 (d, *J* = 5.2 Hz, 3H), 1.42 (d, *J* = 4.8 Hz, 3H), 0.89 (s, 9H), 0.15 (s, 6H).

**Synthesis of *tert*-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-6-methyl-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-19):**

[00179] To a stirring solution of compound **C-18** (700 mg, 1.42 mmol) in dry THF (10 mL) was added TBAF (744 mg, 2.85mmol) at 0 °C. The reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 80% EtOAc/hexane to afford **C-19** (0.16 g, 30%) as yellow thick syrup.

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**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.77 (d, *J* = 5.0 Hz, 2H), 7.42(t, *J* = 4.5 Hz, 1H), 4.76-4.63 (m, 2H), 4.14-4.11 (m, 1H), 3.85-3.83 (m, 1H), 3.54-3.34 (m, 1H), 2.25-2.21 (m, 2H), 2.08-1.93 (m, 1H), 1.53-1.47 (m, 1H), 1.39 (s, 9H), 1.15(d, *J* = 6.0 Hz, 3H), 1.03-0.80 (m, 4H).

**LCMS (ESI):** 377.4 [*M*<sup>+</sup>+1].

5 **HPLC:** 94.6% (both isomers).

**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-6-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-20):**

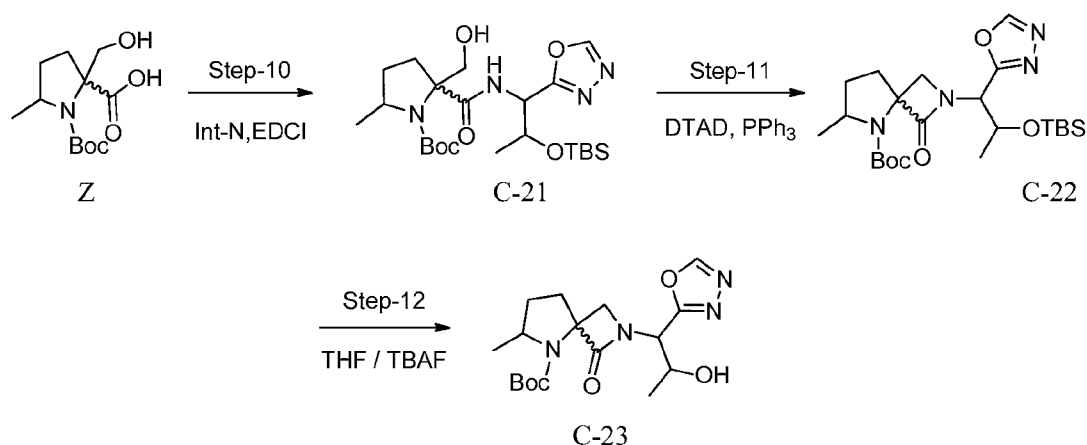
[00180] To a stirring solution of compound **C-19** (260 mg, 0.69 mmol) in DCM (10 mL) was added 4A molecular sieves (70 mg), BF<sub>3</sub>·OEt<sub>2</sub> (0.08 mL) at 0° C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at RT for 30 min. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford crude, which was purified by preparative HPLC method to afford **C-20** (65 mg, 34%) as white solid.

15 **<sup>1</sup>H-NMR:** (400 MHz, D<sub>2</sub>O): δ 8.88-8.86 (m, 2H), 7.63-7.57 (m, 1H), 4.92-4.89 (m, 1H), 4.61-4.56 (m, 1H), 4.03-3.91 (m, 3H), 2.61-2.41 (m, 3H), 1.92-1.84 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.37 (d, *J* = 4.8 Hz, 3H);

**LCMS (ESI):** 295.3 [*M*<sup>+</sup>+H<sub>2</sub>O].

**HPLC:** 91.2% (both enantiomers).

20 **Scheme 5**



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**Synthesis of tert-butyl 2-((2-(((tert-butyldimethylsilyl) oxy)-1-(1,3,4-oxadiazol-2-yl)propyl)-carbamoyl)-2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate (C-21):**

[00181] To a stirring solution of compound Z (4 g, 15.4 mmol) in DCM (30 mL) were added *N,N*-diisopropylethylamine (8 mL, 46.33mmol), intermediate N (4.74 g, 18.48 mmol) followed by HATU ( 7 g, 18.48 mmol) at 0 °C and stirred at RT for 12 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL). The separated organic layer was washed with 10% citric acid solution (1 x 50 mL) followed by saturated brine solution (1x50 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography eluting 30% EtOAc/*n*-hexane to obtained compound **C-21** (5.5g, 71.8%) as pale yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 5.50-5.41 (m, 1H), 5.19-5.06 (m, 2H), 4.38-4.36 (m, 1H), 4.05-3.90 (m, 3H), 2.69-1.98 (m, 2H), 1.39(s, 9H), 1.37-1.26 (m, 2H), 1.23-1.16 (m, 6H), 0.76 (s, 9H), -0.01 (s, 6H).

**Synthesis of tert-butyl 2-(2-(((tert-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)propyl)-6-methyl-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (C-22):**

[00182] To a stirring solution of triphenylphosphine (5.5 g, 11.04 mmol) in THF (55 mL) was added DTAD (5.07 g, 22.05 mmol) at RT and stirred for 10 min. After added compound C-21 (5.5g, 11.04mmol) and the reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 30% EtOAc/hexane to afford compound **C-22** (4 g, 75.4%) as yellow liquid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.36 (s, 1H), 5.30-4.48 (m, 1H), 4.47-4.31 (m, 1H), 4.03-3.88 (m, 2H), 3.62-3.58(m, 1H), 2.38-1.98 (m, 3H), 1.57-1.53 (m, 1H), 1.41 (s, 9H), 1.38-1.15 (m, 6H), 0.69 (s, 9H), -0.01 (s, 6H).

**Synthesis tert-butyl 2-(2-hydroxy-1- (1,3,4-oxadiazol-2-yl)propyl) -6-methyl-1-oxo-2,5-diazaspiro [3.4] octane-5-carboxylate (C-23):**

[00183] To a stirring solution of compound **C-22** (3.5 g, 7.29 mmol) in THF (35 mL) was added TBAF (1M THF) (14.5 mL, 14.58 mmol) at 0 °C. The reaction mixture was stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was

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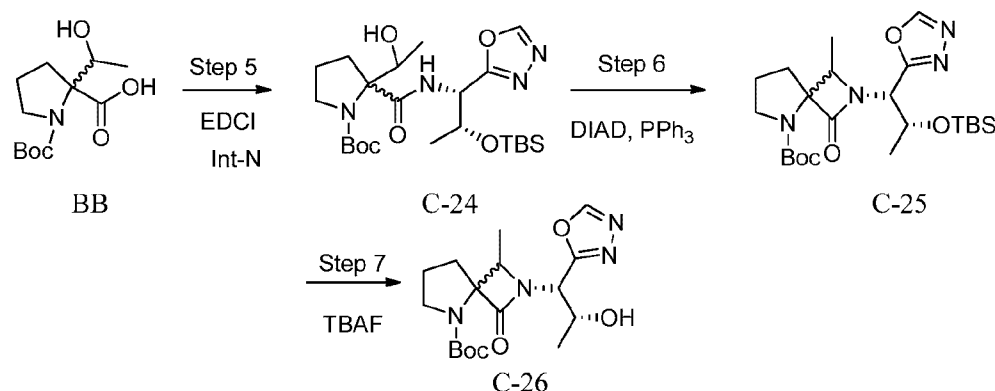
concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 60% EtOAc/hexane to afford **C-23** (800 mg, 30.7%) as an off-white solid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.30 (s, 1H), 5.30-5.21 (m, 1H), 5.13-5.02 (m, 1H), 4.13-4.03 (m, 1H), 3.90-3.83 (m, 1H), 3.74-3.68 (m, 1H), 3.62-3.49 (m, 1H), 2.29 (m, 3H), 1.56-1.52 (m, 1H), 1.40 (s, 9H), 1.25-1.14 (m, 6H).

LCMS (ESI) (*m/z*): 377.4 [M<sup>+</sup>+1].

HPLC: 95.38%.

# 10 **Scheme 6**



## Synthesis of tert-butyl 2-(((1*R*, 2*S*)-2-((tert-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)propyl)carbamoyl)-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (**C-24**):

15 **[00185]** To a stirring solution of compound **BB** (3 g, 11.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added DIPEA (6 mL, 34.5 mmol), intermediate **N** (2.95 g, 11.5 mmol), HATU (5.24 g, 13.8 mmol) at 0 °C and stirred to RT for 12 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The combined organic layer was washed with citric acid (1 x 50 mL) followed by brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 35% EtOAc/*n*-hexane to afford compound **C-24** (3.6 g, 62.5%) as yellow thick syrup.

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**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 8.74 (d, *J* = 8.5 Hz, 2H), 5.30-5.12 (m, 1H), 4.61-4.58 (m, 1H), 4.38-4.35 (m, 2H), 3.57-3.54 (m, 1H), 2.68-1.98 (m, 2H), 1.97-1.69 (m, 2H), 1.40 (s, 9H), 1.19-1.00 (m, 6H), 0.85 (s, 6H), -0.25 (s, 9H).

**Mass (ESI):** *m/z* 497.6[M<sup>-</sup>1].

5 **Synthesis of tert-butyl 2-((1*R*, 2*S*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-25):**

[00186] To a stirring solution of triphenylphosphine (3.6 g, 14.05 mmol) in THF (20 mL) was added DIAD (2.8 g, 14.05 mmol) at RT and stirred for 30 min. After added compound C-24 (3.5 g, 7.02 mmol) in (15 mL) THF slowly and reaction mixture was stirred at RT for 6 h.  
10 After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was purified by column chromatography by eluting 30% EtOAc/*n*-hexane to afford compound C-25 (3 g, 89.2%) as thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.33 (s, 1H), 5.33-5.29 (m, 2H), 4.79-4.75 (m, 1H), 4.50-4.45 (m, 1H), 4.06-3.96 (m, 1H), 2.16-2.08 (m, 1H), 2.01-1.89 (m, 1H), 1.81-1.76 (m, 2H),  
15 1.40 (s, 9H), 1.24-1.15 (s, 6H), 0.80 (s, 9H), -0.08 (s, 6H).

**Mass (ESI):** *m/z* 319.3 [M<sup>+</sup>+1].

**Synthesis of tert-butyl 2-((1*R*, 2*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-26):**

[00187] To a stirring solution of compound C-25 (3 g, 6.25 mmol) in THF (25 mL) was  
20 added TBAF (12.5 mL, 12.5 mmol) at 0 °C and stirred for 30 min. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 60% EtOAc/*n*-hexane to afford C-26 (0.8 g, 35%) as white solid.

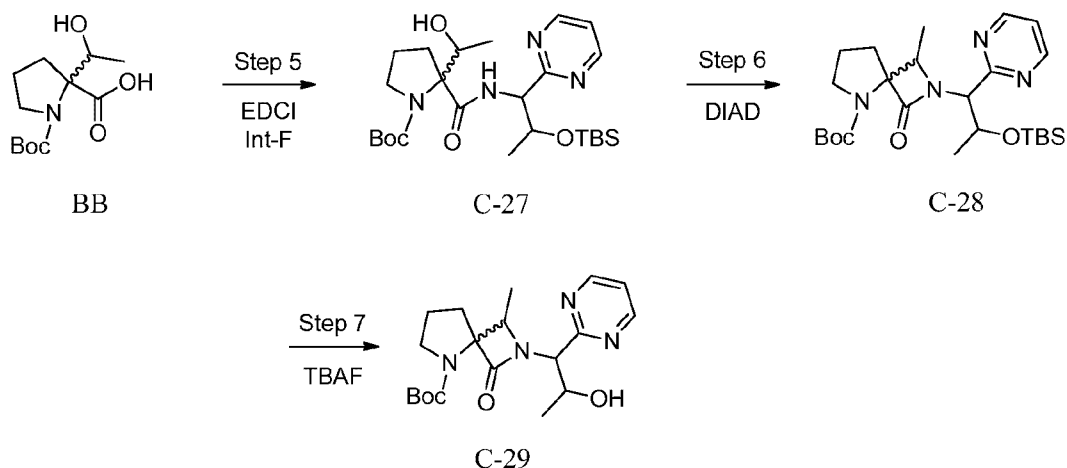
**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.29 (s, 1H), 5.28-5.15 (m, 1H), 5.08-4.89 (m, 1H), 4.43-  
25 4.35 (m, 1H), 3.97-3.79 (m, 1H), 3.65-3.40 (m, 1H), 3.31-3.25 (m, 1H), 2.15-2.00 (m, 2H), 1.93-1.86 (m, 1H), 1.80-1.68 (m, 1H), 1.40 (s, 9H), 1.18-1.04 (m, 6H);

**Mass (ESI):** *m/z* 367.4 [M<sup>+</sup>+1].

**HPLC:** 95.85% (both isomers).

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Scheme 7



**Synthesis of tert-butyl 2-((2-((tert-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-1-methyl-3-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (C-27):**

[00188] To a stirring solution of compound **BB** (200 mg, 0.77 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added DIPEA (298 mg, 2.31 mmol), EDCI (221 mg, 1.15 mmol), HOBT (177 mg, 1.15 mmol) followed by intermediate **F** (206 mg, 0.77 mmol) at 0 °C and stirred for 16 h at RT. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 4% MeOH/DCM to afford compound **C-27** (210 mg, 53.6%) as pale yellow thick syrup.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.77 (d, *J* = 4.5 Hz, 2H), 7.40 (t, *J* = 5.0 Hz, 1H), 4.95-4.92 (m, 2H), 4.21-4.05 (m, 2H), 3.34-3.25 (m, 2H), 3.20-3.12 (m, 1H), 1.81-1.63 (m, 4H), 1.48 (s, 9H), 1.12-1.06 (m, 3H), 0.99-0.85 (m, 3H), 0.70 (s, 9H), -0.06 (s, 6H);

