(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2014 (07.08.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/120800 A1

(51) **International Patent Classification**:
C07D 487/10 (2006.01) ***A61P 25/00*** (2006.01)
A61K 31/40 (2006.01)

(21) **International Application Number**:
PCT/US2014/013639

(22) **International Filing Date**:
29 January 2014 (29.01.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/757,942 29 January 2013 (29.01.2013) US

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/120800 A1

(54) **Title**: SPIRO-LACTAM NMDA RECEPTOR MODULATORS AND USES THEREOF

(57) **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.

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. 61/757,942, filed on January 29, 2013, which is incorporated by reference in its entirety.

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 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 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 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 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

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 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 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 also been implicated in certain types of spatial learning.

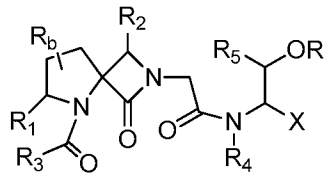
[0005] The NMDA receptor is believed to consist of several protein chains embedded in the postsynaptic membrane. The first two types of subunits discovered so far form a large extracellular region, which probably contains most of the allosteric binding sites, several transmembrane regions looped and folded so as to form a pore or channel, which is permeable to 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.

[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 Ca^{++} flow through the receptor. In the absence of or lowered level of the principal site ligand, the partial agonist acts to increase Ca^{++} flow through the receptor 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.

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:



(I)

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

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

R is H, C_1-C_6 alkyl or –C(O)-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, or a 4-6 membered heteroaryl with one, two or three heteroatoms each selected from O, S or N, wherein R_3 may be optionally substituted with one two or three substituents each selected from the group consisting of amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a) or benzyl (optionally substituted by one two or three substituents each independently selected from R^a);

R^a is selected from the group consisting of halogen, C_1-C_6 alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), or C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, -CO_2H, -C(O)NR^cR^d, and a 4- to 6-membered heteroaryl ring with one, two or three heteroatoms each selected from O, S or N, wherein the heteroaryl ring may be optionally substituted with one two or three substituents each selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl;

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

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl (e.g., H);

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is C_1-C_6 alkyl; C_1-C_6 alkoxy; -O-C_1-C_6 alkylene-phenyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl; phenyl; or 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, wherein R_3 is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one, two, or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), and C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

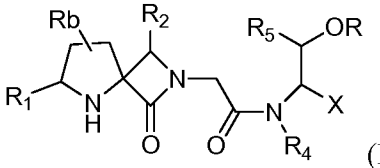
R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

Also 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:



(II)

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

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents

independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

[0009] Also provided herein are pharmaceutically acceptable compositions comprising a disclosed compound, and a pharmaceutically acceptable excipient. For example, such compositions may be suitable for oral or intravenous administration to a patient.

[0010] 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 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, 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 pharmaceutically acceptable salts, stereoisomers, N-oxides, and hydrates thereof.

[0011] 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 embodiments, a contemplated method may treat schizophrenia. Such schizophrenia may be, 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

[0012] **Figure 1** shows the potentiation of [^{3}H]MK-801 binding in the presence of Compound B.

[0013] **Figure 2** shows the potentiation of [^{3}H]MK-801 binding in the presence of Compound C.

[0014] **Figure 3** shows the potentiation of [^{3}H]MK-801 binding in the presence of Compound D.

[0015] **Figure 4** shows the potentiation of [^{3}H]MK-801 binding in the presence of Compound H.

[0016] **Figure 5** shows results of long term potentiation in hippocampal slices using Compound B.

DETAILED DESCRIPTION

[0017] 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

[0018] "Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0019] 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_2-C_6 alkenyl, and C_3-C_4 alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[0020] 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_1-C_6 alkoxy, and C_2-C_6 alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[0021] The term "alkenyloxy" used herein refers to a straight or branched alkenyl group attached to an oxygen (alkenyl-O). Exemplary alkenoxy groupd include, but are not limited to, groups with an alkenyl group of 3-6 carbon atoms, (also e.g. referred to as C_3-C_6 alkenyloxy). Exemplary "alkenoxy" groups include, but are not limited to allyloxy, butenyloxy, etc.

[0022] 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_3-C_6alkynyloxy, e.g., propynyloxy.

[0023] 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_1-C_6 alkyl, C_1-C_4 alkyl, and C_1-C_3 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_2F, CH_2CH_2Cl, CF_3, $CHFCH_2Cl$.

[0024] 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_2-C_6 alkynyl, and C_3-C_6 alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[0025] 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_2 or CH_2CH_2 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.

[0026] 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 $-NO_2$. The term "H" refers to hydrogen.

[0027] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen (cycloalkyl-O-).

[0028] The term "cycloalkyl" as used herein refers to a monocyclic saturated or partically unsatured hydrocarbon group of for example 3-6, or 4-6 carbons, referred to herein, e.g., as "C_{3-6}cycloalkyl" or "C_{4-6}cycloalkyl," and derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclohexenyl, cyclopentyl, cyclobutyl, cyclopropyl or cyclopentyl.

[0029] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[0030] The terms "heteroaryl" as used herein refers to a monocyclic aromatic 4-6 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 though 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), pyridyl, and pyrimidinyl.

[0031] 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 groups include but are not limited to pyrrolidine, piperidine, morpholine, thiomorpholine, and piperazine.

[0032] The term "heterocyclylalkoxy" as used herein refers to a heterocyclyl- alkyl-O- group.

[0033] The term "heterocyclyloxyalkyl" refers to a heterocyclyl-O-alkyl- group.

[0034] The term "heterocycloxy" refers to a heterocyclyl-O- group. The term "cycloalkyloxy" refers to a cycloalkyl-O- group.

[0035] The term "heteroaryloxy" referes to a heteroaryl-O- group.

[0036] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[0037] The term "oxo" as used herein refers to the radical =O.

[0038] The terms "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 (protects) 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-butoxycarbonyl (Boc), carbobenzyloxycarbonyl (Cbz), p-methoxybenzyloxycarbonyl, acetyl, 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: $-C(O)OR_{31}$ or $-C(O)R_{32}$ as defined herein. In certain embodiments, 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, wherein the C_3-C_{10} cycloalkyl is optionally substituted with from 1-3 independently selected C_1-C_3 alkyl; -CH_2-C_3-C_{10} cycloalkyl wherein the C_3-C_{10} cycloalkyl is optionally substituted with from 1-3 independently selected C_1-C_3 alkyl; -CH_2-phenyl, 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 -CH_2-pyridyl. In certain embodiments, R_{32} is selected from the group consisting of: H; C_1-C_6 alkyl; C_1-C_6 haloalkyl; phenyl, 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 pyridyl.

[0039] 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.

[0040] "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.

[0041] 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 supplemental, additional, or enhanced therapeutic functions.

[0042] 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.

[0043] "Individual," "patient," or "subject" are used interchangeably and include any 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 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.

[0044] In the present specification, the term "therapeutically effective amount" means the 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 amount which results in lessening a symptom of depression.

[0045] 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

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, glucaronate, 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 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.

[0046] 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.

[0047] 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 $\overset{\cdots\cdots}{}$ 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. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0048] 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.

[0049] Individual enantiomers and diasteriomers 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 steroselective 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.

[0050] 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.

[0051] 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 invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

[0052] Certain isotopically-labeled disclosed compounds (*e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.,* ^{3}H) and carbon-14 (*i.e.,* ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.,* ^{2}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.

[0053] 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 $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_{12})$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

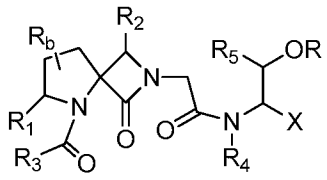
having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

[0054] 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 group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0055] 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 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 Simplício, *et al., Molecules* 2008, *13,* 519 and references therein.

Compounds

[0056] Disclosed compounds include those represented by the formula:



(I)

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

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

R is H, C_1-C_6 alkyl or –C(O)-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 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, or a 4-6 membered heteroaryl with one, two or three heteroatoms each selected from O, S or N, wherein R_3 may be optionally substituted with one two or three substituents each selected from the group consisting of amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a) or benzyl (optionally substituted by one two or three substituents each independently selected from R^a);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), or C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, $-CO_2H$, $-C(O)NR^cR^d$, and a 4- to 6-membered heteroaryl ring with one, two or three heteroatoms each selected from O, S or N, wherein the heteroaryl ring may be optionally substituted with one two or three substituents each selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl;

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

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl (e.g., H);

R is H, C_1-C_6 alkyl or $-C(O)$-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is C_1-C_6 alkyl; C_1-C_6 alkoxy; -O-C_1-C_6 alkylene-phenyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl; phenyl; or 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, wherein R_3 is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one, two, or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), and C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

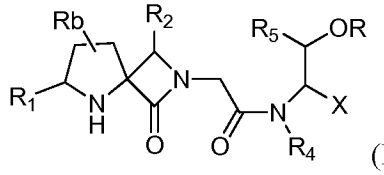
R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

Also 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:



(II)

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

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

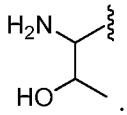
R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

[0057] In some embodiments , R_1 is H.

[0058] In some embodiments, R_2 is H.

[0059] In some embodiments, R_3 is unsubstituted C_1-C_6 alkyl. In certain embodiments, R_3 is methyl.

[0060] In some embodiments, R_3 is C_1-C_6 alkyl substituted with one, two or three substituents each selected from the group consisting of amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one two or three substituents each independently selected from R^a) and benzyl (optionally substituted by one two or three substituents each independently selected from R^a). In some embodiments, R_3 is C_1-C_6 alkyl substituted with one, two or three substituents each selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independently selected from halogen and C_1-C_6 alkyl). In certain embodiments, R_3 is



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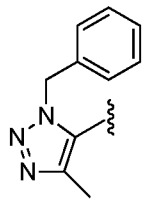
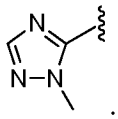
[0061] In certain embodiments, R_3 is heteroaryl. In some embodiments, R_3 is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl). In certain embodiments, R_3 (here, heteroaryl) is optionally substituted with one, two, or three substituents independently selected from the group consisting of C_1-C_6 alkyl (e.g., CH_3) and benzyl (optionally substituted by one two or three substituents each independently selected from R^a). In certain embodiments, R_3 (here, heteroaryl) is optionally substituted with one, two, or three substituents independently selected

from the group consisting of $-CH_3$ and benzyl. In some embodiments, R_3 is selected from the group consisting of $-CH_3$,  and  .