**LCMS (*m/z*):** 509.4 [*M*<sup>+</sup>+1]

**Synthesis of tert-butyl 2-((2-((tert-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-1-methyl-3-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (C-28):**

[00189] To a stirring solution of triphenylphosphine (206 mg, 0.78 mmol) in THF (6 mL) was added DIAD (179 mg, 0.78 mmol) at RT and stirred for 30 min. To this added compound **C-27** (200 mg, 0.39 mmol) in (5 mL) THF slowly and reaction mixture was stirred at RT for 2 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was triturated with diethylether/*n*-

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pentane (10 mL/10 mL). The filtered solvent was concentrated and purified by silica gel column chromatography eluting 30% EtOAc/*n*-hexane to afford compound **C-28** (80 mg, 41.8%) as pale yellow liquid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81-8.77 (m, 2H), 7.72 (d, *J* = 5.5 Hz, 1H), 4.92-4.80 (m, 1H), 4.70-4.65 (m, 2H), 4.46-4.20 (m, 1H), 3.30-3.16 (m, 1H), 1.86-1.65 (m, 2H), 1.64-1.43 (m, 2H), 1.40 (s, 9H), 1.20-1.01 (m, 3H), 0.92-0.85 (m, 3H), 0.74 (s, 9H), -0.06 (s, 6H);

**LCMS** (*m/z*): 491.4 [*M*<sup>+</sup>+1].

**Synthesis of tert-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-29):**

10 **[00190]** To a stirring solution of compound **C-28** (450 mg, 0.91 mmol) in THF (10 mL) was added TBAF (1.8 mL, 1.83 mmol) in 5 mL THF at 0 °C and stirred to RT for 4 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 2% MeOH/DCM followed by preparative HPLC purification to afford **C-29** (100 mg, 29%) as a

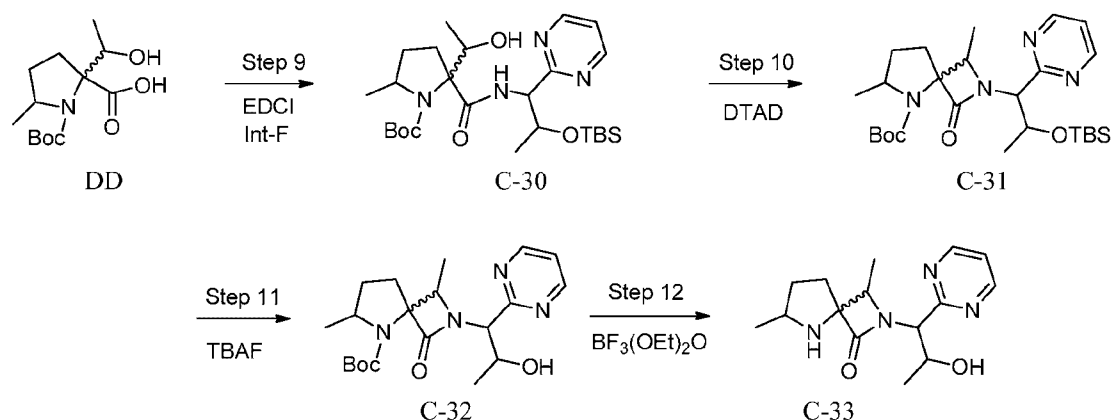
15 semi solid.

**<sup>1</sup>H-NMR:** (400 MHz, CD<sub>3</sub>OD): δ 8.82-8.79 (m, 2H), 8.78-7.43 (m, 1H), 4.94-4.89 (m, 1H), 4.63-4.44 (m, 1H), 3.99-3.73 (m, 1H), 3.56-3.36 (m, 2H), 2.29-2.22 (m, 2H), 1.99-1.73 (m, 2H), 1.40 (s, 9H), 1.24-1.20 (m, 3H), 1.13-1.05 (m, 3H).

**LCMS**(*m/s*): 377.5 [*M*<sup>+</sup>+1].

20 **HPLC:** 94.4% (both isomers).

**Scheme 9**



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**Synthesis of tert-butyl 2-((2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) carbamoyl)-2-(1-hydroxyethyl)-5-methylpyrrolidine-1-carboxylate (C-30):**

[00191] To a stirring solution of compound **DD** (500 mg, 1.83 mmol) in DCM (10 mL) were added *N,N*-diisopropylethylamine (0.84 mL, 4.57 mmol), intermediate **F** (586 mg, 2.19 mmol), followed by EDCI (296 mg, 2.19 mmol), HOBT (338 mg, 2.19 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL). The separated organic layer was washed with brine solution (1 x 20 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/DCM to obtained compound **C-30** (800 mg, 83.6%) as pale yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-d<sub>6</sub>): δ 8.78-8.75 (m, 2H), 7.42-7.39 (m, 1H), 5.01-4.92 (m, 1H), 4.21-4.09 (m, 1H), 4.05-4.02 (m, 2H), 1.98 (s, 2H), 1.44-1.31 (m, 7H), 1.29-1.11 (m, 10H), 1.02-0.96 (m, 4H), 0.70-0.63 (m, 9H), -0.25 (s, 3H), -0.32 (s, 3H).

15 LCMS (ESI) : 523.6 [M<sup>+</sup>+1].

**Synthesis of tert-butyl 2-(2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)-1, 6-dimethyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-31):**

[00192] To a stirring solution of triphenylphosphine (1.23 g, 4.87 mmol) in dry THF (10 mL) was added DTAD (1.09 g, 4.77 mmol) as portion-wise and stirred for 15 min at RT. To this precipitated solution, added compound **C-30** (1.0 g, 1.91 mmol) in dry THF (10 mL) slowly at RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was triturated with *n*-pentane (20 mL) and filtered solid (TPPO). The filtrate was concentrated under reduced pressure to obtained crude compound was purified by silica gel column chromatography eluting 30% EtOAc/hexane to afford compound **C-31** (400 mg, 41.4%) as yellow liquid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.82-8.79 (m, 2H), 7.44-7.42 (m, 1H), 3.88-3.70 (m, 2H), 1.82-1.78 (m, 2H), 1.49-1.41 (m, 4H), 1.40 (s, 9H), 1.21-1.08 (m, 9H), 0.57 (s, 6H), - 0.05 (s, 9H); LCMS (ESI): 505.5 [M<sup>+</sup>+1].

30

**Synthesis of tert-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-1, 6-dimethyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-32):**



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[00193] To a stirring solution of compound **C-31** (220 mg, 0.43 mmol) in dry THF (3 mL) was added TBAF (227 mg) slowly at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford crude, which was purified by silica gel column chromatography eluting 80% EtOAc/hexane to afford compound **C-32** (150 mg, 88.2%) as yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.81-8.79 (m, 2H), 7.43-7.41 (m, 1H), 4.36-4.33 (m, 1H), 4.27-4.24 (m, 1H), 3.86-3.80 (m, 2H), 2.15-1.86 (m, 4H), 1.53-1.50 (m, 1H), 1.43 (s, 9H), 1.19-1.03 (m, 9H).

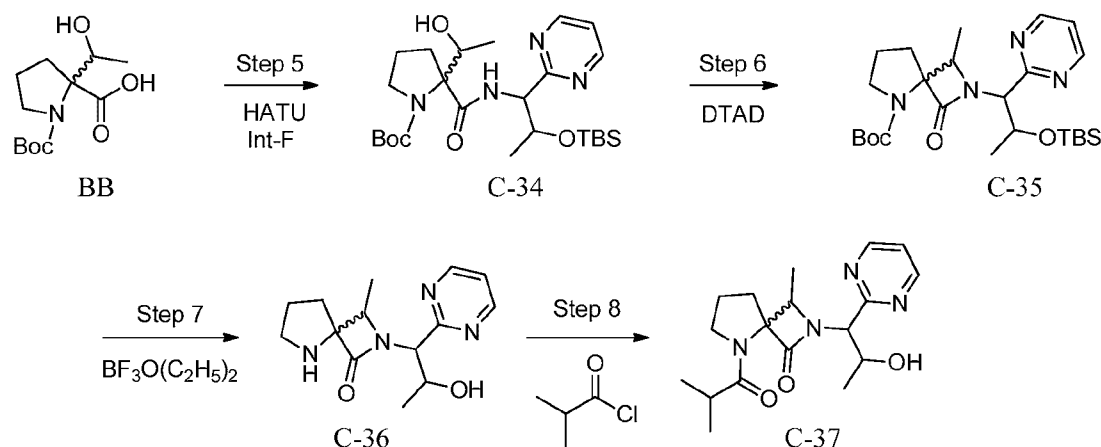
10 **Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-3, 6-dimethyl-2, 5-diazaspiro [3.4] octan-1-one (C-33):**

[00194] To a stirring solution of compound **C-32** (120 mg, 0.25 mmol) in DCM (10 mL) was added molecular sieves (100 mg), BF<sub>3</sub>(OEt)<sub>2</sub> (72 mg, 0.51 mmol) at 0 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at RT for 10 min. After consumption of the starting material (by TLC), the obtained precipitate was triturated with *n*-pentane/diethylether (5 mL/5 mL) and the filtered solid was dried on vacuum to afford **C-33** (80 mg, 89.8%) as white solid.

<sup>1</sup>H-NMR: (400 MHz, D<sub>2</sub>O): δ 8.90 (t, *J* = 4.8 Hz, 2H), 7.64-7.60 (m, 1H), 4.72-4.62 (m, 2H), 4.24-4.15 (m, 1H), 4.08-4.00 (m, 1H), 2.60-2.32 (m, 3H), 2.02-1.91 (m, 1H), 1.55-1.51 (m, 3H), 1.48-1.45 (m, 3H), 1.39-1.25 (m, 3H).

LCMS (ESI): 581.3 [2M<sup>+</sup>+1].

**Scheme 10**



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**Synthesis of tert-butyl 2-((2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) carbamoyl)-2-(1-hydroxyethyl) pyrrolidine-1-carboxylate (C-34):**

[00195] To a stirring solution of compound **BB** (2.5 g, 9.65 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) were added DIPEA (5 mL, 28.95 mmol), intermediate **F** (2.57 g, 9.65 mmol) followed by HATU (4.4 g, 11.58 mmol) at 0 °C and stirred for 12 h at RT. After consumption of the starting material (by TLC), the reaction mixture was the reaction was diluted with water (20 mL). The separated organic layer was washed with citric acid solution (1 x 50 mL) followed by brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 50% EtOAc/*n*-hexane to afford compound **C-34** (3.1 g, 63.2%) as an off-white solid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-d<sub>6</sub>): δ 8.76 (d, *J* = 13.5 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 4.60-4.41 (m, 1H), 4.23-4.11 (m, 1H), 3.58-3.40 (m, 3H), 2.37-1.62 (m, 4H), 1.39 (s, 9H), 1.28-1.19 (m, 3H), 1.18-1.15 (m, 3H), 1.09 (s, 9H), -0.04 (s, 6H);

LCMS (ESI): *m/z* 509.7 [M<sup>+</sup>+1]

**Synthesis of tert-butyl 2-(2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-35):**

[00196] To a stirring solution of triphenylphosphine (1.6 g, 6.29 mmol) in THF (15 mL) was added DIAD (1.44 g, 6.29 mmol) at RT and stirred for 30 min. To this added compound **C-34** (1.6 g, 3.14 mmol) in (5 mL) THF slowly and reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was triturated with diethyl ether/*n*-pentane (10 mL/10 mL). The filtered solvent was concentrated and purified by silica gel column chromatography eluting 20% EtOAc/*n*-hexane to afford compound **C-35** (1 g, 65.3%) as pale yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-d<sub>6</sub>): δ 8.80 (d, *J* = 14.5 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 1H), 4.72-4.46 (m, 2H), 3.36-3.23 (m, 3H), 2.06-1.61 (m, 4H), 1.40 (s, 9H), 1.35-1.23 (m, 3H), 1.16-1.12 (m, 3H), 1.00 (s, 9H), -0.01 (s, 6H);

LCMS (ESI): *m/z* 491.4 [M<sup>+</sup>+1]

**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-3-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-36):**

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[00197] To a stirring solution of compound C-35 (1 g, 2.04 mmol) in DCM (5 mL) was added  $\text{BF}_3\text{O}(\text{C}_2\text{H}_5)_2$  (0.05 mL, 4.08 mmol) followed by molecular sieves (50 mg) at 0 °C and stirred to RT for 3 h. After consumption of the starting material (by TLC), the reaction was diluted with *n*-pentane and filtered the obtained solid. The filtered solid was purified by silica gel column chromatography eluting 5% MeOH/DCM to afford C-36 (180 mg, 32%) as an off-white solid.

<sup>1</sup>H-NMR: (400 MHz, D<sub>2</sub>O): δ 8.89 (d, *J* = 4.8 Hz, 2H), 7.61 (t, *J* = 4.8 Hz, 1H), 4.85-4.73 (m, 2H), 4.18-4.13 (m, 1H), 3.54-3.41 (m, 2H), 2.43-2.36 (m, 1H), 2.31-2.12 (m, 3H), 1.43-1.37 (m, 6H)

10 LCMS (ESI): *m/z* 277.3 [*M*<sup>+</sup>+1];

HPLC: 98.85% .

Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-5-isobutyryl-3-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-37):

15 [00198] To a stirring solution of compound C-36 (600 mg, 2.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added TEA (1.05 mL, 7.59 mmol) at 0 °C. After added isobutyryl chloride (253 mg, 2.39 mmol) slowly and stirred for 1 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL). The separated organic layer was washed with brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>,  
20 filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting 3% MeOH/DCM followed by preparative HPLC purification to afford C-37 (120 mg, 16%) as an off-white solid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.81 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 11.5 Hz, 1H), 5.05-4.34 (m, 2H), 3.64-3.44 (m, 3H), 2.01-1.81 (m, 5H), 1.35-1.13 (m, 6H), 1.10-1.04 (m, 6H);

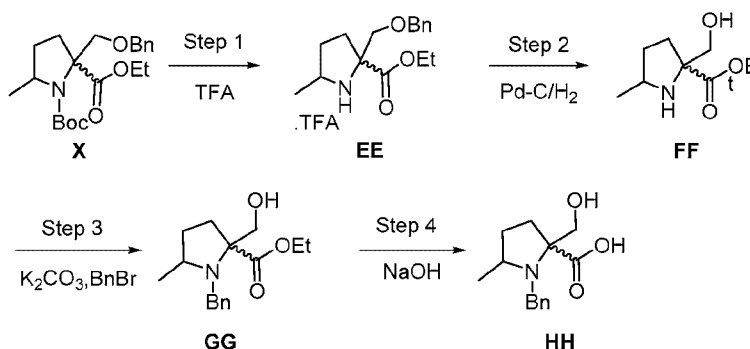
25 LCMS (ESI): *m/z* 347.4 [*M*<sup>+</sup>+1]

HPLC: 91.1%

**Preparation of key intermediates, schemes I-8 to I-10:**

**Scheme I-8**

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**Synthesis of ethyl 2-((benzyloxy) methyl)-5-methylpyrrolidine-2-carboxylate (EE):**

[00199] To a stirring solution of **X** (8.5 g, 22.51 mmol) in DCM (50 mL) was added TFA (8.6 mL, 112.58 mmol) at 0 °C. The reaction mixture was stirred at RT for 4 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **EE** (14 g, crude) as pink liquid (TFA salt).

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.71 (br s, 1H), 7.45-7.30 (m, 5H), 4.62 (s, 2H), 4.27-4.22 (m, 2H), 3.90-3.73 (m, 3H), 2.26-2.08 (m, 2H), 2.01-1.95 (m, 1H), 1.59-1.51 (m, 1H), 1.36-1.31 (m, 3H), 1.22-1.18 (m, 3H);

LCMS (ESI): *m/z* 278.36 [*M*<sup>+</sup>+1]

**Synthesis of ethyl 2-(hydroxymethyl)-5-methylpyrrolidine-2-carboxylate (FF):**

[00200] To a stirring solution of **EE** (14 g (crude), 35.80 mmol) in methanol (100 mL) was added (50% wet) 10% Pd/C (5 g) under N<sub>2</sub> atmosphere. The reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon pressure) at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and the pad was washed with methanol (100 mL). Obtained filtrate was concentrated under reduced pressure to afford **FF** (8 g, crude) as yellow syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.52 (s, 1H), 8.74 (s, 1H), 4.28-4.20 (m, 2H), 3.94-3.69 (m, 3H), 2.22-2.16 (m, 2H), 2.13-1.92 (m, 1H), 1.60-1.53 (m, 1H), 1.32-1.18 (m, 6H);

LCMS (ESI): *m/z* 188.24 [*M*<sup>+</sup>+1]

**Synthesis of ethyl 1-benzyl-2-(hydroxymethyl)-5-methylpyrrolidine-2-carboxylate (GG):**

[00201] To a stirring solution of **FF** (8 g, 26.57 mmol) in CH<sub>3</sub>CN (50 mL) was added K<sub>2</sub>CO<sub>3</sub> (11.02 g, 79.73 mmol) followed by benzyl bromide (3.78 mL, 31.89 mmol) at RT and stirred for 16 h. After consumption of the starting material, filtered the reaction mass through celite bed and filtrate was washed with EtOAc (250 mL). The filtrate was concentrated under

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reduced pressure to afford crude. Obtained crude material was purified by column chromatography eluting with 10% EtOAc/Hexane to afford **GG** (5 g, 68%) as brown syrup.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.33-7.15 (m, 5H), 5.17 (t, *J* = 5.5 Hz, 1H), 4.75 (d, *J* = 5.5 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.14-3.93 (m, 2H), 3.93 (s, 2H), 3.81-3.60 (m, 1H), 3.13-3.09 (m, 1H), 2.20-2.17 (m, 1H), 1.99-1.88 (m, 2H), 1.40-1.36 (m, 3H), 1.14 (t, *J* = 7.0 Hz, 3H)

**LCMS (ESI):** *m/z* 278.36 [*M*<sup>+</sup>+1]

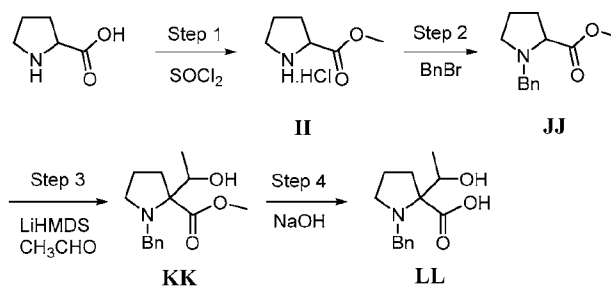
**Synthesis of 1-benzyl-2-(hydroxymethyl)-5-methylpyrrolidine-2-carboxylic acid (HH):**

[00202] To a stirring solution of **GG** (5 g, 18.05 mmol) in EtOH/H<sub>2</sub>O (25 mL/25 mL) were added NaOH (1.44 g, 36.1 mg) at RT. The reaction mixture was heated to 100 °C for 2 h. After consumption of the starting material (by TLC), the solvent from the reaction was evaporated under reduced pressure and extracted with di ethylether (2 x 75 mL). The aqueous layer was acidified by using 1*N* HCl and extracted with 20% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford **HH** (3.5 g, 78%) as brown syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 11.17 (s, 1H), 7.49-7.27 (m, 5H), 4.55 (d, *J* = 14.0 Hz, 1H), 4.06 (d, *J* = 14.4 Hz, 1H), 3.83 (s, 2H), 3.51-3.41 (m, 2H), 2.18-1.90 (m, 3H), 1.45-1.39 (m, 1H), 0.61-0.45 (m, 3H)

**LCMS (ESI):** *m/z* 250.13 [*M*<sup>+</sup>+1]

**Scheme I-9**



**Synthesis of methyl pyrrolidine-2-carboxylate (II):**

[00203] To a stirring solution of L-Proline (50 g, 434 mmol) in methanol was added thionyl chloride (37.5 ml, 521 mmol) at 0 °C and heated to 70 °C for 16 h. The reaction

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mixture was brought to RT and concentrated under vacuum to afford II as (70 g, 99 %) as thick syrup (hydrochloride salt).

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 4.15-4.13 (m, 1H), 3.65 (s, 3H), 3.35-3.30 (m, 2H), 2.23-2.15 (m, 1H), 1.86-1.78 (m, 3H), 1.41 (s, 9H)

5 **LCMS (ESI):** *m/z* 129 [*M*<sup>+</sup>+1]

**Synthesis of methylbenzylprolinate (JJ):**

[00204] To a stirring solution of compound II (18 g, 108 mmol) in DCM (200 mL) was added TEA (45.35 mL, 326 mmol) followed by benzyl bromide (15.5 mL, 130 mmol) at 0 °C and stirred at RT for 24 h. After completion of the reaction (by TLC) was diluted with water  
10 (75 mL) and EtOAc (500 mL). The organic layer was washed with water (2 x 100 mL), brine solution (2 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. Obtained crude material was purified by column chromatography eluting with 10% EtOAc/Hexane to afford JJ (5 g, 21%) as oily liquid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.32-7.22 (m, 5H), 3.86-3.80 (m, 1H), 3.58 (s, 3H), 3.48-  
15 3.24 (m, 2H), 2.85-2.80 (m, 1H), 2.38-2.32 (m, 1H), 2.10-1.98 (m, 1H), 1.85-1.69 (m, 3H)

**LCMS (ESI):** *m/z* 220.28 [*M*<sup>+</sup>+1]

**Synthesis of methyl 1-benzyl-2-(1-hydroxyethyl) pyrrolidine-2-carboxylate (KK):**

[00205] To a stirring solution of JJ (5 g, 22.80 mmol) in THF (50 mL) was added LiHMDS (46 mL, 45.60 mmol) dropwise at -20 °C and stirred for 45 min. To this acetaldehyde  
20 (2.33 mL, 45.60 mmol) was added drop wise and stirred for 3 h at -20 °C. After consumption of the starting material (by TLC), the reaction was quenched with aqueous NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (2 x 150 mL). The separated organic layer was washed with water (200 mL) and brine solution (200 mL). The separated organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford crude which was purified by column chromatography  
25 eluting with 10% EtOAc/Hexane to afford KK (3.5 g, 58%) as yellow syrup.

**LCMS (ESI):** *m/z* 264.3 [*M*<sup>+</sup>+1]

**Synthesis of 1-benzyl-2-(1-hydroxyethyl) pyrrolidine-2-carboxylic acid (LL):**

[00206] To a stirring solution of KK (4.5 g, 17.11 mmol) in MeOH/THF/H<sub>2</sub>O (10 mL/10 mL/10 mL) were added NaOH (1.02 g, 25.66 mmol) at RT. The reaction mixture was heated to  
30 95 °C for 1 h. After consumption of the starting material (by TLC), the solvent was evaporated

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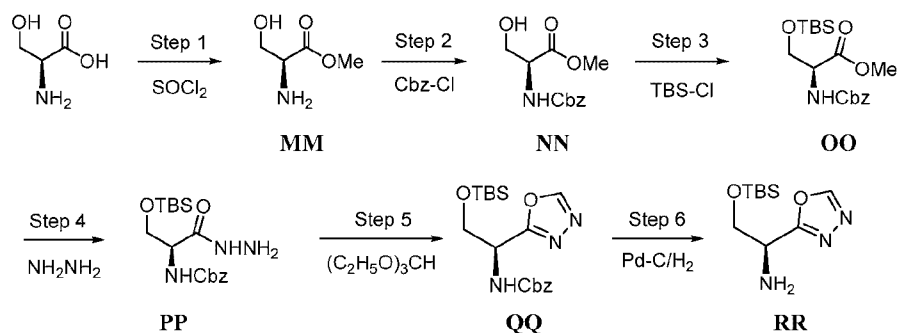
under reduced pressure. The aqueous layer was washed with EtOAc (100 mL). The separated aqueous layer was acidified by using 1N HCl (pH~3). The aqueous layer was extracted with 20% MeOH/DCM (2 x 100 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **LL** (2.7 g, 63%) as an off-white solid.

5 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.31-7.13 (m, 5H), 3.87-3.78 (m, 2H), 3.61-3.57 (m, 1H), 2.75-2.64 (m, 2H), 1.90-1.78 (m, 2H), 1.69-1.65 (m, 1H), 1.53-1.43 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 3H);

**LCMS (ESI):** *m/z* 250.4 [M<sup>+</sup>-1]

#### Scheme I-10

10



#### Synthesis of methyl L-serinate (MM):

[00207] To a stirring solution of L-serine (12 g, 114 mmol) in CH<sub>3</sub>OH (100 mL) was added thionyl chloride (10 mL, 137 mmol) at 0 °C and stirred at 80 °C for 16 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **MM** (16 g, crude, HCl salt) as white solid. This material was directly used for the next step without further purification.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.61 (s, 2H), 4.50 (s, 1H), 4.20-4.16 (m, 1H), 3.82 (d, *J* = 3.6 Hz, 2H), 3.73 (s, 3H)

#### 20 Synthesis of methyl ((benzyloxy)carbonyl)-L-serinate (NN):

[00208] To a stirring solution of **MM** (16 g, 103 mmol) in water/1, 4 dioxane (130 mL/65 mL) were added Na<sub>2</sub>CO<sub>3</sub> (27.3 g, 257 mmol) at RT. After added Cbz-Cl (17.6 mL, 123 mmol) was added at 0 °C drop wise and stirred for 16 h at RT. After completion of starting material (by TLC), diluted the reaction mass with EtOAc (300 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced

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pressure to afford crude material which was purified by column chromatography to afford **NN** (23 g, 88 %) as thick syrup.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.38-7.31 (m, 5H), 5.04 (s, 2H), 4.95-4.92 (m, 1H), 4.17-4.13 (m, 1H), 3.66 (s, 3H), 3.65-3.56 (m, 2H).

5 **LCMS (ESI):** *m/z* 254.2 [*M*<sup>+</sup>+1]

**Synthesis of methyl N-((benzyloxy)carbonyl)-O-(tert-butyldimethylsilyl)-L-serinate (OO):**

[00209] To a stirring solution of **NN** (23 g, 91 mmol) in DCM (700 mL) were added imidazole (12.37 g, 182 mmol), DMAP (2.22 g, 18.2 mmol) followed by TBDMS-Cl (20.4 g, 136 mmol) at 0 °C and stirred at RT for 16 h. After completion of starting material (by TLC),  
10 diluted the reaction mass with water (200 mL). The separated organic layer was washed with brine solution (2 x 200 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 20% EtOAc/hexane to afford **OO** (32 g, 97%) as thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.38-7.30 (m, 5H), 5.07 (s, 2H),  
15 4.24-4.19 (m, 1H), 3.81 (d, *J* = 5.2 Hz, 2H), 3.63 (s, 3H), 0.84 (s, 9H), -0.04 (s, 6H)

**LCMS (ESI):** *m/z* 368.5 [*M*<sup>+</sup>+1]

**Synthesis of benzyl (S)-(3-((tert-butyldimethylsilyl)oxy)-1-hydrazinyl-1-oxopropan-2-yl)carbamate (PP):**

[00210] To a stirred solution of **OO** (20 g, 54.5 mmol) in methanol (120 mL) was added  
20 hydrazine hydrate (27 g, 545 mmol) at 0 °C and after stirred at 80 °C for 2 h. After completion of starting material (by TLC), ethanol was evaporated under reduced pressure. The crude residue was triturated with *n*-pentane (100 mL) to afford **PP** (17 g, 85%) as an off-white solid.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.17 (s, 1H), 9.10 (s, 1H), 7.35-7.14 (m, 5H), 5.02 (s, 2H), 4.48 (s, 2H), 4.16-4.07 (m, 2H), 3.73-3.58 (m, 1H), 0.81 (s, 9H), -0.04 (s, 6H).