[0062] In some embodiments, R_3 is -O-C_1-C_6 alkylene-phenyl (e.g., -O-CH_2-phenyl), which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl). In certain embodiments, R_3 is benzyloxy.

[0063] In some embodiments, X is -C(O)NR^cR^d. In certain embodiments, R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl. For example, R^c and R^d are both H.

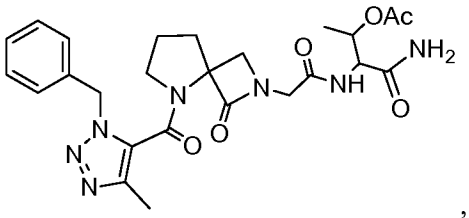
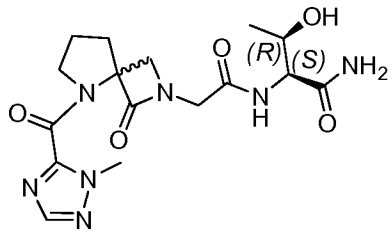
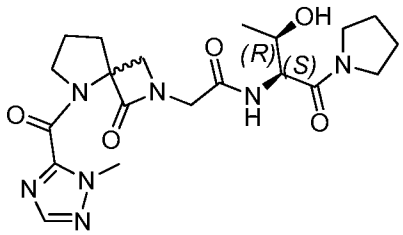
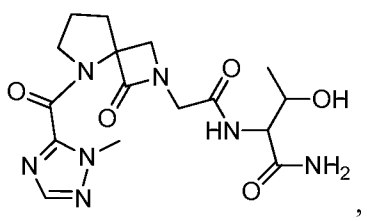
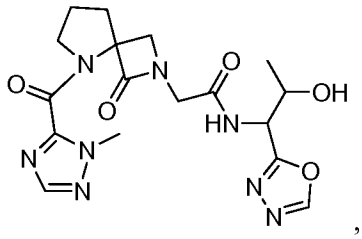
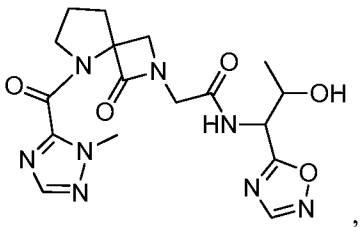
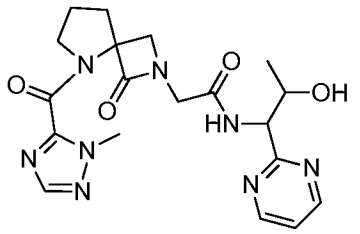
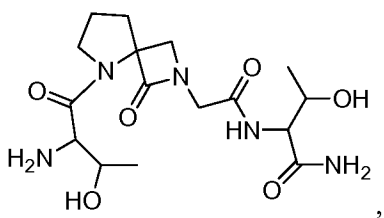
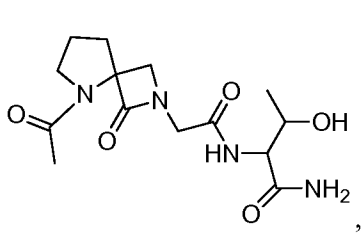
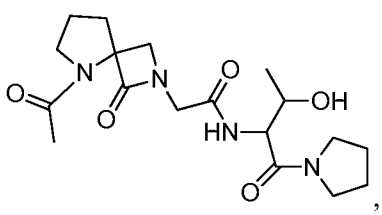
[0064] In other embodiments, X is a 4- to 6-membered heteroaryl ring. In some embodiments, X is heteroaryl including from 5 to 6 ring atoms wherein 1, 2, or 3 of the ring atoms are independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl. In certain embodiments, X is selected from the group consisting of 1,2,4- oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-triazolyl (optionally substituted with from 1-2 independently selected C_1-C_6 alkyl), pyridyl, and pyrimidinyl.

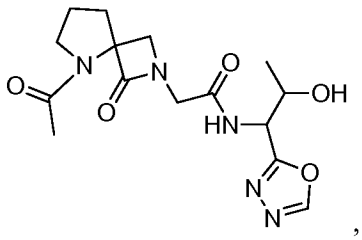
[0065] In some embodiments (including any of the foregoing embodiments described above), R is H or –C(O)-C_1-C_6alkyl (e.g., –C(O)-CH_3). In some embodiments (including any of the foregoing embodiments described above), R_5 is C_1-C_6 alkyl (e.g., $-CH_3$). In some embodiments (including any of the foregoing embodiments described above), R_4 is H. In some embodiments (including any of the foregoing embodiments described above), R_b is H. For example, embodiments described herein, in which R_3 is C_1-C_6 alkyl, substituted C_1-C_6 alkyl, heteroaryl, or -O-C_1-C_6 alkylene-phenyl, can include one or more of the following features: R_1 is H; R_2 is H; X is -C(O)NR^cR^d (e.g., -C(O)NH_2) or heteroaryl (e.g., 1,2,4- oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-triazolyl (optionally substituted with from 1-2 independently selected C_1-C_6

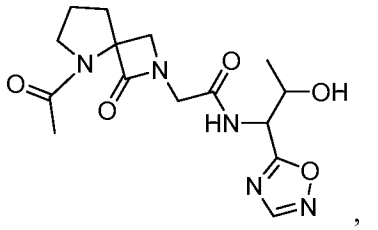
alkyl), pyridyl, or pyrimidinyl)); R is H or –C(O)-C_1-C_6alkyl (e.g., –C(O)-CH_3); R_5 is C_1-C_6 alkyl (e.g., –CH_3); R_4 is H; R_b is H. As another example, compounds of formula (II) can include one or more of the following features: R_1 is H; R_2 is H; X is -C(O)NR^cR^d (e.g., -C(O)NH_2) or heteroaryl (e.g., 1,2,4- oxadiazolyl, 1,3,4- oxadiazolyl, 1,2,4-triazolyl (optionally substituted with from 1-2 independently selected C_1-C_6 alkyl), pyridyl, or pyrimidinyl)); R is H or –C(O)-C_1-C_6alkyl (e.g., –C(O)-CH_3); R_5 is C_1-C_6 alkyl (e.g., –CH_3); R_4 is H; R_b is H.

[0066] In some embodiments, a disclosed compound includes those delineated in Table 1 and/or the Examples, e.g., one having the formula:

[0067]

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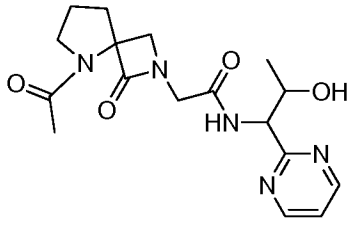
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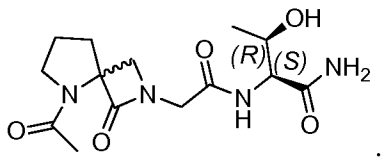
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[0068] The compounds of the present disclosure and formulations thereof may have a plurality of chiral centers. Each chiral center may be independently *R*, *S*, or any mixture of *R* and *S*. For example, in some embodiments, a chiral center may have an *R*:*S* ratio of between 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).

[0069] 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.

[0070] 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.

[0071] 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 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

[0072] In other aspects, formulations and compositions comprising the disclosed 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.

[0073] 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 suitable for oral administration, subcutaneous injection, or other methods for administering an active agent to an animal known in the pharmaceutical arts.

[0074] 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 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 treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0075] 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 such an active compound for the treatment of sensitivity in individuals.

[0076] 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, 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, 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.

[0077] 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.

[0078] 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.

[0079] 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

[0080] 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.

[0081] 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-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 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, spinal cord injury, peripheral neuropathy, acute neuropathic pain, and chronic neuropathic pain.

[0082] 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 contemplated.

[0083] 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 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.

[0084] Paranoid schizophrenia may be characterized where delusions or auditory 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 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 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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).

[0089] 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 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

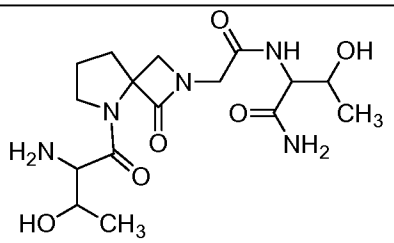
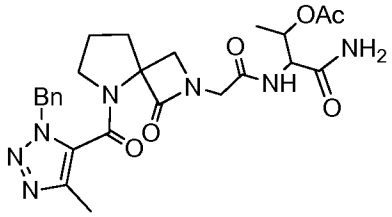
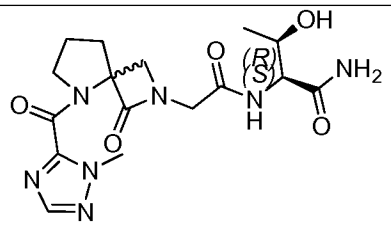
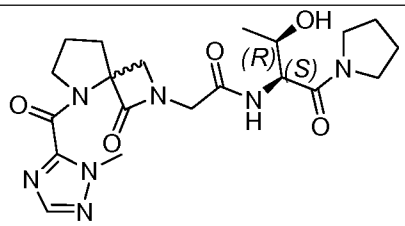
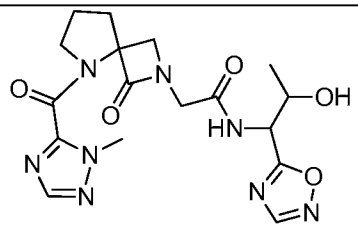
[0094] Also contemplated herein are combination therapies comprising a compound in combination with one or more other active agents. For example, a compound may be combined with one or more antidepressants, such as tricyclic antidepressants, MAO-I's, SSRI's, and double and triple uptake inhibitors and/or 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.