25 **Synthesis of benzyl ((1S, 2R)-2-((tert-butyldimethylsilyl)oxy)-1-(1, 3, 4-oxadiazol-2-yl)propyl) carbamate (QQ):**

[00211] A solution of **PP** (17 g, 46.3 mmol) in triethylorthoformate (68.5 g, 463 mmol) was added *p*-TSA (8.8 g, 4.63 mmol) at RT and after stirred at 80 °C for 2 h. After completion of starting material (by TLC), triethylorthoformate was evaporated under reduced pressure. The  
30 crude residue was purified by column chromatography eluting 10% EtOAc/hexane to afford **QQ** (5 g, 29%) as thick syrup.



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**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.22 (s, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.36-7.30 (m, 5H), 5.08 (s, 2H), 5.05-4.97 (m, 1H), 4.03-3.91 (m, 2H), 0.84 (s, 9H), 0.03 (s, 6H);

**LCMS (ESI):** *m/z* 378.5 [*M*<sup>+</sup>+1]

**Synthesis of (S)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) ethan-1-amine**

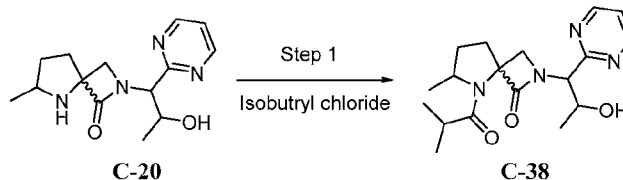
5 **(RR):**

**[00212]** To a stirring solution of **QQ** (5 g, 13.2 mmol) in methanol (30 mL) was added 50% wet 10% Pd/C (1.2 g) and stirred under H<sub>2</sub> atmosphere (balloon pressure) for 2 h at RT. After completion of reaction, the reaction mixture was filtered through a pad of celite and triturated with methanol (20 mL). The filtrate was concentrated under reduced pressure to afford **RR** (2 g, 63%) as thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.16 (s, 1H), 4.19-4.16 (m, 1H), 3.85-3.75 (m, 2H), 2.11 (s, 2H), 0.77 (s, 9H), -0.04 (s, 6H)

**LCMS (ESI):** *m/z* 244.3 [*M*<sup>+</sup>+1]

15 **Scheme 11**



**Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-5-isobutyryl-6-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-38):**

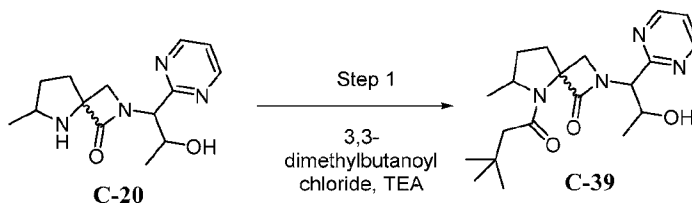
**[00213]** To a stirring solution of **C-20** (500 mg, 1.81 mmol) in DCM (10 mL) was added DIPEA (0.94 mL, 5.43 mmol) at 0 °C. After added iso butyrylchloride (578 mg, 5.43 mmol) at 0 °C and stirred at RT for 4 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/DCM to obtained **C-38** (150 mg, 24%) as pale yellow solid.

**<sup>1</sup>H-NMR:** (400 MHz, CD<sub>3</sub>OD): δ 8.82-8.77 (m, 2H), 7.39 (t, *J* = 5.2 Hz, 1H), 4.76 (d, *J* = 8.0 Hz, 1H), 4.47-4.44 (m, 1H), 4.20-4.14 (m, 1H), 3.82-3.74 (m, 1H), 3.51-3.40 (m, 1H), 2.78-2.72 (m, 1H), 2.46-2.37 (m, 1H), 2.18-2.12 (m, 2H), 1.77-1.72 (m, 1H), 1.34-1.29 (m, 3H), 1.26-1.22 (m, 3H), 1.06-1.02 (m, 6H)

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LCMS (ESI):  $m/z$  347.2 [ $M^+ + 1$ ];

HPLC: 99.7%

**Scheme 12**

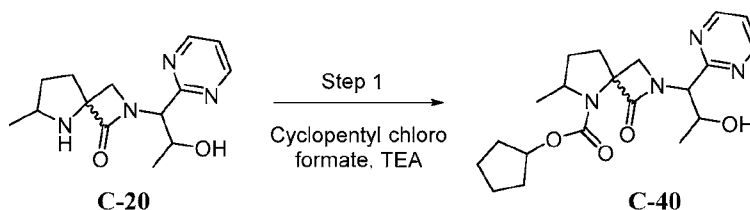
**5    Synthesis of 5-(3,3-dimethylbutanoyl)-2-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-6-methyl-2,5-diazaspiro[3.4]octan-1-one (C-39):**

[00214]        To a stirring solution of **C-20** (150 mg, 0.54 mmol) in DCM (10 mL) was added TEA (137 mg, 1.35 mmol) at 0 °C. After added 3, 3-dimethylbutanoyl chloride (87 mg, 0.65 mmol) at 0 °C and stirred at RT for 1 h. After consumption of the starting material (by TLC),  
 10    the reaction mixture was diluted with water (10 mL). The separated organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/DCM to obtained **C-39** (150 mg, 24%) as sticky solid.

$^1\text{H-NMR}$ : (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.80-8.75 (m, 2H), 7.43-7.37 (m, 1H), 4.73-4.65 (m, 2H),  
 15    4.24-4.17 (m, 2H), 3.78-3.59 (m, 1H), 3.23-3.16 (m, 1H), 2.36 (s, 2H), 2.32-2.08 (m, 3H), 1.58-1.50 (m, 1H), 1.20-1.08 (m, 6H), 0.86 (s, 9H)

LCMS (ESI):  $m/z$  375.49 [ $M^+ + 1$ ];

HPLC: 96.9%

**20    Scheme 13**

**Synthesis of cyclopentyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-6-methyl-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-40):**

[00215]        To a stirring solution of **C-20** (150 mg, 0.54 mmol) in DCM (5 mL) was added  
 25    TEA (0.23 mL, 1.63 mmol) at 0 °C. After added cyclopentyl chloroformate (88 mg, 0.59

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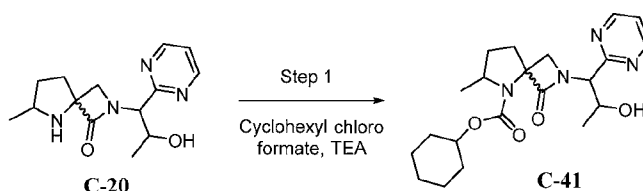
mmol) at 0 °C and stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL). The separated organic layer was washed with saturated brine solution (20 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 3% MeOH/DCM to obtained **C-40** (110mg, 52%) as sticky solid.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.81-8.76 (m, 2H), 7.45-7.42 (m, 1H), 5.20-4.91 (m, 1H), 4.77-4.64 (m, 2H), 4.30-3.63 (m, 1H), 3.57-3.31 (m, 3H), 2.16-1.86 (m, 4H), 1.77-1.32 (m, 8H), 1.18-1.08 (m, 6H)

LCMS (ESI): *m/z* 389.4 [M<sup>+</sup>+1];

UPLC: 97.6%

#### Scheme 14



#### Synthesis of cyclohexyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-6-methyl-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-41):

**[00216]** To a stirring solution of **C-20** (150 mg, 0.54 mmol) in DCM (5 mL) was added TEA (0.2 mL, 1.35 mmol) at 0 °C. After added cyclohexyl chloroformate (105 mg, 0.65 mmol) at 0 °C and stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL). The separated organic layer was washed with citric acid solution (20 mL), saturated brine solution (20 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/DCM to obtained **C-41** (90 mg, 41%) as sticky solid.

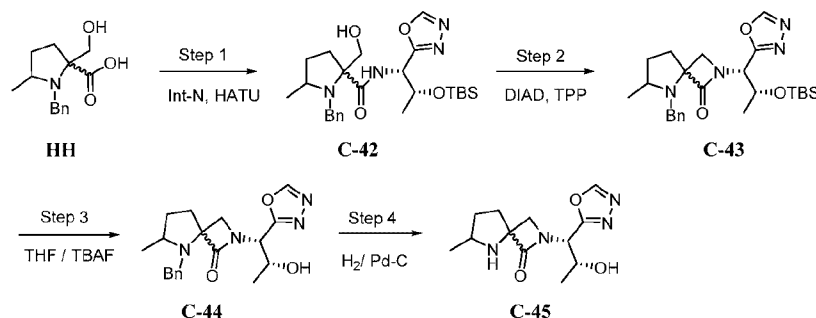
<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.82-8.78 (m, 2H), 7.48-7.41 (m, 1H), 4.78-4.61 (m, 2H), 4.24-4.13 (m, 2H), 3.94-3.87 (m, 1H), 3.76-3.53 (m, 2H), 2.27-1.99 (m, 3H), 1.97-1.92 (m, 1H), 1.56-1.32 (m, 10H), 1.29-1.10 (m, 2H)

LCMS (ESI): *m/z* 403.5 [M<sup>+</sup>+1];

UPLC: 98.06%

#### Scheme 15

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**Synthesis of 1-benzyl-N-((1*S*, 2*R*)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(hydroxymethyl)-5-methylpyrrolidine-2-carboxamide (C-42):**

[00217] To a stirring solution of **HH** (2.5 g, 10.04 mmol) in DMF (15 mL) were added  
 5 *N, N*-diisopropylethylamine (5.4 mL, 30.12 mmol), Int **N** (2.58 g, 10.04 mmol) followed by  
 HATU (4.57 g, 12.04 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the  
 starting material (by TLC), the reaction mixture was diluted with water (100 mL) and EtOAc  
 (100 mL). The organic layer was washed with water (100 mL), saturated sodium bicarbonate  
 solution (50 mL) followed by brine solution (50 mL). The organic layer was dried over  
 10 anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude compound  
 which was purified by column chromatography by eluting 20% EtOAc/*n*-hexane to obtained **C-42**  
 (3.2 g, 65%) as brown syrup.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 8.78 (d, *J* = 10.0 Hz, 1H), 7.30-7.21 (m, 5H),  
 5.26 (d, *J* = 10.0 Hz, 1H), 4.43 (s, 2H), 4.05-4.02 (m, 2H), 3.87-3.72 (m, 1H), 3.15-3.10 (m,  
 15 1H), 2.81-2.65 (m, 1H), 1.39-1.26 (m, 4H), 1.25-1.16 (m, 6H), 0.05 (s, 6H)

LCMS (ESI): *m/z* 489.70 [M<sup>+</sup>+1]

**Synthesis of 5-benzyl-2-((1*S*, 2*R*)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-6-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-43):**

[00218] To a stirring solution of triphenylphosphine (4.02 g, 15.36 mmol) in dry THF  
 20 (30 mL) was added DIAD (2.48 g, 12.29 mmol) at RT and stirred for 15 min. After added **C-42**  
 (3 g, 6.14 mmol) in THF (30 mL) was added dropwise and the reaction mixture was stirred at  
 RT for 4 h. After consumption of the starting material (by TLC), the reaction mixture was  
 concentrated under reduced pressure. The crude material was purified by column  
 chromatography by eluting 20% EtOAc/*n*-hexane to afford **C-43** (1.3 g, 45%) as pale green  
 25 syrup.

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<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.28 (s, 1H), 7.33-7.19 (m, 5H), 5.24-5.19 (m, 1H), 4.73 (s, 2H), 4.47-4.41 (m, 1H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.68 (s, 2H), 2.49-2.28 (m, 1H), 2.27-2.10 (m, 1H), 1.98-1.94 (m, 1H), 1.47-1.40 (m, 1H), 1.23-1.15 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H)

LCMS (ESI): *m/z* 491.6 [M<sup>+</sup>+1]

5 **Synthesis of 5-benzyl-2-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-6-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-44):**

[00219] To a stirring solution of C-43 (1.3 g, 2.76 mmol) in dry THF (30 mL) was added TBAF (1M in THF) (4.13 mL, 4.14 mmol) at 0 °C and stirred for 2 h at RT. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced  
10 pressure. The crude material was diluted with water (100 mL) and EtOAc (100 mL). The organic layer was washed with water (100 mL), brine solution (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to obtained C-44 (350 mg, 35%) as thick syrup.

15 <sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.18 (s, 1H), 7.34-7.16 (m, 5H), 5.21 (t, *J* = 5.6 Hz, 1H), 5.01-4.83 (m, 1H), 4.22-4.18 (m, 1H), 3.88 (s, 2H), 3.84-3.67 (m, 1H), 3.54-3.35 (m, 1H), 2.98-2.89 (m, 1H), 2.31-1.89 (m, 3H), 1.45-1.41 (m, 1H), 1.39-1.14 (m, 3H), 0.90-0.81 (s, 3H)

LCMS (ESI): *m/z* 357.43 [M<sup>+</sup>+1]

HPLC: 92.46%

20 **Synthesis of 5-benzyl-2-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-6-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-45):**

[00220] To a stirring solution of C-44 (1.3 g, 2.76 mmol) in dry THF (30 mL) was added TBAF (1M in THF) (4.13 mL, 4.14 mmol) at 0 °C and stirred for 2 h at RT. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced  
25 pressure. The crude material was diluted with water (100 mL) and EtOAc (100 mL). The organic layer was washed with water (100 mL), brine solution (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to obtained C-45 (350 mg, 35%) as thick syrup.