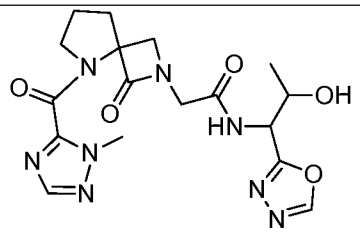
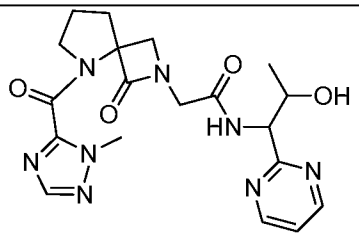
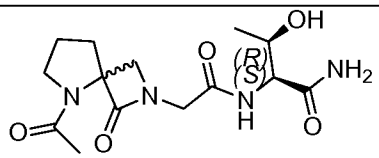
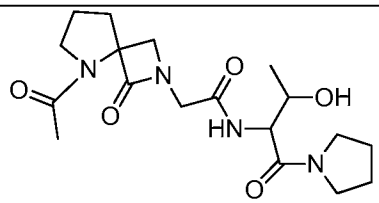
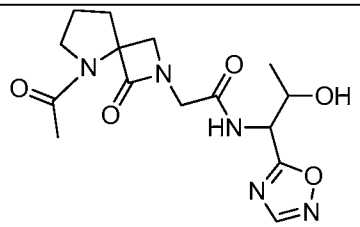
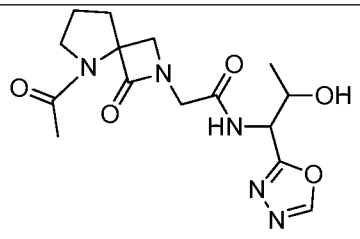
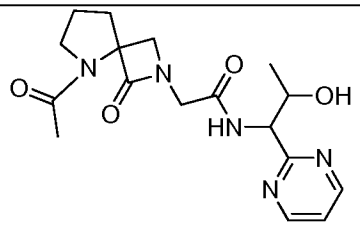
EXAMPLES

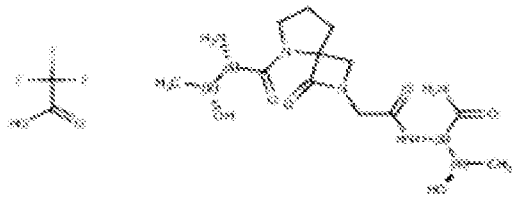
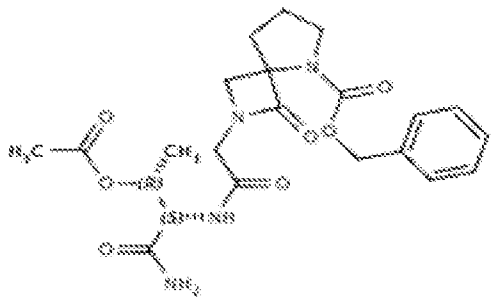
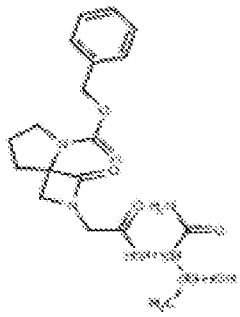
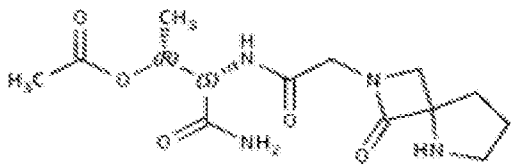
[0095] The following examples are provided for illustrative purposes only, and are not intended to limit the scope of the disclosure.

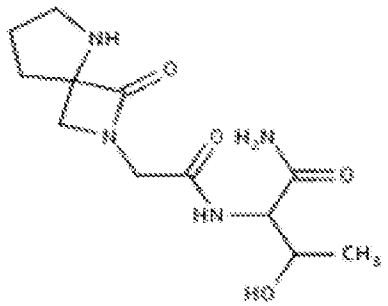
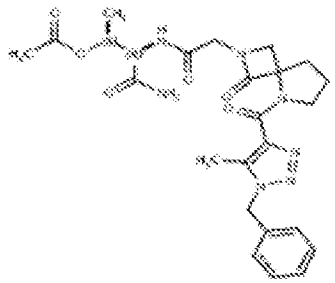
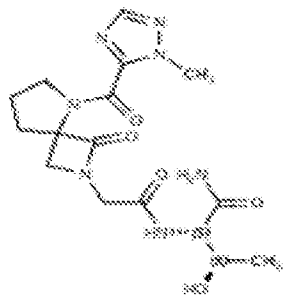
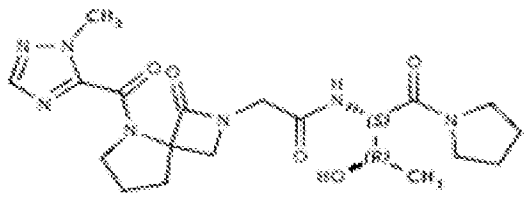
[0096] Table 1 below shows some exemplary compounds of the disclosure and provides physiochemical characteristics of the compounds.

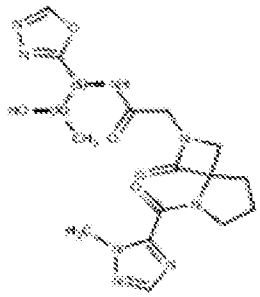
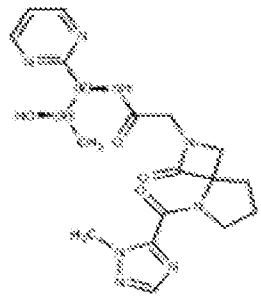
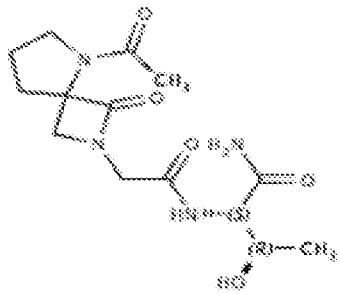
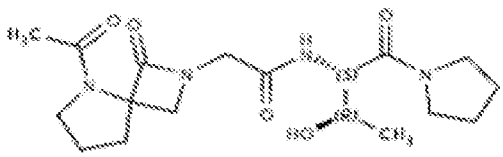
Table 1.

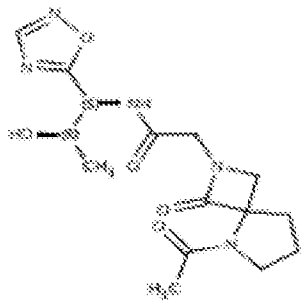
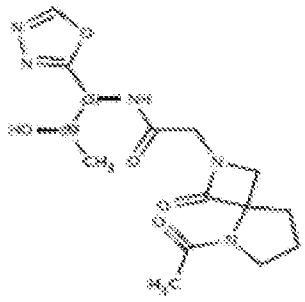
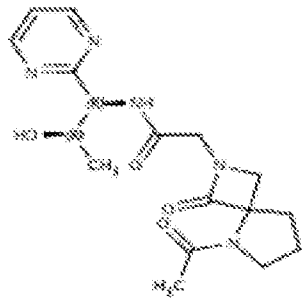
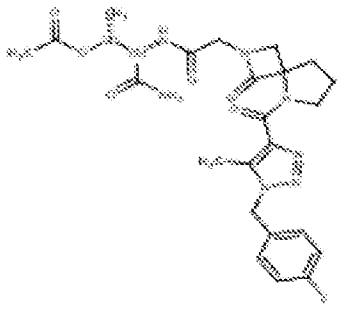
Compound	Structure	Molecular Weight (Da)	cLogP	tPSA
Compound A		385	-4.42	179
Compound B		525	-0.79	169.8
Compound C		393	-3.47	163.7
Compound D		447	-2.61	141
Compound E		418	-2.66	159.6

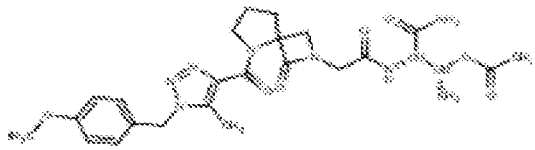
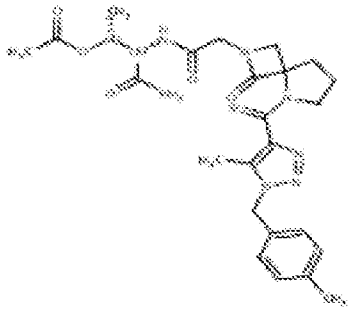
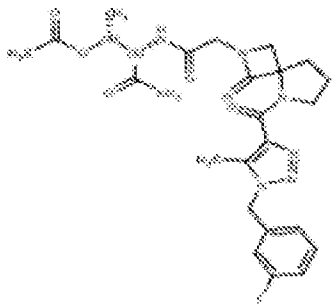
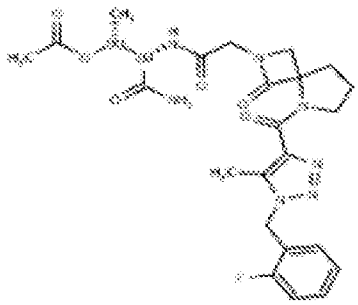
Compound F		418	-3.36	159.6
Compound G		428	-2.14	146.4
Compound H		326	-3.44	133
Compound I		380	-2.59	110.3
Compound J		351	-2.63	128.9
Compound K		351	-3.33	159.6
Compound L		361	-1.88	115.7

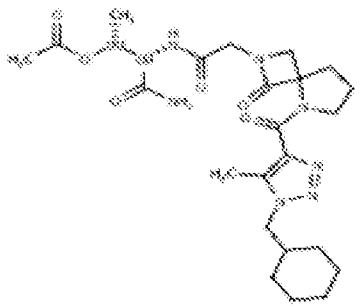
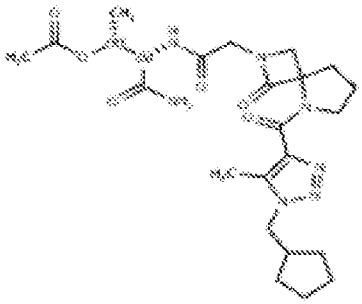
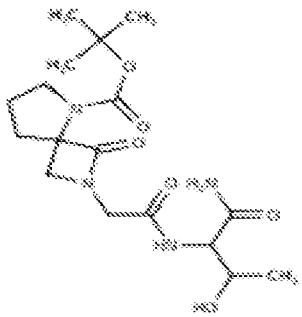
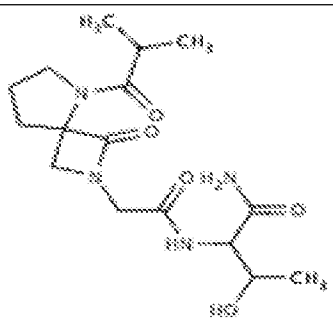
6S-FNL-6		499.4388	-4.42387	179.29
6S-FNL-2		460.4803	-0.65328	148.34
6S-FNL-4		418.4436	-1.09441	142.27
6S-FNL-3		326.3483	-2.60699	130.83