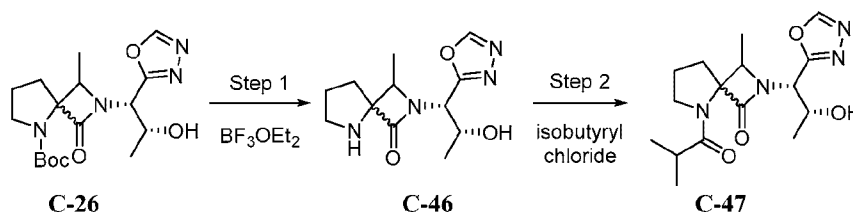
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**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.18 (s, 1H), 7.34-7.16 (m, 5H), 5.21 (t, *J* = 5.6 Hz, 1H), 5.01-4.83 (m, 1H), 4.22-4.18 (m, 1H), 3.88 (s, 2H), 3.84-3.67 (m, 1H), 3.54-3.35 (m, 1H), 2.98-2.89 (m, 1H), 2.31-1.89 (m, 3H), 1.45-1.41 (m, 1H), 1.39-1.14 (m, 3H), 0.90-0.81 (s, 3H)

**LCMS (ESI):** *m/z* 357.43 [*M*<sup>+</sup>+1]

5 **HPLC:** 92.46%

#### Scheme 16



#### Synthesis of 2-((1*S*,2*R*)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)-3-methyl-2,5-

##### 10 diazaspiro[3.4]octan-1-one (C-46):

[00221] To a stirring solution of **C-26** (800 mg, 2.18 mmol) in DCM (10 mL) were added BF<sub>3</sub>·OEt<sub>2</sub> (620 mg, 4.37 mmol), molecular sieves (150 mg) at 0 °C and stirred for 3 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with *n*-pentane (5 mL). The precipitated solid was filtered and filtrate was concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 3% MeOH/DCM to afford **C-46** (700 mg, crude) as yellow liquid.

**Mass (ESI):** *m/z* 267.3 [*M*<sup>+</sup>+1]

#### Synthesis of 2-((1*S*,2*R*)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)-5-isobutyryl-3-methyl-2,5-diazaspiro[3.4]octan-1-one (C-47):

20 [00222] To a stirring solution of **C-46** (700 mg (crude), 2.63 mmol) in DCM (10 mL) was added TEA (0.53 mL, 3.94 mmol) at 0 °C. After 10 min added isobutyryl chloride (0.41 mL, 3.94 mmol) at 0 °C and stirred for 2 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (5 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Obtained

25 crude material was purified by silica gel column chromatography eluting with 3% MeOH/DCM followed by preparative HPLC purification to afford **C-47** (150 mg, 17%) as thick syrup.

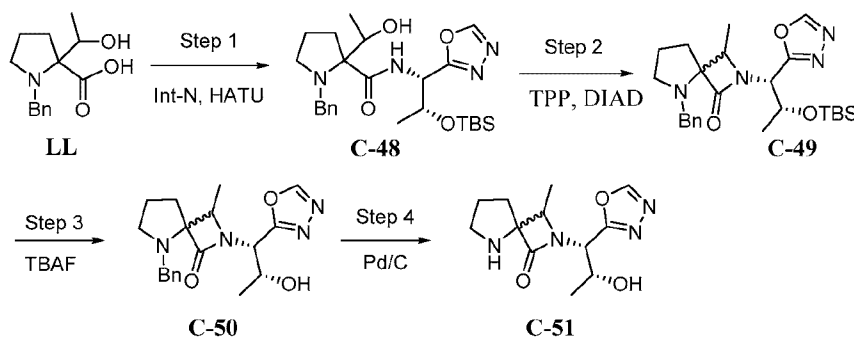
- 85 -

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.27 (s, 1H), 5.20-5.17 (m, 1H), 4.87-4.85 (m, 1H), 4.30-4.25 (m, 1H), 3.84-3.79 (m, 1H), 3.64-3.50 (m, 2H), 2.72-2.66 (m, 1H), 2.13-2.09 (m, 1H), 2.01-1.79 (m, 3H), 1.37-1.19 (m, 3H), 1.10-0.94 (m, 9H)

**Mass (ESI):** *m/z* 337.4 [*M*<sup>+</sup>+1]

5 **HPLC:** 99.5%

**Scheme 17**



**Synthesis of 1-benzyl-*N*-((1*S*, 2*R*)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(1-hydroxyethyl) pyrrolidine-2-carboxamide (C-48):**

10 **[00223]** To a stirring solution of LL (3.9 g, 15.66 mmol) in DMF (10 mL) were added *N*,*N*-diisopropylethylamine (8.16 mL, 46.98 mmol), Int-N (4.03 g, 15.66 mmol) followed by HATU (7.14 g, 18.79 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (100 mL) and EtOAc (150 mL). The separated organic layer was washed with water (100 mL) followed by brine solution (100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 30% EtOAc/n-hexane to obtained C-48 (1.8 g, 24%) as yellow syrup.

20 **<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 7.34-7.21 (m, 5H), 5.47-5.27 (m, 1H), 5.26-5.23 (m, 1H), 4.42-4.40 (m, 1H), 4.13-4.01 (m, 2H), 3.82-3.77 (m, 1H), 2.70-2.60 (m, 2H), 1.99-1.82 (m, 2H), 1.69-1.64 (m, 2H), 1.29-1.21 (m, 6H), 0.72 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H);

**LCMS (ESI):** *m/z* 489.6 [*M*<sup>+</sup>+1]

**Synthesis of 5-benzyl-2-((1*S*, 2*R*)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-3-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-49):**

25 **[00224]** To a stirring solution of triphenylphosphine (2.41 g, 9.22 mmol) in dry THF (20 mL) was added DIAD (1.49 g, 7.37 mmol) as portionwise and stirred for 15 min at RT. To this

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precipitated solution added **C-48** (1.8 g, 3.68 mmol) in dry THF (15 mL) dropwise at RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The obtained solid was triturated with 20% di ethylether/*n*-hexane (2 x 100 mL). The filtrate was concentrated under reduced pressure to  
 5 obtained crude compound which was purified by silica gel column chromatography eluting 20% EtOAc/hexane to afford **C-49** (400 mg, crude) as pale green syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.30 (s, 1H), 7.40-7.24 (m, 5H), 5.26-5.22 (m, 1H), 4.80-4.73 (m, 2H), 4.62-4.48 (m, 1H), 4.15-4.00 (m, 1H), 3.81-3.75 (m, 1H), 2.85 (t, *J* = 8.0 Hz, 1H), 2.49-2.39 (m, 3H), 2.26-2.11 (m, 1H), 1.71-1.64 (m, 3H), 1.25-1.15 (m, 3H), 0.78 (s, 9H),  
 10 0.02 (s, 6H);

**LCMS (ESI):** *m/z* 471.6 [*M*<sup>+</sup>+1]

**Synthesis of 5-benzyl-2-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-3-methyl-2, 5-diazaspiro [3.4] octan-1-one (C-50):**

**[00225]** To a stirring solution of **C-49** (1.5 g, 3.19 mmol) in dry THF (30 mL) was added  
 15 TBAF (1M in THF) (4.78 mL, 1.5 mmol) at 0 °C and stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (75 mL) and EtOAc (100 mL). The organic layer was washed with water (2 x 50 mL), brine solution (2 x 50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude  
 20 compound which was purified by column chromatography by eluting 30% EtOAc/*n*-hexane to obtained **C-50** (500 mg, 44%) as white solid.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 7.37-7.22 (m, 5H), 5.29-5.21 (m, 1H), 4.96-4.75 (m, 1H), 4.33-4.02 (m, 1H), 4.00-3.94 (m, 2H), 3.77-3.70 (m, 2H), 2.91-2.80 (m, 1H), 2.42-2.38 (m, 1H), 2.16-2.08 (m, 2H), 1.80-1.63 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.12 (d, *J* =  
 25 6.0 Hz, 3H);

**LCMS (ESI):** *m/z* 357.43 [*M*<sup>+</sup>+1]

**HPLC:** 99.61%

**Synthesis of 2-((1*S*,2*R*)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)-3-methyl-2,5-diazaspiro[3.4]octan-1-one (C-51):**

**[00226]** To a stirring solution of compound **C-50** (420 mg, 1.17 mmol) in methanol (10 mL) was added 10%Pd/C (400 mg) under N<sub>2</sub> atmosphere. The reaction mixture was stirred under H<sub>2</sub> atmosphere at RT for 3 h. After consumption of the starting material (by TLC), the



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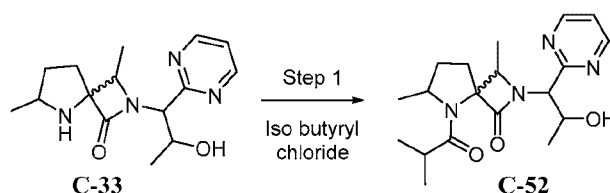
reaction mixture was filtered through a pad of celite and the pad was washed with methanol (10 mL). Obtained filtrate was concentrated under reduced pressure to afford **C-51** (220 mg, 70%) as an off-white solid.

**<sup>1</sup>H-NMR:** (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 5.25-5.17 (m, 1H), 4.89-4.69 (m, 1H), 4.28-4.21 (m, 1H), 3.84-3.56 (m, 2H), 2.95-2.79 (m, 2H), 1.99-1.84 (m, 2H), 1.77-1.59 (m, 2H), 1.24-1.10 (m, 6H);

**LCMS (ESI):** *m/z* 260 [*M*<sup>+</sup>+1]

**HPLC:** 97.94%

#### Scheme 18



#### Synthesis of 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-3, 6-dimethyl-2, 5-diazaspiro [3.4] octan-1-one (C-52):

[00227] To a stirring solution of **C-33** (500 mg, 1.72 mmol) in dry DCM (10 mL) was added DIPEA (556 mg, 4.31 mmol) followed by isobutryl chloride (273 mg, 2.58 mmol) slowly at 0 °C and stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude residue was diluted with water (10 mL). The separated organic layer was washed with brine solution (20 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 1% MeOH/DCM to obtained **C-52** (90 mg, 14.5%) as pale brown syrup.

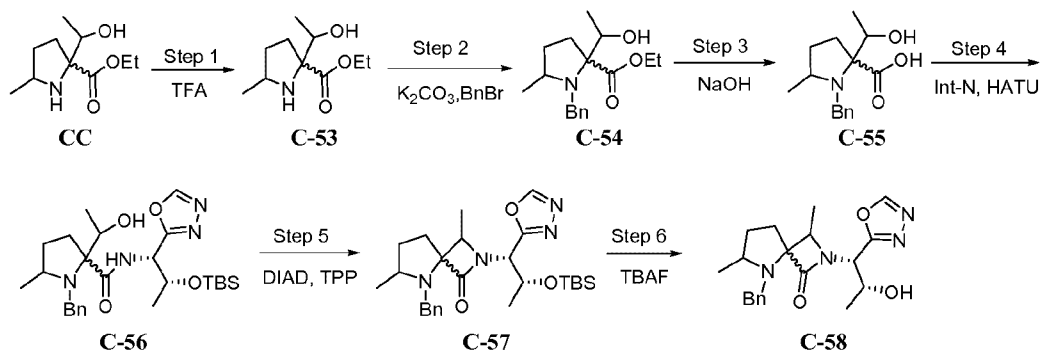
**<sup>1</sup>H-NMR:** (400 MHz, CD<sub>3</sub>OD): δ 8.81-8.77 (m, 2H), 7.41-7.37 (m, 1H), 4.63-4.53 (m, 2H), 4.24-4.18 (m, 2H), 2.87-2.72 (m, 1H), 2.33-2.27 (m, 1H), 2.16-2.08 (m, 2H), 1.73-1.69 (m, 1H), 1.40-1.35 (m, 3H), 1.28-1.20 (m, 3H), 1.15-1.02 (m, 9H);

**LCMS (ESI):** *m/z* 361.3 [*M*<sup>+</sup>+1];

**HPLC:** 94.85%

#### Scheme 19

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### Synthesis of ethyl 2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxylate (C-53):

[00228] To a stirring solution of CC (5 g, 16.61 mmol) in  $CH_2Cl_2$  (50 mL) was added  
 5 TFA (6.34 mL, 83.05 mmol) at 0 °C. After being stirred at RT for 4 h, the reaction mixture was concentrated under reduced pressure to afford crude compound which was triturated with n-pentane (50 mL) to obtained C-53 (5 g, crude) as black syrup was directly taken for the next step without further purification.

$^1H$ -NMR: (500 MHz,  $DMSO-d_6$ ):  $\delta$  8.71 (br s, 1H), 4.29-4.25 (m, 1H), 4.25-4.21 (m, 3H),  
 10 4.14-4.03 (m, 1H), 2.31-2.10 (m, 4H), 1.36-1.18 (m, 6H), 1.18-1.10 (m, 3H)

LCMS (ESI):  $m/z$  202.38 [ $M^+ + 1$ ]

### Synthesis of ethyl 1-benzyl-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxylate (C-54: C-54-A & C-54-B) :

[00229] To a stirring solution of C-53 (5 g (crude), 15.87 mmol) in acetonitrile (50 mL)  
 15 was added  $K_2CO_3$  (6.57 g, 47.61 mmol) followed by benzyl bromide (2.82 mL, 23.80 mmol) at RT and stirred for 16 h. After completion of the reaction, diluted the reaction mixture with EtOAc (150 mL) and water (75 mL). The organic layer was washed with brine solution (2 x 150 mL). The organic layer was dried over anhydrous  $Na_2SO_4$  and concentrated under vacuum. Obtained crude material was purified by column chromatography eluting with 10%  
 20 EtOAc/Hexane to afford 1 g of C-54-A and 1.2 g of C-54-B (separated isomers of C-54) (48%) as yellow syrups.