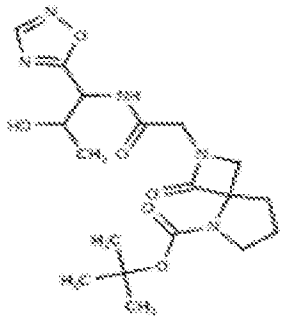
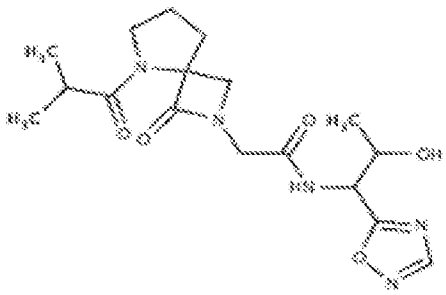
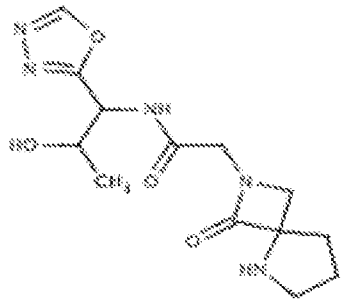
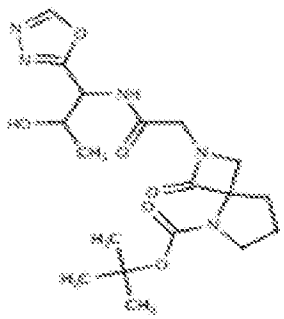
6S-FNL-5		284.3116	-3.04811	124.76
6S-FNL-24		525.5569	-0.786001	169.82
6S-FNL-8		393.3977	-3.46511	163.75
6S-FNL-9		447.4882	-2.61196	140.97

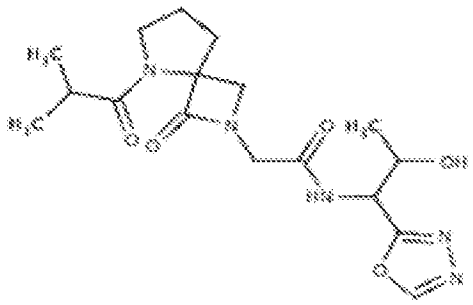
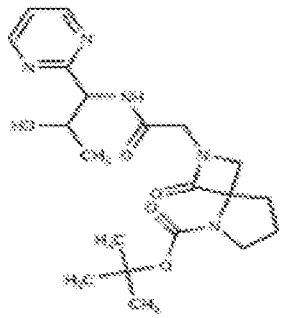
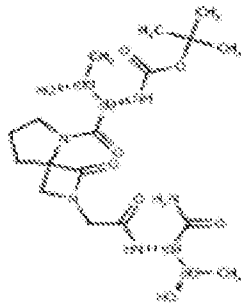
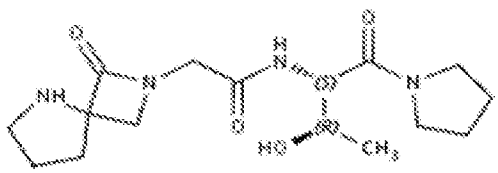
6S-FNL-12		418.4072	-3.35707	159.58
6S-FNL-21		428.4451	-2.14114	146.44
6S-FNL-7-F1, 6S-FNL-7-F2		326.3483	-3.43817	133.04
6S-FNL-10		380.4387	-2.58502	110.26

6S-FNL-16		351.3577	-2.63355	128.87
6S-FNL-14		351.3577	-3.33013	128.87
6S-FNL-19		361.3956	-1.88186	115.73
6S-FNL-25		543.5474	-0.643299	169.82

6S-FNL-26		555.5829	-0.943672	179.05
6S-FNL-27		539.5835	-0.27258	169.82
6S-FNL-28		543.5474	-0.643299	169.82
6S-FNL-29		543.5474	-0.643299	169.82

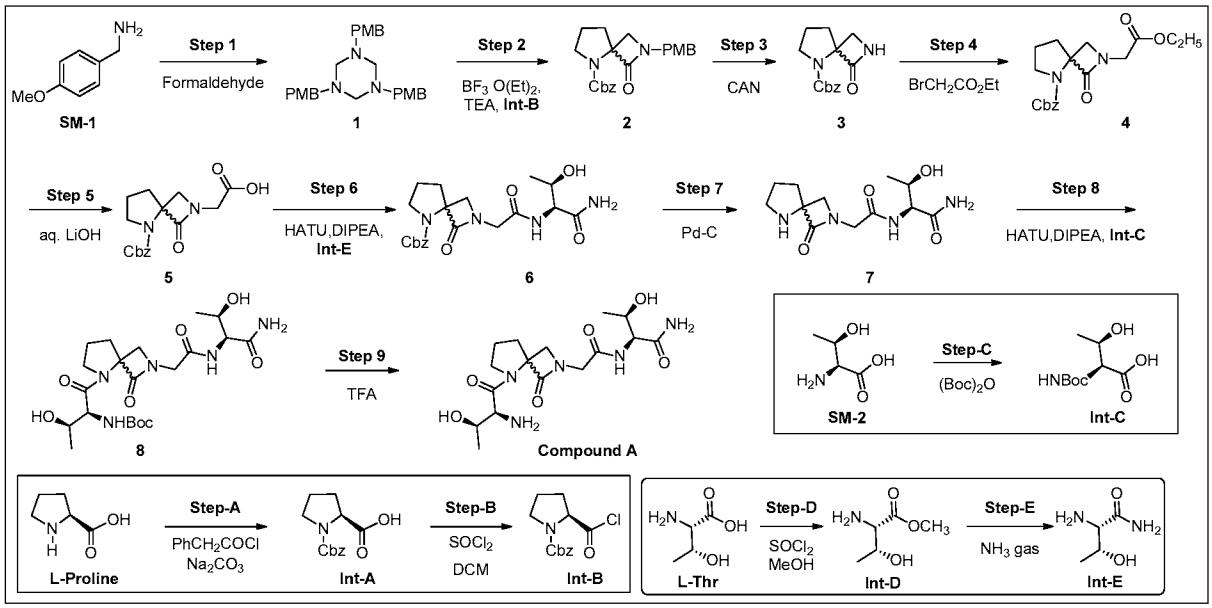
6S-FNL-30		531.6046	-0.396191	169.82
6S-FNL-31		517.578	-0.84076	169.82
6S-FNL-23		384.4274	-1.76492	142.27
6S-FNL-22		354.4014	-2.19465	133.04

6S-FNL-18		409.4369	-0.960294	138.1
6S-FNL-17		379.4109	-1.39002	128.87
6S-FNL-11		309.3211	-2.94007	120.59
6S-FNL-15		409.4369	-1.65688	138.1

6S-FNL-13		379.4109	-2.08661	128.87
6S-FNL-20		419.4748	-0.35934	124.96
6S-1		485.5313	-2.93177	191.6
6S-3		338.402	-2.19496	101.98

Example 1 – Synthesis of Compound A

Scheme 1.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[0097] To a stirring solution of **SM-1** (200 g, 1.46 mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtained crude; which was triturated with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[0098] To a stirring solution of **1** (45 g, 100 mmol) in CH_2Cl_2 (150 mL) was added $BF_3.OEt_2$ (37 mL, 301 mmol) drop wise at -40 °C. The above mixture was added to a stirring solution of **Int-B** (95 g, 342 mmol) and Et_3N (210.2 mL, 1.50 mol) in dry CH_2Cl_2 (500 mL) drop wise. The reaction mixture was stirred at -40 °C for 45 min. The resulting reaction mixture was allowed to warm to RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution (1 x 150 mL) followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for

crystallization. Obtained crystals were filtered and washed with cold EtOAc (50 mL) and dried under vacuum to afford **2** (90g, 65%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): 7.36-7.30 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, *J* = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, *J* = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m, 2H), 1.20-1.15 (m, 2H).

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[0099] To a stirring solution of **2** (46 g, 121 mmol) in MeCN (460 mL) and H_2O (200 mL) were cooled to 0 °C and added a solution of CAN (199 g, 0.23 mol) in H_2O (460 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water (100 mL) and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 x 150 mL) followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by silica gel column chromatography eluting with EtOAc to obtained **3** (12 g, 38%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, *J* = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H).

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00100] To a stirred solution of **3** (12 g, 46.1 mmol) in acetonitrile (120 mL) was added Cs_2CO_3 (37.6 g, 115.2 mmol) and ethyl 2-bromoacetate (7.7 mL, 69.2 mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/hexane to afford **4** (12.5 g, 78.6%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H).

LCMS m/z: 369.3 [M^++Na]

Synthesis of 2-(5-((benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00101] To a stirred solution of **4** (9.0 g, 26.0 mmol) in THF/ H_2O (80 mL/30 mL) was added LiOH.H_2O (2.73 g, 65.0 mmol) at RT and stirred for 3 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with EtOAc (2 x 50 mL). The separated aqueous layer was acidified to pH~3 using 2N HCl and extracted with EtOAc (3 x 50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (7.0 g, 85.3%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H)

Synthesis of benzyl 2-(2-(((2*S*, 3*R*)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00102] To a stirring solution of **5** (4 g, 12.5 mmol) in DCM (50 mL) were added *N, N*-diisopropylethylamine (5.79 mL, 31.2 mmol), Int-E (1.78 g, 15.0 mmol), followed by HATU (7.16 g, 18.7 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 organic layer was washed with citric acid solution (1 x 75 mL) followed by brine solution (1 x 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude which was purified by column chromatography to obtained **6** (2.1 g, 40.3%) as off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.80-7.73 (m, 1H), 7.38-7.31 (m, 5H), 7.23 (d, *J* = 10.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.08-5.01 (m, 1H), 4.86 (t, *J* = 4.0 Hz, 1H), 4.12-4.00 (m, 1H), 3.88-3.83 (m, 1H), 3.70-3.67 (m, 2H), 3.60-3.51 (m, 3H), 2.18-2.11 (m, 2H), 1.33-1.22 (m, 4H), 1.00 (d, *J* = 6.5 Hz, 3H)

Synthesis of (2*S*, 3*R*)-3-hydroxy-2-(2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)acetamido)butanamide (7)