$^1H$ -NMR (C-54-A isomer): (500 MHz,  $DMSO-d_6$ ):  $\delta$  7.35-7.14 (m, 5H), 4.55 (s, 2H), 4.24-4.19 (m, 1H), 4.13-4.02 (m, 2H), 3.96-3.91 (m, 2H), 2.14-1.99 (m, 1H), 1.95-1.82 (m, 3H), 1.25-1.18 (m, 3H), 1.10-1.06 (m, 3H), 0.75 (d,  $J$  = 6.0 Hz, 3H)

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LCMS (ESI):  $m/z$  292.3 [ $M^{+}+1$ ]

<sup>1</sup>H-NMR (C-54-B isomer): (500 MHz, DMSO- $d_6$ ):  $\delta$  7.34-7.18 (m, 5H), 5.15 (t,  $J$  = 5.5 Hz, 2H), 4.63-4.49 (m, 1H), 4.24-4.22 (m, 1H), 4.10-4.06 (m, 2H), 3.18-3.10 (m, 1H), 2.39-2.33 (m, 1H), 1.89-1.83 (m, 3H), 1.42-1.39 (m, 3H), 1.20-1.13 (m, 3H), 0.76 (d,  $J$  = 6.0 Hz, 3H)

5 LCMS (ESI):  $m/z$  292.3 [ $M^{+}+1$ ]

**Synthesis of 1-benzyl-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxylic acid (C-55-A):**

[00230] To a stirring solution of C-54-A (1 g, 3.43 mmol) in MeOH/THF/H<sub>2</sub>O (5 mL/5 mL/5 mL) were added NaOH (206 mg, 5.14 mmol) at 0 °C. The reaction mixture was heated to 90 °C for 6 h. After consumption of the starting material (by TLC), the solvent was evaporated under reduced pressure. The aqueous layer was washed with di ethylether (50 mL). The separated aqueous layer was acidified by using 2N HCl (pH~3). The aqueous layer was extracted with 10% MeOH/DCM (2 x 100 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford compound C-55-A (1 g, crude) as yellow solid.

15 <sup>1</sup>H-NMR: (400 MHz, DMSO- $d_6$ ):  $\delta$  9.84 (s, 1H), 7.60 (d,  $J$  = 6.8 Hz, 2H), 7.50-7.30 (m, 3H), 5.12 (br s, 1H), 4.48-4.35 (m, 2H), 4.09-3.81 (m, 1H), 2.39-2.22 (m, 2H), 2.16-2.08 (m, 2H), 1.66-1.57 (m, 1H), 1.16-0.86 (m, 6H);

LCMS (ESI):  $m/z$  264.3 [ $M^{+}+1$ ]

**Synthesis of 1-benzyl-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxylic acid (C-55-B):**

20 [00231] To a stirring solution of C-54-B (1.2 g, 4.12 mmol) in MeOH/THF/H<sub>2</sub>O (5 mL/5 mL/5 mL) were added NaOH (206 mg, 5.14 mmol) at 0 °C. The reaction mixture was heated to 90 °C for 6 h. After consumption of the starting material (by TLC), the solvent was evaporated under reduced pressure. The aqueous layer was washed with di ethylether (50 mL). The separated aqueous layer was acidified by using 2N HCl (pH~3). The aqueous layer was extracted with 10% MeOH/DCM (2 x 100 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford compound C-55-B (780 mg) as yellow solid.

25 <sup>1</sup>H-NMR (C-55-B isomer): (400 MHz, DMSO- $d_6$ ):  $\delta$  9.14 (s, 1H), 7.64 (d,  $J$  = 6.0 Hz, 2H), 7.49-7.44 (m, 3H), 4.99 (d,  $J$  = 12.8 Hz, 1H), 4.48 (s, 2H), 4.45-4.41 (m, 1H), 3.98-3.93 (m, 1H), 2.32-2.13 (m, 4H), 1.40 (d,  $J$  = 6.4 Hz, 3H), 0.76 (d,  $J$  = 6.4 Hz, 3H);

30 LCMS (ESI):  $m/z$  272.4 [ $M^{+}-1$ ]

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**Synthesis of 1-benzyl-N-((1S, 2R)-2-((tert-butyldimethylsilyl)oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxamide (C-56):**

[00232] To a stirring solution of C-55 (1.78 g, 6.75 mmol) (mixture of two isomers C-55-A & C-55-B) in DMF (10 mL) were added *N, N*-diisopropylethylamine (3.51 mL, 20.27 mmol), Int N (1.74 g, 6.75 mmol) followed by HATU (3.08 g, 8.11 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (100 mL) and EtOAc (150 mL). The separated organic layer was washed with water (100 mL) followed by brine solution (100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 30% EtOAc/n-hexane to obtained C-56 (1.2 g, 35%) as brown syrup.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.31 (s, 1H), 8.42 (s, 1H), 7.44-7.19 (m, 5H), 5.26-4.95 (m, 1H), 4.36 (s, 2H), 4.33-4.18 (m, 2H), 4.09-3.94 (m, 1H), 2.32-2.22 (m, 1H), 2.15-1.86 (m, 4H), 1.37-1.05 (m, 9H), 0.85 (s, 9H), 0.04 (s, 6H);

LCMS (ESI): *m/z* 503.7 [M<sup>+</sup>+1]

**Synthesis of 1-benzyl-N-((1S, 2R)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(1-hydroxyethyl)-5-methylpyrrolidine-2-carboxamide (C-57):**

[00233] To a stirring solution of triphenylphosphine (1.56 g, 5.97 mmol) in dry THF (15 mL) was added DIAD (967 mg, 4.78 mmol) as portionwise and stirred for 15 min at RT. To this precipitated solution added C-56 (1.2 g, 2.39 mmol) in dry THF (15 mL) slowly at RT and stirred for 4 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The obtained solid was triturated with 20% di ethylether/*n*-hexane (2 x 100 mL). The filtrate was concentrated under reduced pressure to obtained crude compound which was purified by silica gel column chromatography eluting 20% EtOAc/hexane to afford C-57 (400 mg, crude) as brown thick syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.27 (s, 1H), 7.43-7.18 (m, 5H), 4.91-4.73 (m, 2H), 4.42-4.02 (m, 2H), 3.96-3.75 (m, 2H), 2.11-1.84 (m, 3H), 1.42-1.37 (m, 1H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.23-1.11 (m, 6H), 0.70 (s, 9H), 0.02 (s, 6H);

LCMS (ESI): *m/z* 485.7 [M<sup>+</sup>+1]

**Synthesis of 5-benzyl-2-((1S, 2R)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-3, 6-dimethyl-2, 5-diazaspiro [3.4] octan-1-one (C-58):**

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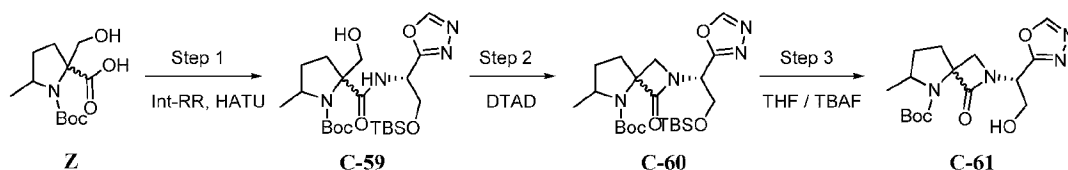
[00234] To a stirring solution of **C-57** (400 mg, 0.82 mmol) in dry THF (5 mL) was added TBAF (1M in THF) (1.23 mL, 1.5 mmol) at 0 °C and stirred for 1 h at RT. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (30 mL) and EtOAc (50 mL). The organic layer was washed with water (2 x 20 mL), brine solution (2 x 20 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 30% EtOAc/*n*-hexane to obtained **C-58** (90 mg, 29%) as thick syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 7.41-7.18 (m, 5H), 5.28-5.17 (m, 1H), 4.97-4.62 (m, 1H), 4.43-4.20 (m, 1H), 4.02-3.89 (m, 1H), 3.77-3.64 (m, 2H), 3.20-3.01 (m, 1H), 2.09-1.80 (m, 3H), 1.44-1.40 (m, 1H), 1.38-1.30 (m, 1H), 1.28-1.21 (m, 4H), 1.19-1.06 (m, 1H), 0.90-0.85 (m, 3H)

LCMS (ESI):*m/z* 371.45 [M<sup>+</sup>+1]

HPLC: 94.53%

#### 15 Scheme 20



#### Synthesis of *tert*-butyl 2-(((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)ethyl)carbamoyl)-2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate (**C-59**):

[00235] To a stirring solution of **Z** (2 g, 7.72 mmol) in DCM (25 mL) were added *N,N*-diisopropylethylamine (4 mL, 23.16 mmol), Int **RR** (2.06 g, 8.49 mmol), followed by HATU (3.52 g, 9.26 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (50 mL). The separated organic layer was washed with citric acid solution (1 x 50 mL), saturated brine solution (1 x 50 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 50% EtOAc/*n*-hexane to obtained **C-59** ( 2.5 g, 67%) as thick syrup.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 7.99 (d, *J* = 3.5 Hz, 1H), 5.29-5.26 (m, 2H), 4.05-3.99 (m, 3H), 3.57-3.54 (m, 2H), 2.28-1.91 (m, 3H), 1.42 (s, 9H), 1.38-1.31 (m, 1H), 1.18-1.11 (m, 3H), 0.84 (s, 9H), -0.01 (s, 6H)

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**Synthesis of tert-butyl 2-(((S)-2-((tert-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)ethyl)-6-methyl-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (C-60):**

[00236] To a stirring solution of triphenylphosphine (2.7 g, 10.33 mmol) in dry THF (20 mL) was added DTAD (2.37 g, 10.33 mmol) at RT and stirred for 15 min. After added C-59 (2.5 g, 5.16 mmol) and the reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was triturated with di ethylether/*n*-pentane and obtained solid was filtered. The filtrate was evaporated, purified by silica gel column chromatography eluting 30% EtOAc/hexane to afford C-60 (2.1 g, 87.5%) as yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.32 (s, 1H), 5.19-5.08 (m, 1H), 4.12-3.87 (m, 3H), 3.58-3.45 (m, 2H), 1.56-1.42 (m, 3H), 1.40 (s, 9H), 1.38-1.20 (m, 1H), 1.18-1.12 (m, 3H), 0.80 (s, 9H), 0.02 (s, 6H)

**Synthesis of tert-butyl 2-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-6-methyl-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-61):**

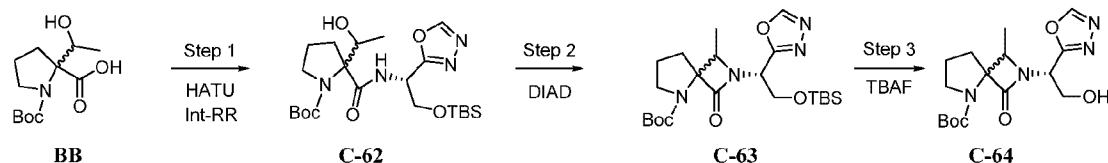
[00237] To a stirring solution of C-60 (2.1 g, 4.5 mmol) in dry THF (10 mL) was added TBAF (2.34 g, 9 mmol) at 0 °C. The reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting 2% MeOH/DCM to afford C-61 (800 mg, 51%) as thick syrup.

<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 5.33-5.08 (m, 2H), 3.94-3.75 (m, 3H), 3.67-3.51 (m, 1H), 3.39-3.31 (m, 1H), 2.13-1.93 (m, 3H), 1.55-1.50 (m, 1H), 1.40 (s, 9H), 1.15-1.08 (m, 3H),

LCMS (ESI): *m/z* 353.3 [M<sup>+</sup>+1];

HPLC: 96.6%

**Scheme 21**



**Synthesis of tert-butyl 2-(((S)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) ethyl) carbamoyl)-2-(1-hydroxyethyl) pyrrolidine-1-carboxylate (C-62):**

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[00238] To a stirring solution of **BB** (3.5 g, 13.51 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) were added DIPEA (7.0 mL, 40.53 mmol), **RR** (3.2 g, 13.51 mmol), HATU (5.6 g, 14.85 mmol) at 0 °C and stirred for 12 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The separated  
 5 organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford **C-62** (3.5 g, crude) as colorless liquid.

Mass (ESI): *m/z* 485.67 [M<sup>+</sup>+1]

**Synthesis of *tert*-butyl 2-((*S*)-2-((*tert*-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) ethyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-63):**

10 [00239] To a stirring solution of triphenylphosphine (2.03 g, 7.75 mmol) in THF (25 mL) was added DIAD (1.59 g, 7.75 mmol) at 0 °C and stirred for 30 min. **C-62** (1.5 g, 3.10 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting  
 15 30% EtOAc/hexane to afford **C-63** (600 mg, 43%) as pale yellow liquid.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.24 (s, 1H), 5.93-4.75 (m, 2H), 4.16-3.91 (m, 2H), 3.78-3.70 (m, 2H), 3.91 (d, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 7.0 Hz, 2H), 3.44-3.34 (m, 4H), 2.01-1.91 (m, 2H), 1.85-1.68 (m, 6H), 2.11-1.68 (m, 4H), 1.40 (s, 9H), 1.38-1.18 (m, 3H), 0.80 (s, 9H), -0.02 (s, 6H).

20 Mass (ESI): *m/z* 467.6 [M<sup>+</sup>+1]

**Synthesis of *tert*-butyl 2-((*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) ethyl)-1-methyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-64):**

[00240] To a stirring solution of **C-63** (0.5 g, 1.07 mmol) in dry THF (10 mL) was added TBAF (1M in THF) (1.07 mL, 1.91 mmol) at 0 °C and stirred at RT for 3 h. After consumption  
 25 of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was diluted with water (15 mL) and EtOAc (30 mL). The organic layer was washed with water (2 x 15 mL), brine solution (2 x 10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 70% EtOAc/*n*-hexane to  
 30 obtained **C-64** (95 mg, 25%) as white solid.

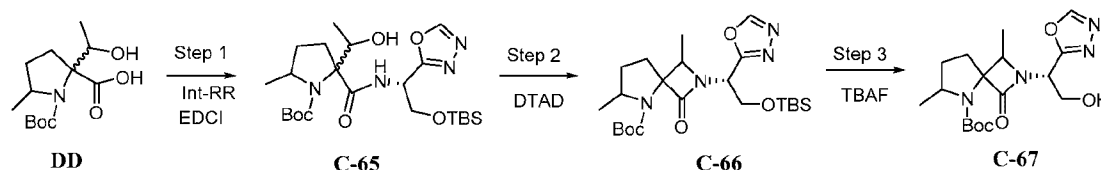
<sup>1</sup>H-NMR: (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 5.32-5.04 (m, 2H), 3.98-3.72 (m, 4H), 2.14-1.66 (m, 4H), 1.39 (s, 1H), 1.37-1.09 (m, 3H)

LCMS (ESI): *m/z* 353.3 [M<sup>+</sup>+1]

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HPLC: 88.9%

Scheme 22



5

**Synthesis of tert-butyl 2-(((S)-2-((tert-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)ethyl)carbamoyl)-2-(1-hydroxyethyl)-5-methylpyrrolidine-1-carboxylate (C-65):**

[00241] To a stirring solution of DD (1 g, 3.66 mmol) in DCM (20 mL) were added *N,N*-diisopropylethylamine (1.9 mL, 10.98 mmol), Int RR (978 mg, 4.02 mmol), EDCI (1.04 g, 5.49 mmol) followed by HOBT (741 mg, 5.49 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL). The separated organic layer was washed with brine solution (30 mL). The separated organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 40% EtOAc/n-hexane to obtained C-65 (700 mg, 38.4%) as thick syrup.

<sup>1</sup>H-NMR: (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 5.22-5.18 (m, 1H), 4.58-4.50 (m, 2H), 4.04-3.92 (m, 3H), 1.47-1.41 (m, 1H), 1.38 (s, 9H), 1.29-1.16 (m, 6H), 1.14-1.11 (m, 3H), 0.83 (s, 9H), -0.02 (s, 6H);

LCMS (ESI): *m/z* 523.6 [M<sup>+</sup>+1]

**Synthesis of tert-butyl 2-(((S)-2-((tert-butyldimethylsilyl)oxy)-1-(1,3,4-oxadiazol-2-yl)ethyl)-1,6-dimethyl-3-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (C-66):**

[00242] To a stirring solution of triphenylphosphine (736 mg, 2.81 mmol) in dry THF (10 mL) was added DTAD (646 mg, 2.81 mmol) as portionwise and stirred for 15 min at RT. To this precipitated solution added C-65 (700 mg, 1.4 mmol) in dry THF (15 mL) slowly at RT and stirred for 6 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure. The crude material was triturated with *n*-pentane (20 mL) /di ethylether (20 mL). The filtrate was concentrated under reduced pressure to obtained crude compound which was purified by silica gel column chromatography eluting 25% EtOAc/hexane to afford C-66 (430 mg, 64%) as thick syrup.

25



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**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 5.20-5.16 (m, 1H), 4.16-4.00 (m, 1H), 3.88-3.70 (m, 3H), 2.17-2.08 (m, 1H), 1.96-1.85 (m, 1H), 1.40 (s, 9H), 1.26-1.07 (m, 8H), 0.82 (s, 9H), -0.02 (s, 6H);

**LCMS (ESI):** *m/z* 505.5 [M<sup>+</sup>+1]

5 **Synthesis of tert-butyl 2-((*S*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) ethyl)-1, 6-dimethyl-3-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (C-67):**

**[00243]** To a stirring solution of **C-66** (430 mg, 0.89 mmol) in dry THF (10 mL) was added TBAF (1.8 mL, 1.79 mmol) slowly at 0 °C and stirred at RT for 6 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced  
10 pressure. The crude residue was purified with column chromatography by eluting 90% EtOAc/n-hexane to afford **C-67** (80 mg, 24.5%) as thick syrup.

**<sup>1</sup>H-NMR:** (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.25 (s, 1H), 5.20-5.03 (m, 2H), 3.98-3.72 (m, 3H), 2.50-1.85 (m, 3H), 1.56-1.50 (m, 1H), 1.40 (s, 9H), 1.27-1.11 (m, 6H)

**LCMS (ESI):** *m/z* 291.3 [M<sup>+</sup>+1];

15 **HPLC:** 91.4%

**Example 3 - [<sup>3</sup>H] MK-801 binding assay**

**Methods**

**[00244]** Assays were conducted as described in Moskal et al. (Moskal, J.R., Kuo, A.G.,  
20 Weiss, C., Wood, P.L., O'Connor Hanson, A., Kelso, S., Harris, R.B., Disterhoft, J.F., 2005. GLYX-13: a monoclonal antibody-derived peptide that acts as an N-methyl-D-aspartate receptor modulator. *Neuropharmacology*. 49, 1077-87) The potentiation of [<sup>3</sup>H]MK-801 binding (5 nM; 22.5 Ci / mmol) to well washed rat cortical membranes (200 µg) was measured under non-equilibrium conditions (15 min @ 25 °C) in the presence of increasing  
25 concentrations of test compounds and 50µM glutamate. Zero levels were determined in the absence of any glycine ligand and in the presence of 30µM 5,7 DCKA. Maximal stimulation was measured in the presence of 1 mM glycine, and 50µM glutamate was present in all samples. The facilitation of [<sup>3</sup>H]MK-801 binding by tests compounds was calculated by using a 3 parameter log agonist vs. response equation (Graph pad Prism, USA) and potency (EC<sub>50</sub>,  
30 expressed in pM) and maximal activity (% maximal stimulation) were calculated for the test compound.

Results

[00245] The potency and maximal activity for Compound Y is 288 pM, 14%.

**Table 2.** Additional Biological Data

Compound	Unified Activity Data: LTP Augmentation (Percent)	Unified Activity Data: LTP Concentration (uM)	Unified Activity Data: LTP, Significant (S) or Non-significant (NS)	Unified Activity Data: Porsolt Floating Time Inhibition (Percent)	Unified Activity Data: Porsolt Dose (mg/kg)	Unified Activity Data: Porsolt Dose, route	Unified Activity Data: Porsolt Time Post Dose (Hours)	MK-801 Glycine Site Binding Assay: Rat Cortex EC50 (M)
C-4	140	1	S	92	3	IV	1	2.879E-10
C-15	120	1	S	86	1	PO	1	

5 **Table 3.** Additional Biological Data

Compound	MK-801 Glycine Site Binding Assay: Rat Cortex EC50 (M)	LTP: LTP Augmentation (%)	LTP: LTP Concentration (uM)	LTP: LTP Significance, S or NS
C-33	7.129E-12	30	1	NS
C-19	1.096E-10	110	1	S
C-26	7.23E-13	65	1	NS
C-29	1.353E-10	125	1	S

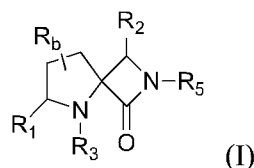
## EQUIVALENTS

[00246] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention

10 described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A compound represented by formula I:



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

R<sub>b</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>1</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl and a nitrogen protecting group;

wherein the nitrogen protecting group is selected from the group consisting of 9-fluorenylmethyloxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, acetyl, trifluoroacetyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxyphenyl, 3,4-dimethoxybenzyl, triphenylmethyl, p-toluenesulfonyl, -C(O)OR<sub>31</sub> and -C(O)R<sub>32</sub>; wherein

R<sub>31</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, -CH<sub>2</sub>-C<sub>3</sub>-C<sub>10</sub> cycloalkyl, -CH<sub>2</sub>-phenyl, and -CH<sub>2</sub>-pyridyl, wherein any aforementioned cycloalkyl is optionally substituted with from 1-3 independently selected C<sub>1</sub>-C<sub>3</sub> alkyl, and wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy, nitro, halo, SO<sub>2</sub>Me, cyano, and -OC(O)CH<sub>3</sub>; and

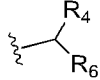
R<sub>32</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl, and pyridyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy, nitro, halo, SO<sub>2</sub>Me, cyano, and -OC(O)CH<sub>3</sub>;

R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of:

(i) heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and

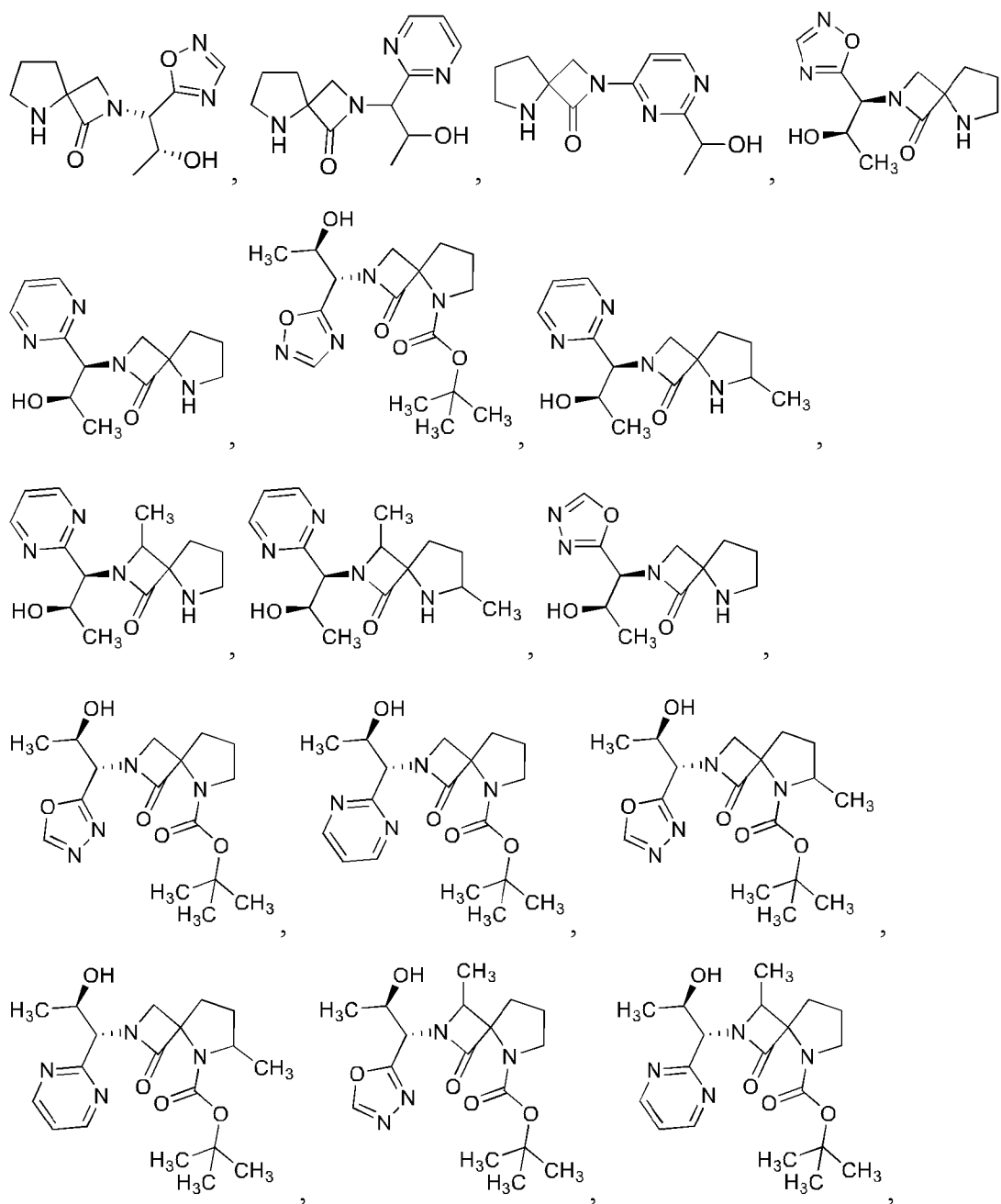
(ii) heterocyclyl including from 3 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O,

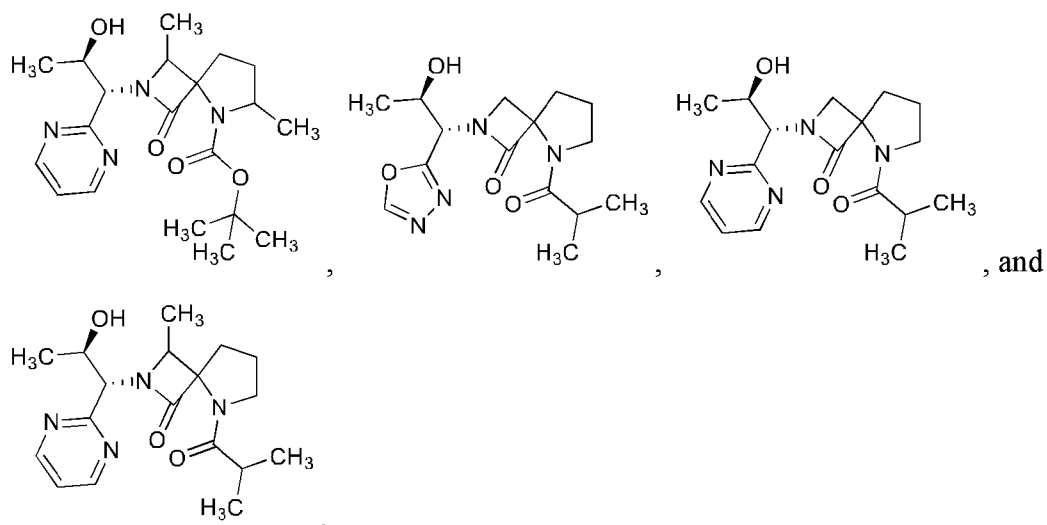
and S; wherein R<sub>5</sub> is unsubstituted or substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy.