[00103] To a stirring solution of **6** (2.1 g, 5.02 mmol) in MeOH (20 mL) was added (50% wet) 10% Pd/C (1.0 g) and stirred under H_2 atmosphere (balloon pressure) at RT for 2 h. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite using EtOAc/MeOH (10 mL/10 mL). The filtrate was concentrated under reduced pressure to afford **7** (1.4 g, 98.5%) as off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.75 (d, J = 8.0 Hz, 1H), 7.24 (s, 2H), 4.08-4.06 (m, 2H), 4.01-3.95 (m, 2H), 3.93-3.84 (m, 1H), 3.37-3.34 (m, 2H), 3.33 (d, J = 4.5 Hz, 1H), 2.90-2.87 (m, 2H), 1.90 (t, J = 7.0 Hz, 2H), 1.77-1.66 (m, 2H), 1.01 (d, J = 6.5 Hz, 3H)

LCMS m/z: 285.3 [M^++1]

Synthesis of *tert*-butyl ((2*S*, 3*R*)-1-(2-(2-(((2*S*, 3*R*)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octan-5-yl)-3-hydroxy-1-oxobutan-2-yl) carbamate (8)

[00104] To a stirring solution of **7** (300 mg, 1.05 mmol) in DCM (25 mL), DMF (0.5 mL) were added *N, N*-diisopropylethylamine (0.58 mL, 3.15 mmol), Int-**C** (277 mg, 1.26 mmol), followed by HATU (481 mg, 1.26 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 6% MeOH/DCM to afford **8** (400mg, 70% pure by LCMS) which was further purified by preparative HPLC to yield pure **8** (230 mg, LCMS purity 96%) as off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.83 (d, J = 8.5 Hz, 1H), 7.25 (s, 2H), 6.33 (d, J = 9.0 Hz, 1H), 4.80-4.75 (m, 2H), 4.24-3.98 (m, 4H), 3.71-3.60 (m, 3H), 3.39-3.33 (m, 1H), 2.14-1.89 (m, 4H), 1.41 (s, 9H), 1.14-1.05 (m, 6H)

LCMS m/z: 486.3 [M^++1]

Synthesis of (2*S*, 3*R*)-2-(2-(5-((2*S*, 3*R*)-2-amino-3-hydroxybutanoyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-3-hydroxybutanamide (Compound A)

[00105] To a stirring solution of **8** (130 mg, 0.26 mmol) in DCM (3 mL) was added TFA (152 mg, 1.34 mmol) at 0 °C and stirred at RT for 2 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure and co-distilled with DCM to afford **Compound A** (110 mg, 82.7% LCMS purity 93.32%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 4.33-4.28 (m, 1H), 4.23-4.19 (m, 4H), 4.05-4.01 (m, 1H), 3.91-3.87 (m, 1H), 3.71-3.65 (m, 2H), 3.55-3.49 (m, 1H), 2.30-2.24 (m, 2H), 2.02-1.97 (m, 2H), 1.27 (t, J = 4.0 Hz, 3H), 1.15 (t, J = 5.5 Hz, 3H)

LCMS m/z: 386.3 [M^++1]

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int A):

[00106] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61 mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified with 6*N* HCl. The aqueous layer was extracted with EtOAc (3 x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int A** (450 g, 84%) as pale yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00107] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of (2*S*, 3*R*)-2-((*tert*-butoxycarbonyl) amino)-3-hydroxybutanoic acid (Int-C)

[00108] To a stirring solution of (2*S*, 3*R*)-2-amino-3-hydroxybutanoic acid **(SM-2)** (30 g, 0.25 mol) in THF (150 mL) and water (150 mL) was added $NaHCO_3$ (65 g, 0.75 mol) followed by Boc-anhydride (66 mL, 0.302 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 extracted with EtOAc (2 x 150 mL). The aqueous layer was acidified using 2N HCl and then extracted with 10% MeOH/CH_2Cl_2. The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **Int-C** (30 g, 63%).

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 5.92-5.70 (m, 2H), 5.55 (d, 1H), 4.42 (br s, 1H), 4.29 (d, 1H), 1.47 (s, 9H), 1.25 (d, 3H)

LCMS m/z: 218 [M^+-1]

Synthesis of (2*S*, 3*R*)-methyl 2-amino-3-hydroxybutanoate (Int-D)

[00109] To a stirring solution of L-threonine (200 g, 1.68 mol) in methanol (1.2 L) was added $SOCl_2$ (244 mL, 3.36 mol) drop wise at 0 °C and stirred for 1 h. The resulting reaction mixture was refluxed for 24 h. After consumption of the starting material (by TLC), the reaction mixture was warmed to RT and concentrated under vacuum and decanted with *n*-hexane (2 x 50 mL). The residue was dissolved in EtOH (1 L) and neutralized with Et_3N (471 mL, 3.36 mol) and again stirred for 2 h. The precipitated solid was filtered off; obtained filtrate was concentrated under vacuum to afford **Int-D** (195 g, 80%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.51 (br s, 3H), 4.13-4.10 (m, 1H), 3.91 (br s, 1H), 1.20 (d, 3H)

LCMS m/z: 134.1 [M^++1]

Synthesis of (2*S*, 3*R*)-2-amino-3-hydroxybutanamide (Int-E)

[00110] A solution of **Int-D** (190 g, 1.35 mol) in IPA (2 L) was taken in autoclave and purged NH_3 gas (7-8 kg) and stirred at 35 °C for 24 h. Then removed NH_3 gas and reaction mixture was concentrated under reduced pressure and added CH_2Cl_2 and filtered. Obtained solid was refluxed in EtOH for 1 h at 78 °C. The reaction mass was filtered in heating condition and *n*-hexane was added to the filtrate and again stirred for another 4 h. Obtained precipitated solid was filtered and dried under vacuum to afford **Int-E** (160 g, 47%).

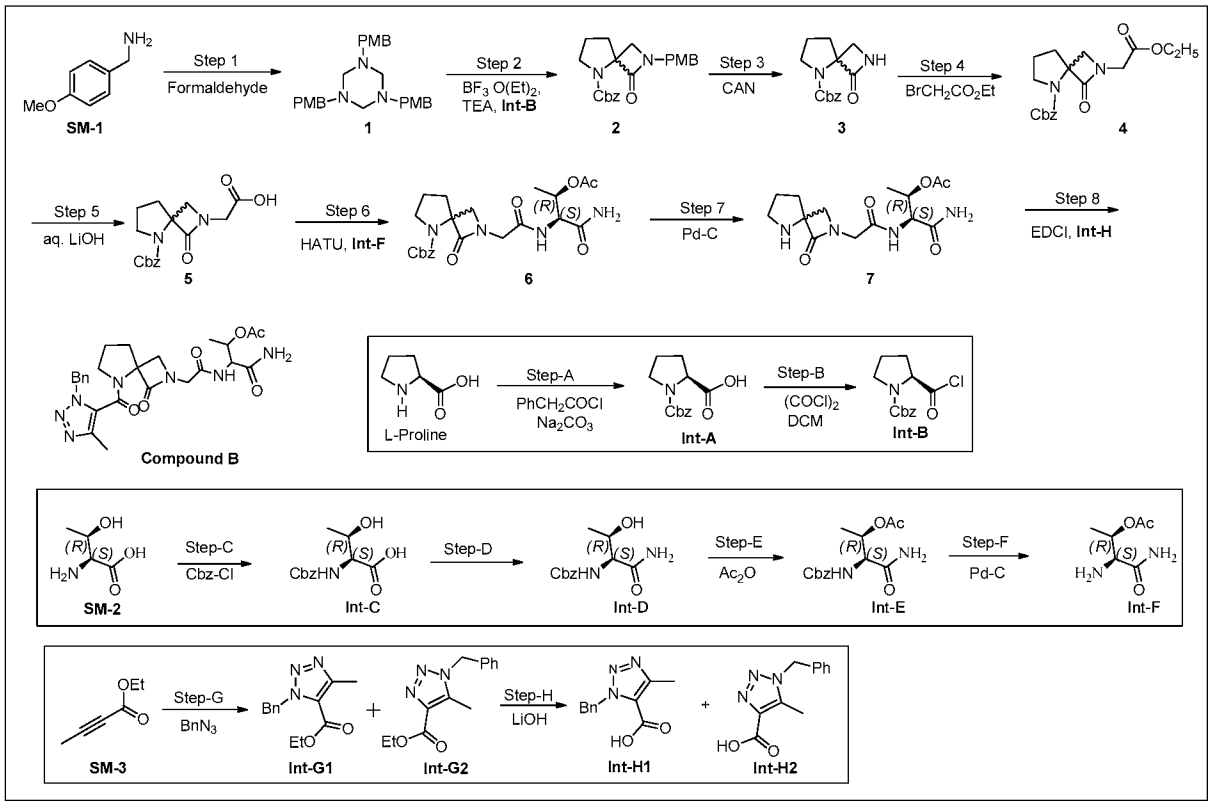
^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.38 (br s, 1H), 7.02 (br s, 1H), 4.66 (br s, 1H), 3.77-3.70 (m, 1H), 2.93 (d, 1H), 2.72 (br m, 1H), 1.05 (d, 3H)

LCMS m/z: 119.1 [M^++1]

UPLC (ELSD purity): 99.9%

Example 2 - Synthesis of Compound B

Scheme 2.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00111] To a stirring solution of (4-methoxyphenyl) methanamine **SM-1** (200g, 1.46mol) in EtOH (600mL) at room temperature was added formaldehyde (33%aq, 105mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H)

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00112] A stirring solution of **Int-B** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) was cooled to -40 °C and Et_3N (210.2 mL, 1.50 mol) was added drop wise. The reaction mixture was stirred at -40 °C for 45 min. To this a mixture of **1** (50g, 0.12 mol) and BF_3OEt_2 (47.6 g,

0.33 mol) in CH_2Cl_2 (150 mL) was added drop wise at -40 °C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): δ 7.36-7.30 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, *J* = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, *J* = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m,2H), 1.20-1.15 (m, 2H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00113] To a stirring solution of **2** (30 g, 78.94mmol) in MeCN (300 mL) and H_2O (150 mL) were cooled to 0 °C and added a solution of CAN (129 g, 0.23 mol) in H_2O (300 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 150mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. Obtained material was purified by silica gel column chromatography eluting with EtOAc to afford **3** (8 g, 40%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, *J* = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00114] To a stirred solution of **3** (10.0 g, 38.46 mmol) in acetonitrile (100 mL) were added Cs_2CO_3 (31.34 g, 96.19 mmol) and ethyl 2-bromoacetate (6.42 mL, 57.60 mmol) at RT and stirred for 16 h at RT. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 100 mL). The separated organic layer

was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/Hexane to afford **4** (10.0 g, 75%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H)

LCMS m/z: 261 [M^++1]

Synthesis of 2-(5-((benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00115] To a stirred solution of **4** (6.0 g, 17.34 mmol) in THF: H_2O (75mL/40 mL) was added LiOH.H_2O (1.82 g, 43.33 mmol) at RT and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~2 using 2N HCl and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (4.5 g, 88.2%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H),1.87-1.80 (m, 2H)

LCMS m/z: 319 [M^++1]

Synthesis of 2 benzyl 2-(2-(((2S, 3R)-3-acetoxy-1-amino-1-oxobutan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00116] To a stirring solution of **5** (10 g, 31.44 mmol) in DMF (120 mL) was added *N, N*-diisopropylethyl amine (14.48 mL, 78.6 mmol), Int-F (5.95 g, 37.7 mmol), followed by HATU (14.33 g, 37.7 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 and washed with saturated $NaHCO_3$ solution. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography by 1% MeOH/DCM to afford **6** (5.5 g, 38.1%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.97-7.88 (m, 1H), 7.49-7.46 (m, 5H), 7.35 (s, 1H), 7.17 (s, 1H), 5.11 (s, 2H), 5.08-5.02 (m, 1H), 4.41 (d, J = 9.0 Hz, 1H), 4.21-4.11 (m, 1H), 3.87-3.79 (m, 4H), 3.13 (s, 1H), 2.18-2.21 (m, 2H), 1.98 (s, 3H), 1.90-1.84 (m, 2H), 1.81-1.10 (m, 3H)

LCMS m/z: 483.5 [M^++Na]

Synthesis of (2R, 3S)-4-amino-4-oxo-3-(2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido) butan-2-yl acetate (7)

[00117] To a stirring solution of **6** (5.5 g, 11.95mmol) in methanol (50 mL) was added 50% wet 10% Pd/C (2.0 g) and stirred under H_2 atmosphere (balloon pressure) for 4 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (5 mL). The filtrate was concentrated under reduced pressure to give **7** (3.80 g, 97.6%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.97 (d, J = 9.6 Hz, 1H), 7.49 (s, 1H), 7.16 (s, 1H), 5.19-5.13 (m, 1H), 4.46-4.41 (m, 1H), 4.03-3.90 (m, 2H), 3.39-3.30 (m, 3H), 2.91 (t, J = 6.4 Hz, 2H), 1.97 (s, 3H), 1.78-1.70 (m, 2H), 1.29-1.15 (m, 3H), 1.50-1.10 (m, 2H).

LCMS m/z: 327.3 [M^++1]

Synthesis of (2R, 3S)-4-amino-3-(2-(5-(1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-4-oxobutan-2-yl acetate (Compound B)

[00118] To a stirring solution of **Int-H2** (4.0 g, 18.43mmol) in CH_2Cl_2 (20 mL), DMF (0.1 mL) was added oxalyl chloride (3.34 mL, 36.86mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride. To a stirred solution of acid chloride in DCM (40 mL) was added d **7** (3.8 g, 11.65 mmol), *N, N*-diisopropylethylamine (6.44 mL, 37.04 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 2 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (2x 30 mL). Combined organic extracts were washed by $NaHCO_3$ (2x25 mL). The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford **Compound B** (2.6 g, 42.5%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.87, 7.89 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H), 7.47 (d, J = 11.0 Hz, 2H), 7.38-7.31 (m, 2H), 7.17 (t, 3H), 5.63 (s, 2H), 5.20-5.16 (m, 1H), 4.43-4.41 (m,

1H), 4.24-4.14 (m, 1H), 4.02 (t, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.38-3.33 (m, 1H), 2.20-2.14 (m, 2H), 1.97 (s, 3H), 1.92-1.80 (m, 5H), 1.16 (t, J = 7.5 Hz, 3H)

LCMS m/z: 526.6 [M^++1]; HPLC: 51.34% & 46.08% (enantiomers)

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00119] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified using 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as light yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H).

LCMS m/z: 250.4 [M^++1]

Synthesis of (S)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00120] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of (2*S*, 3*R*)-2-(((benzyloxy) carbonyl) amino)-3-hydroxybutanoic acid (Int-C)

[00121] To a stirring solution of $NaHCO_3$ (529 g, 6.30 mol) in water (1 L) was added L-threonine (**SM-2**) (250 g, 2.10 mol) at RT and stirred for 30 min. The reaction mixture was cooled to 0 °C. Cbz-Cl (850 mL, 2.52 mol, 50% in $PhCH_3$) was added drop wise and stirred for 1 h. The reaction mixture was warmed to RT and again stirred for 28 h. To this MTBE (1L) was added and stirred for 20 min. Separated aqueous layer in toluene was stirred for 20 min. Aqueous layer was acidified with 1N HCl (pH~1-2) and extracted with EtOAc (3x 1.5 L). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was stirred with dicyclohexylamine (819 mL, 4.20mol) for 4 h to get white solid, filtered and dried. Obtained solid was refluxed with EtOAc (1.5 L)

for 1h and then filtered. The solid material was dissolved in water (1 L) and acidified with dil.H_2SO_4 and again stirred for 30 min. The aqueous layer was extracted with EtOAc (3x 1 L). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was triturated with *n*-hexane to afford **Int-C** (230 g, 43%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.55 (br m, 1H), 7.37-7.30 (m, 5H), 6.94 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H), 4.08-3.94 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H)

ELSD purity: 84.66%

Synthesis of benzyl ((2S, 3R)-1-amino-3-hydroxy-1-oxobutan-2-yl) carbamate (Int-D)

[00122] To a solution of **Int-C** (25 g, 98.8 mmol) in DCM (250 mL) was added ammonium chloride (7.86 g, 147 mmol), HATU (45 g, 118 mmol), *N, N*-diisopropylethyl amine (45.5 mL, 261 mmol) and stirred at RT for 16 h. After completion of starting material (by TLC), the organic layer was washed by saturated sodium bicarbonate solution (1x150 mL) followed by 2N HCl (1x100 mL). After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 2% MeOH/DCM to afford **Int-D** (16 g, 66%) as an off- white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.36-7.32 (m, 5H), 7.04 (s, 1H), 7.25 (s, 1H), 5.03 (s, 2H), 4.75 (d, J = 6.0 Hz, 1H), 3.95-3.92 (m, 1H), 3.86-3.83 (m, 1H), 1.27-1.23 (m, 1H), 1.04 (d, J = 6.5 Hz, 3H)

LCMS m/z: 253.3 [M^++1]

Synthesis of (2R, 3S)-4-amino-3-(((benzyloxy) carbonyl) amino)-4-oxobutan-2-yl acetate (Int-E)

[00123] To a stirring solution of **Int-D** (16 g, 63.4 mmol) in CH_2Cl_2 (250mL) were added Et_3N (10.5 mL, 76.0 mmol) and DMAP (773 mg, 6.34 mmol), Ac_2O (7.12 mL, 76.0 mmol) at 0 °C and stirred at RT for 2 h. After completion of starting material (by TLC), the organic layer was washed with water (1x150 mL) followed by brine (1x100 mL) washing. After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 1% MeOH/DCM to afford **Int-E** (15 g, 80.3%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.45 (s, 1H), 7.35-7.30 (m, 5H), 7.24 (d, J = 9.2 Hz, 1H), 7.17 (s, 1H), 5.09-5.05 (m, 1H), 5.01 (s, 2H), 4.14-4.10 (m, 1H), 1.93 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H)

LCMS m/z: 295.1 [M^++1]

Synthesis of (2R, 3S)-3, 4-diamino-4-oxobutan-2-yl acetate (Int-F)

[00124] To a stirring solution of **Int-E** (15 g, 51 mmol) in methanol (500 mL) was added 50% wet 10% Pd/C (4 g) and stirred under H_2 atmosphere (balloon pressure) at RT for 4 h. The reaction mixture was filtered through a pad of celite and triturated with methanol (50 mL). The filtrate was concentrated under reduced pressure to afford **Int-F** (7.5 g, 91.9%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.59 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 4.78 (d, J = 5.2 Hz, 1H), 4.10 (m, 1H), 4.00-3.96 (m, 1H), 1.89 (s, 3H), 1.01 (d, J = 6.4 Hz, 3H).

LCMS m/z: 161.5 [M^++1]

Synthesis of (azidomethyl) benzene (SM-4)

[00125] To a stirring solution of benzyl bromide (30 g, 175mmol) in dimethyl formamide (300 mL) was added sodium azide (45.6 g, 701 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 70 °C for 16 h. After completion of reaction (monitored by TLC), the reaction mixture was allowed to RT; the volatiles were diluted with water (300 mL) and ether (200 mL). The separated organic layer was washed by (3x200 mL) of chilled water. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **SM-4** (18 g, crude) as an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 4.32 (s, 2H).

Synthesis of ethyl 1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (Int-G1 & Int-G2)

[00126] To a stirring solution of **SM-3** (8.0 g, 71.3 mmol) in toluene (80 mL) was added **SM4** (12.0 g, 107 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 16 h. The reaction mixture was allowed to RT; the volatiles were evaporated under reduced pressure to which, crude residue was purified by column chromatography by eluting 40% EtOAc/hexane to afford two isomers **Int-G1** (8 g) & **Int-G2** (8.2 g).

^{1}H-NMR(Int-G1): (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 5H), 5.86 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H)

LCMS m/z: 246.3 [M^++1].