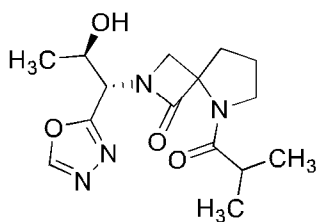
2. The compound of claim 1, wherein R<sub>1</sub> is H.
3. The compound of claim 1 or 2, wherein R<sub>2</sub> is H.
4. The compound of any one of claims 1-3, wherein R<sub>3</sub> is H.
5. The compound of any one of claims 1-3, wherein R<sub>3</sub> is a nitrogen protecting group.
6. The compound of claim 5, wherein R<sub>3</sub> has formula -C(O)OR<sub>31</sub>.
7. The compound of claim 6, wherein R<sub>31</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl.
8. The compound of claim 7, wherein R<sub>31</sub> is *tert*-butyl.
9. The compound of claim 5, wherein R<sub>3</sub> has formula -C(O)R<sub>32</sub>.
10. The compound of claim 9, wherein R<sub>32</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl.
11. The compound of claim 10, wherein R<sub>32</sub> is -CH<sub>3</sub> or *iso*-propyl.
12. The compound of any one of claims 1-11, wherein R<sub>5</sub> is X.
13. The compound of claim 10, wherein X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C<sub>1</sub>-C<sub>3</sub> alkyl), O, and S.
14. The compound of claim 13, wherein X is selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, and pyrimidinyl.
15. The compound of any one of claims 12-14, wherein R<sub>5</sub> is substituted with -CH(R<sub>4</sub>)(R<sub>6</sub>).

16. The compound of claim 15, wherein  $R_4$  is  $C_1$ - $C_6$  alkyl.
17. The compound of claim 15 or 16, wherein  $R_4$  is methyl.
18. The compound of any one of claims 15-17, wherein  $R_6$  is selected from the group consisting of hydroxyl,  $-O-C(O)-C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy.
19. The compound of claim 18, wherein  $R_6$  is hydroxyl.
20. The compound of any one of claims 1-11, wherein  $R_5$  is  $-C_1$ - $C_6$  alkylene-X.
21. The compound of any one of claims 1-11, wherein  $R_5$  is  $-C_1$ - $C_2$  alkylene-X.
22. The compound of claim 20 or 21, wherein  $R_5$  is substituted with  $-CH(R_4)(R_6)$ .
23. The compound of claim 22, wherein  $R_5$  is substituted on the alkylene portion with  $-CH(R_4)(R_6)$ .
24. The compound of claim 23, wherein  $R_5$  has the formula  $-CH(CHR_4R_6)-X$ .
25. The compound of any one of claims 22-24, wherein  $R_4$  is  $C_1$ - $C_6$  alkyl.
26. The compound of any one of claims 22-25, wherein  $R_4$  is methyl.
27. The compound of any one of claims 22-26, wherein  $R_6$  is selected from the group consisting of hydroxyl,  $-O-C(O)-C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy.
28. The compound of claim 27, wherein  $R_6$  is hydroxyl.
29. The compound of claim 20 or 21, wherein X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH,  $N(C_1$ - $C_3$  alkyl), O, and S.
30. The compound of any one of claims 20-22, wherein X is selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, and pyrimidinyl.
31. The compound of any one of claims 1-30, wherein  $R_b$  is H.
32. The compound of claim 1, wherein the compound is selected from the group consisting of





33. The compound of claim 1, wherein the compound is



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

34. The compound of claim 1, wherein

$R_b$  is H;

$R_1$  is H;

$R_2$  is H;

$R_3$  is  $-\text{C}(\text{O})\text{R}_{32}$ , wherein  $\text{R}_{32}$  is  $-\text{CH}_3$ ;

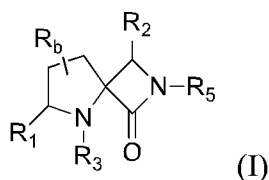
$R_4$  is methyl;

$R_5$  has the formula  $-\text{CH}(\text{CHR}_4\text{R}_6)-\text{X}$ , wherein X is pyrimidinyl; and

$R_6$  is hydroxyl.

35. A pharmaceutical composition comprising a compound of any one of claims 1-34, and a pharmaceutically acceptable excipient.

36. The pharmaceutical composition of claim 35, suitable for oral administration.
37. The pharmaceutical composition of claim 35, suitable for intravenous administration.
38. A use of a pharmaceutically effective amount of a compound of any one of claims 1-34 for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.
39. A compound represented by formula I:



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

$R_b$  is selected from the group consisting of H, halogen, hydroxyl, cyano and  $C_1$ - $C_6$  alkyl;

$R_1$  is H or  $C_1$ - $C_6$  alkyl;

$R_2$  is H or  $C_1$ - $C_6$  alkyl;

$R_3$  is selected from the group consisting of H,  $C_1$ - $C_6$  alkyl and a nitrogen protecting group;

wherein the nitrogen protecting group is selected from the group consisting of 9-fluorenylmethyloxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, acetyl, trifluoroacetyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxyphenyl, 3,4-dimethoxybenzyl, triphenylmethyl, p-toluenesulfonyl,  $-C(O)OR_{31}$  and  $-C(O)R_{32}$ ; wherein


$R_{31}$  is selected from the group consisting of  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ - $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ -phenyl, and  $-CH_2$ -pyridyl, wherein any aforementioned cycloalkyl is optionally substituted with from 1-3 independently selected  $C_1$ - $C_3$  alkyl, and wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy, nitro, halo,  $SO_2Me$ , cyano, and  $-OC(O)CH_3$ ; and



R<sub>32</sub> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, phenyl, and pyridyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy, nitro, halo, SO<sub>2</sub>Me, cyano, and -OC(O)CH<sub>3</sub>;

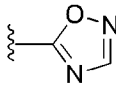
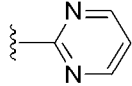
R<sub>4</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>5</sub> is X or -C<sub>1</sub>-C<sub>6</sub> alkylene-X, wherein X is selected from the group consisting of a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, and a 4- to 6-membered heterocyclyl ring having 1, 2, or 3 heteroatoms selected from O, S, or N;

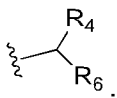
wherein R<sub>5</sub> is unsubstituted or substituted with ; and

R<sub>6</sub> is selected from the group consisting of H, halogen, hydroxyl, cyano, -O-C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy.

40. The compound of claim 39, wherein R<sub>1</sub> is H.
41. The compound of claim 39 or 40, wherein R<sub>2</sub> is H.
42. The compound of any one of claims 39-41, wherein R<sub>3</sub> is H.
43. The compound of any one of claims 39-41, wherein R<sub>4</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl.
44. The compound of any one of claims 39-42, wherein R<sub>4</sub> is methyl.
45. The compound of any one of claims 39-44, wherein R<sub>b</sub> is H.
46. The compound of any one of claims 39-45, wherein R<sub>5</sub> is X, and wherein X is a 5- to 6-membered heteroaryl ring selected from the group consisting of azetidiny, pyrrolidiny, pyrazolidiny, pyridiny, pyrimidiny, isooxazolidiny, imidazolidiny, oxazolidiny, thiazolidiny, and isothiazolidiny.

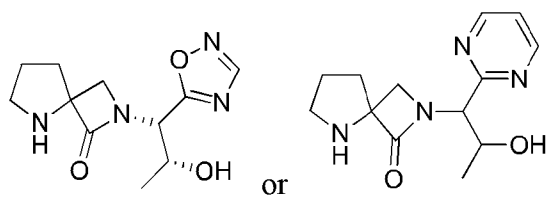
47. The compound of any one of claims 39-45, wherein R<sub>5</sub> is  or .

48. The compound of any one of claims 39-45, wherein  $R_5$  is X, and wherein X is

unsubstituted or substituted with .

49. The compound of any one of claims 39-48, wherein  $R_6$  is hydroxyl.

50. The compound of claim 39, wherein the compound is



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof.

51. The compound of claim 39, wherein

$R_b$  is H;

$R_1$  is H;

$R_2$  is H;

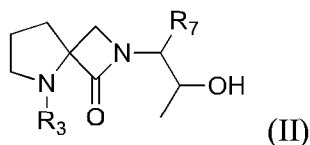
$R_3$  is  $-C(O)R_{32}$ , wherein  $R_{32}$  is  $-CH_3$ ;

$R_4$  is methyl;

$R_5$  has the formula  $-CH(CHR_4R_6)-X$ , wherein X is 1,3,4-oxadiazolyl; and

$R_6$  is hydroxyl.

52. A compound represented by formula II:



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

$R_3$  is selected from the group consisting of H,  $C_1$ - $C_6$ alkyl and a nitrogen protecting group;

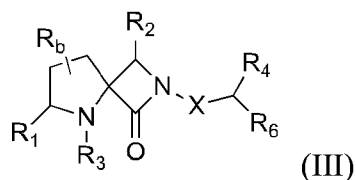
wherein the nitrogen protecting group is selected from the group consisting of 9-fluorenylmethyloxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, acetyl, trifluoroacetyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxyphenyl, 3,4-dimethoxybenzyl, triphenylmethyl, p-toluenesulfonyl,  $-C(O)OR_{31}$  and  $-C(O)R_{32}$ ; wherein

$R_{31}$  is selected from the group consisting of  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ - $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ -phenyl, and  $-CH_2$ -pyridyl, wherein any aforementioned cycloalkyl is optionally substituted with from 1-3 independently selected  $C_1$ - $C_3$  alkyl, and wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy, nitro, halo,  $SO_2Me$ , cyano, and  $-OC(O)CH_3$ ; and

$R_{32}$  is selected from the group consisting of H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl, and pyridyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy, nitro, halo,  $SO_2Me$ , cyano, and  $-OC(O)CH_3$ ; and

$R_7$  is a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, unsubstituted or substituted on a free carbon by a substituent selected from the group consisting of: halogen,  $C_1$ - $C_6$ alkyl, hydroxyl, cyano, and phenyl.

53. A compound represented by formula III:



or a pharmaceutically acceptable salt, a stereoisomer, or an N-oxide thereof, wherein

$R_b$  is selected from the group consisting of H, halogen, hydroxyl, cyano and  $C_1$ - $C_6$  alkyl;

$R_1$  is H or  $C_1$ - $C_6$  alkyl;

$R_2$  is H or  $C_1$ - $C_6$  alkyl;

$R_3$  is selected from the group consisting of H,  $C_1$ - $C_6$  alkyl and a nitrogen protecting group;


wherein the nitrogen protecting group is selected from the group consisting of 9-fluorenylmethyloxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, acetyl, trifluoroacetyl, benzoyl, benzyl, p-methoxybenzyl, p-methoxyphenyl, 3,4-dimethoxybenzyl, triphenylmethyl, p-toluenesulfonyl,  $-C(O)OR_{31}$  and  $-C(O)R_{32}$ ; wherein

$R_{31}$  is selected from the group consisting of  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ - $C_3$ - $C_{10}$  cycloalkyl,  $-CH_2$ -phenyl, and  $-CH_2$ -pyridyl, wherein any aforementioned cycloalkyl is optionally substituted with from 1-3 independently selected  $C_1$ - $C_3$  alkyl, and wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy, nitro, halo,  $SO_2Me$ , cyano, and  $-OC(O)CH_3$ ; and

$R_{32}$  is selected from the group consisting of H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl, phenyl, and pyridyl, wherein the phenyl is optionally substituted with from 1-2 substituents independently selected from  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  haloalkyl,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy, nitro, halo,  $SO_2Me$ , cyano, and  $-OC(O)CH_3$ ;

$R_4$  is H or  $C_1$ - $C_6$  alkyl;

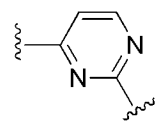
X is selected from the group consisting of a 4- to 6-membered heteroaryl ring having 1, 2, or 3 heteroatoms selected from O, S, or N, and a 4- to 6-membered heterocyclyl ring having 1, 2, or 3 heteroatoms selected from O, S, or N;

wherein  is present on a free carbon of X; and

$R_6$  is selected from the group consisting of H, halogen, hydroxyl, cyano,  $-O-C(O)-C_1-C_6$  alkyl,  $C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy.

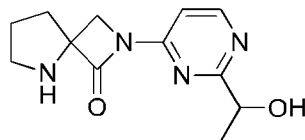
54. The compound of claim 53, wherein  $R_1$  is H.
55. The compound of claim 53 or 54, wherein  $R_2$  is H.
56. The compound of any one of claims 53-55, wherein  $R_3$  is H.
57. The compound of any one of claims 53-56, wherein  $R_4$  is  $C_1$ - $C_6$  alkyl.
58. The compound of any one of claims 53-56, wherein  $R_4$  is methyl.

59. The compound of any one of claims 53-58, wherein  $R_b$  is H.



60. The compound of any one of claims 53-59, wherein X is

61. The compound of any one of claims 53-60, wherein  $R_6$  is hydroxyl.



62. The compound of claim 53, wherein the compound is

63. A pharmaceutical composition comprising a compound of any one of claims 39-62, and a pharmaceutically acceptable excipient.

64. The pharmaceutical composition of claim 63, suitable for oral administration.

65. The pharmaceutical composition of claim 63, suitable for intravenous administration.

66. A use of a pharmaceutically effective amount of a compound of any one of claims 39-62 for treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof.

Figure 1