^{1}H-NMR(Int-G2): (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 3H), 7.16 (t, *J* = 6.0 Hz, 2H), 5.53 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H)

LCMS m/z: 246.3 [M^++1]

Synthesis of 1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (Int-H2)

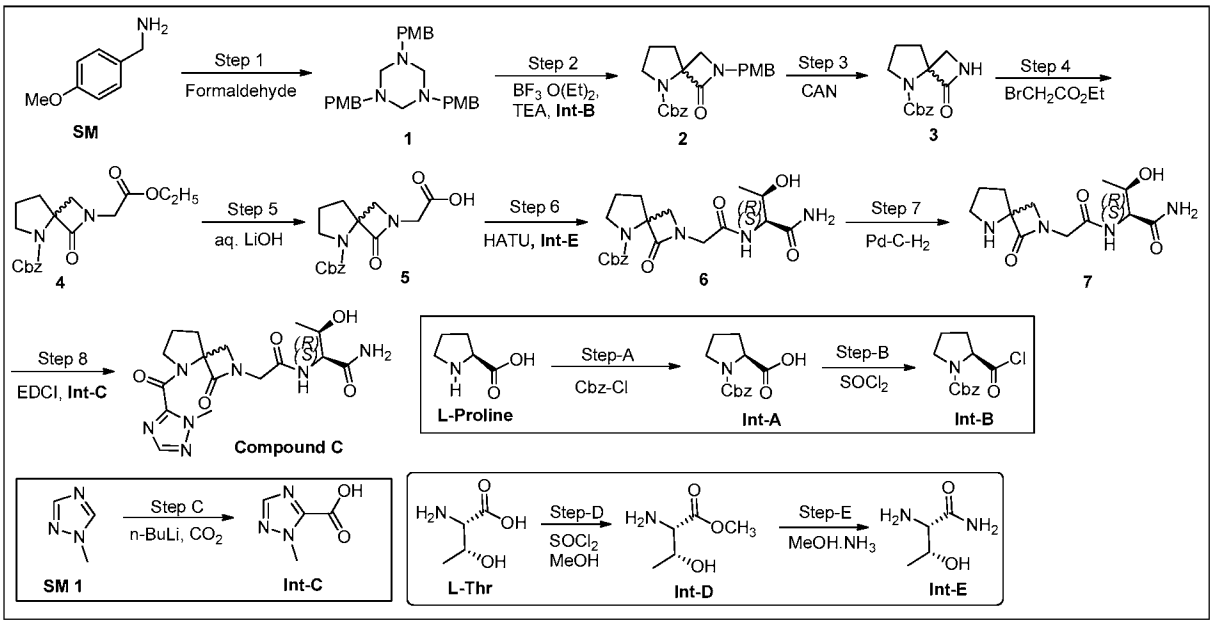
[00127] To a stirring solution of compound **Int-G2** (8.2 g, 33.4 mmol) in THF/H_2O (82 mL/82 mL, 1:1) was added LiOH.H_2O (4.2 g, 0.40mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2N HCl and the precipitated solid was filtered and washed with water (25 mL), dried under reduced pressure to afford compound **Int-H2** (7.0 g, 97.2%) as an off-white solid.

^{1}H-NMR(H_2): (400 MHz, DMSO-d_6): δ 13.01 (br s, 1H), 7.40-7.32 (m, 5H), 5.63 (s, 2H), 2.45 (s, 3H).

LCMS m/z: 218.3[M^++1].

Example 3 - Synthesis of Compound C

Scheme 3.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00128] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (as determined by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was finally washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, 6H), 6.84 (d, 6H), 3.73 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (Int-B)

[00129] To a stirring solution of **Int-A** (100 g, 0.40 mol) in CH_2Cl_2 (500 mL) was added catalytic amount of DMF (1 mL) and the reaction mixture was cooled to 0°C. To this oxalyl chloride (112.3 mL, 0.60 mol) was added drop wise and the reaction mixture was stirred at room temperature for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-B** (100 g) as crude. This material was directly used for the next step without further purification.

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2,5-diazaspiro [3.4] octane-5-carboxylate (2)

[00130] To a stirring solution of **Int-B** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) was cooled to -40 °C and added Et_3N (210.2 mL, 1.50 mol) drop wise. The reaction mixture was stirred at -40 °C for 45 min. To this, a mixture of compound **1** (50 g, 0.12 mol) in CH_2Cl_2 (150 mL) and $BF_3.OEt_2$ (47.6 g, 0.33 mol) was added drop wise at -40°C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. The obtained crystals were filtered and washed with cold EtOAc and dried under reduced pressure to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.35 (d, 5H), 7.20 (d, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 5.15-5.10 (m, 2H), 4.29 (d, 1H), 3.79 (d, 3H), 3.59 (d, 1H), 3.57-3.49 (m, 2H), 3.10 (dd, 1H), 2.41-2.30 (m, 1H), 2.09-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.37 (t, 1H).

LCMS (m/z): 381 [M^++1]

Synthesis of Benzyl 1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (3)

[00131] A stirring solution of **2** (60 g, 0.16 mol) in MeCN (200 mL) and H_2O (30 mL) was cooled to 0°C and added a solution of CAN (86.5 g, 0.16 mol) in H_2O (30 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. The obtained material was purified by silica gel column chromatography eluting with 70% EtOAc/n-hexane; finally obtained material was triturated with 10% EtOAc/n-hexane to afford **3** (15 g, 36.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 1H), 7.42-7.30 (m, 5H), 5.19-5.00 (m, 2H), 3.55 (d, 1H), 3.50-3.32 (m, 2H), 3.19 (dd, 1H), 2.18-2.00 (m, 2H), 1.91-1.79 (m, 2H)

LCMS (m/z): 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (4)

[00132] To a stirred solution of **3** (5 g, 19.23 mmol) in acetonitrile (100 mL) was added Cs_2CO_3 (8.1 g, 24.99 mmol) and ethyl 2-bromoacetate (3.2 mL, 28.84 mmol) at RT and stirring was continued for 10 h at RT. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 50 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 20% EtOAc/n-hexane to afford **4** (4.4 g, 66%) as syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.38 (d, 5H), 5.19-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.47-2.39 (m, 1H), 2.25-2.21 (m, 1H), 2.05-2.01 (m, 1H), 1.95-1.92 (m, 1H), 1.30-1.25 (m, 3H).

LCMS (m/z): 345 [M^++1]

Synthesis of 2-(5-((Benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00133] To a stirred solution of **4** (0.2 g, 0.63 mmol) in THF: H_2O (6 mL, 5:1) was added LiOH.H_2O (66 mg, 1.57 mmol) at RT and stirred for 2 h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~2 using 2N HCl and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (0.1 g).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.41 (d, 5H), 5.07-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.21-2.09 (m, 2H), 1.95-1.92 (m, 2H).

LCMS (m/z): 319.4 [M^++1]

Synthesis of (*2S,3R*)-methyl 2-amino-3-hydroxybutanoate (Int-D)

[00134] To a stirring solution of (*2S,3R*)-2-amino-3-hydroxybutanoic acid (200 g, 1.68 mol) in methanol (1.2 L) was added $SOCl_2$ (244 mL, 3.36 mol) drop wise at 0°C and stirred for 1 h. The resulting reaction mixture was refluxed for 24 h. After consumption of the starting material (by TLC), the reaction mixture was warmed to RT and concentrated under reduced pressure and washed with *n*-hexane (2x 50 mL). The residue was dissolved in EtOH (1 L) and neutralized with Et_3N (471 mL, 3.36 mol) and again stirred for 2 h. The precipitated solid was filtered off, and the obtained filtrate was concentrated under reduced pressure to afford **Int-D** (195 g, 80%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.51 (br s, 3H), 4.13-4.10 (m, 1H), 3.91 (br s, 1H), 1.20 (d, 3H).

LCMS (m/z): 134.1 [M^++1]

Synthesis of (*2S, 3R*)-2-amino-3-hydroxybutanamide (Int-E)

[00135] A solution of **Int-D** (190 g, 1.35 mol) in IPA (2 L) was taken in autoclave and purged NH_3 gas (7-8 kg) and stirred at 35°C for 24 h. Then removed NH_3 gas and reaction mixture was concentrated under reduced pressure and added CH_2Cl_2 and filtered. Obtained solid was refluxed in EtOH for 1 h at 78 °C. The reaction mass was filtered in heating condition and *n*-hexane was added to the filtrate and again stirred for another 4 h. The precipitated solid was filtered and dried under reduced pressure to afford **Int-E** (160 g, 47%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.38 (br s, 1H), 7.02 (br s, 1H), 4.66 (br s, 1H), 3.77-3.70 (m, 1H), 2.93 (d, 1H), 2.72 (br m, 1H), 1.05 (d, 3H).

LCMS (m/z): 119.1 [M^++1]

UPLC (ELSD purity): 99.9%

Synthesis of Benzyl 2-(2-(((*2S, 3R*)-1-amino-3-hydroxy-1-oxobutan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00136] To a stirring solution of **5** (1 g, 3.13 mmol) in CH_2Cl_2 (50 mL) was added HATU (1.4 g, 3.70 mmol) followed by DIPEA (1.5 mL, 7.82 mmol) and **Int-E** (443 mg, 3.76 mmol) at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water and extracted with CH_2Cl_2 (2x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure . The crude was purified by column chromatography to afford **6** (0.6 g, 46%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.82-7.65 (m, 1H), 7.41-7.38 (m, 5H), 7.27 (d, 1H), 7.12 (d, 1H), 5.10-5.01 (m, 2H), 4.89-4.85 (m, 1H), 4.25-3.99 (m, 3H), 3.94-3.90 (m, 1H), 3.74-3.69 (m, 1H), 3.52-3.45 (m, 2H), 2.22-2.09 (m, 2H), 1.92-1.79 (m, 2H), 1.27-1.25 (m, 1H), 1.09-1.01 (m, 3H).

LCMS (m/z): 419.3 [M^++1]

Synthesis of (*2S, 3R*)-3-hydroxy-2-(2-(1-oxo-2, 5-diazaspiro[3.4]octan-2-yl) acetamido) butanamide (7)

[00137] To a stirring solution of **6** (0.6 g, 1.43 mmol) in CH_3OH (20 mL) was added Pd/C (0.15 g) and stirred under H_2 atmosphere at RT for 6 h. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with MeOH. The obtained filtrate was concentrated under reduced pressure to afford **7** (0.3 g, 74%).

LCMS (m/z): 339.3 [M^++1]

Synthesis of 1-Methyl-1*H*-1,2,4-triazole-5-carboxylic acid (Int-C)

[00138] A solution of 1-methyl-1*H*-1,2,4-triazole **SM 1** (1 g, 12.0 mmol) in dry THF (10 mL) was cooled to -78°C under N_2 atmosphere and added *n*-BuLi (7.5 mL, 12.0 mmol) slowly. The reaction mixture was stirred for 1 h, the reaction mixture was quenched with dry ice and stirred for 30 min and then diluted with water and EtOAc (10 mL). The separated organic layer was concentrated under reduced pressure to afford **Int-C** (0.8 g, 53%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.80 (s, 1H), 4.09 (s, 4H).

LCMS (m/z): 128.1 [M^++1]

Synthesis of (*2S,3R*)-3-hydroxy-2-(2-(5-(1-methyl-1*H*-1,2,4-triazole-5-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl) acetamido) butanamide (Compound C)

[00139] To a stirring solution of **7** (0.25 g, 0.88 mmol) in CH_2Cl_2 (20 mL) was added HOBt (178 mg, 1.32 mmol), EDCI.HCl (0.2 g, 1.00 mmol) followed by DIPEA (0.4 mL, 2.20 mmol) and **Int-C** (134 mg, 1.05 mmol) 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 concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography followed by prep-HPLC purification to afford **Compound C** (0.07 g, 21%).

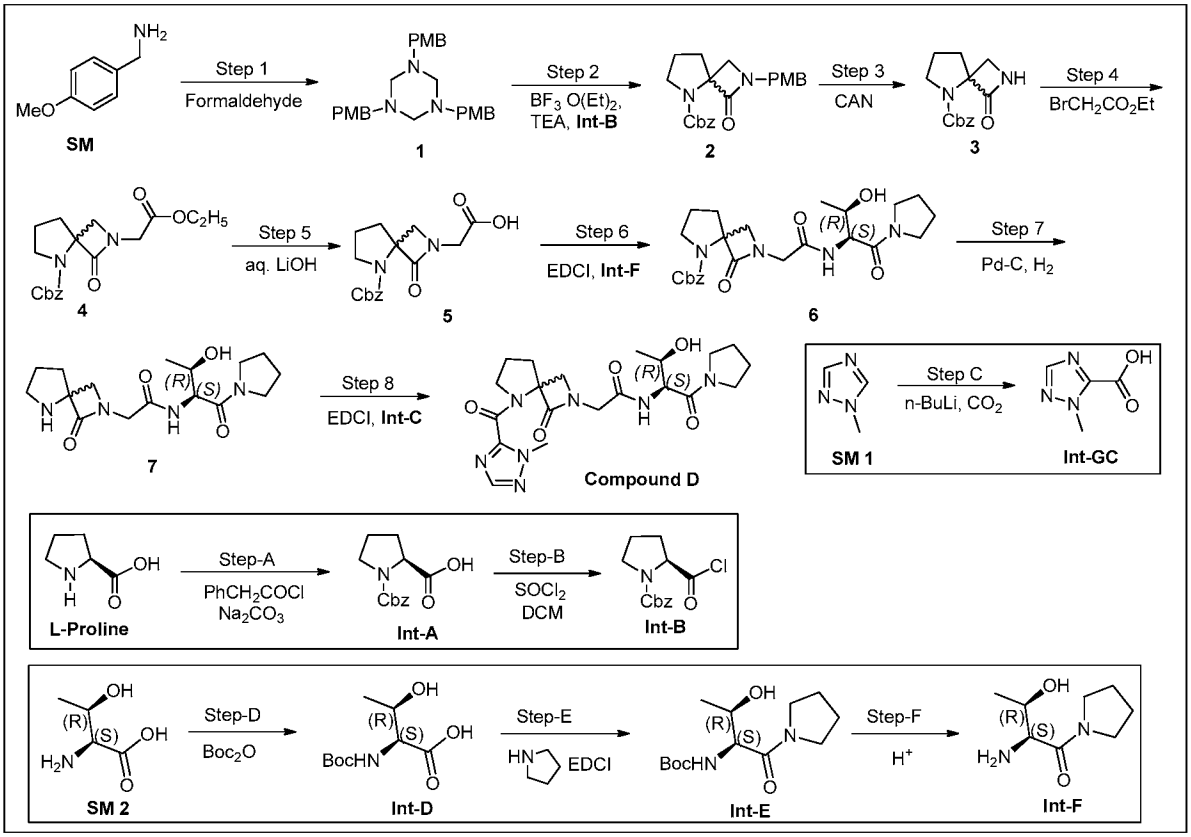
^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.89 (t, 1H), 7.25 (d, 1H), 7.12 (t, 1H), 4.93 (s, 1H), 4.19-4.15 (m, 2H), 4.03 (s, 3H), 3.96-3.91 (m, 4H), 3.44 (d, 1H), 2.25-2.20 (m, 3H), 1.97-1.91 (m, 2H), 1.07 (s, 3H).

LCMS (m/z): 394.2 [M^++1]

HPLC Purity: 93%

Example 4 -- Synthesis of Compound D

Scheme 4.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00140] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain a crude product, which was finally washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, 6H), 6.84 (d, 6H), 3.73 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (Int-B)

[00141] To a stirring solution of **Int-A** (100 g, 0.40 mol) in CH_2Cl_2 (500 mL) was added catalytic amount of DMF (1 mL) and the reaction mixture was cooled to 0°C. To this oxalyl

chloride (112.3 mL, 0.60 mol) was added drop wise and the reaction mixture was stirred at room temperature for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-B** (100 g). This material was used directly in the next step without further purification.

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00142] To a stirring solution of **Int-B** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) was cooled to -40°C and added Et_3N (210.2 mL, 1.50 mol) drop wise. The reaction mixture was stirred at -40°C for 45 min. A mixture of **1** (50 g, 0.12 mol) in CH_2Cl_2 (150 mL) and $BF_3.OEt_2$ (47.6 g, 0.33 mol) was added drop wise at -40°C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (as determined by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. The obtained crystals were filtered and washed with cold EtOAc and dried under reduced pressure to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.35 (d, 5H), 7.20 (d, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 5.15-5.10 (m, 2H), 4.29 (d, 1H), 3.79 (d, 3H), 3.59 (d, 1H), 3.57-3.49 (m, 2H), 3.10 (dd, 1H), 2.41-2.30 (m, 1H), 2.09-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.37 (t, 1H).

LCMS (m/z): 381 [M^++1]

Synthesis of Benzyl 1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (3)

[00143] A stirring solution of **2** (60 g, 0.16 mol) in MeCN (200 mL) and H_2O (30 mL) was cooled to 0°C and added a solution of CAN (86.5 g, 0.16 mol) in H_2O (30 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. The obtained material was purified by silica gel column chromatography eluting with 70% EtOAc/n-hexane. The purified material was triturated with 10% EtOAc/n-hexane to afford **3** (15 g, 36.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 1H), 7.42-7.30 (m, 5H), 5.19-5.00 (m, 2H), 3.55 (d, 1H), 3.50-3.32 (m, 2H), 3.19 (dd, 1H), 2.18-2.00 (m, 2H), 1.91-1.79 (m, 2H)

LCMS (m/z): 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (4)

[00144] To a stirred solution of **3** (5 g, 19.23 mmol) in acetonitrile (100 mL) was added Cs_2CO_3 (8.1 g, 24.99 mmol) and ethyl 2-bromoacetate (3.2 mL, 28.84 mmol) at RT and stirring was continued for 10 h at RT. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 50 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 20% EtOAc/n-hexane to afford **4** (4.4 g, 66%) in the form of a syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.38 (d, 5H), 5.19-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.47-2.39 (m, 1H), 2.25-2.21 (m, 1H), 2.05-2.01 (m, 1H), 1.95-1.92 (m, 1H), 1.30-1.25 (m, 3H).

LCMS (m/z): 345 [M^++1]

Synthesis of 2-(5-((Benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00145] To a stirred solution of **4** (0.2 g, 0.63 mmol) in THF: H_2O (6 mL, 5:1) was added LiOH.H_2O (66 mg, 1.57 mmol) at RT and stirred for 2 h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~2 using 2N HCl and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (0.1 g).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.41 (d, 5H), 5.07-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.21-2.09 (m, 2H), 1.95-1.92 (m, 2H).

LCMS (m/z): 319.4 [M^++1]

Synthesis of (*2S, 3R*)-2-((tert-butoxycarbonyl) amino)-3-hydroxybutanoic acid (Int-D)

[00146] To a stirring solution of (*2S, 3R*)-2-amino-3-hydroxybutanoic acid (**SM 2**) (10 g, 83.9 mmol) in 1,4-dioxane/water (100 mL, 1: 1)) was added $NaHCO_3$ (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_2Cl_2 (2 x 150 mL). The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-D** (15 g, crude). This material was directly used without further purification.

Synthesis of tert-butyl ((2S,3R)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)carbamate (Int-E)

[00147] To a stirring solution of **Int-D** (5 g, 22.8 mmol) in CH_2Cl_2 (50 mL) was added EDCI.HCl (5.2 g, 27.3 mmol), HOBt (4.6 g, 34.2 mmol) followed by DIPEA (10.5 mL, 57 mmol) and pyrrolidine (1.945 g, 27.3 mmol) under N_2 atmosphere 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 DCM and washed with water followed by saturated $NaHCO_3$ and citric acid. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography eluting with 2% MeOH/DCM to afford **Int-E** (3 g, 48%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 6.41 (d, 1H), 4.71 (d, 1H), 4.15 (t, 1H), 3.94 (q, 1H), 3.63-3.42 (m, 2H), 3.24 (q, 1H), 1.90-1.81 (m, 4H), 1.38 (s, 9H), 1.04 (s, 3H).

LCMS (m/z): 273.2 [M^++1]

Synthesis of (*2S,3R*)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (Int-F)

[00148] To a stirred solution of **Int-E** (3 g, 11.0 mmol) in DCM (10 mL) was added ether-HCl (20 mL) at 0°C under N_2 atmosphere. The reaction mixture was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure to get crude product, which was washed with ether to afford **Int-F** (2.0 g, 87%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.19 (br s, 3H), 3.98-3.91 (m, 2H), 3.62-3.59 (m, 1H), 3.49-3.42 (m, 1H), 3.39-3.35 (m, 2H), 1.96-1.90 (m, 4H), 1.17 (d, 3H).

LCMS (m/z): 173.3 [M^++1]

Synthesis of Benzyl 2-(2-(((*2S, 3R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl) butan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00149] To a stirring solution of **5** (1 g, 3.14 mmol) in CH_2Cl_2 (50 mL) was added EDCI (719 mg, 3.76 mmol), HOBt (635 mg, 4.71 mmol) followed by DIPEA (2.8 mL, 15.7 mmol) and **C** (784 mg, 3.77 mmol) and at 0°C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water and

extracted with CH_2Cl_2 (2x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography to afford **6** (0.8 g, 54%).

LCMS (m/z): 473.4 [M^++1]

Synthesis of *N*-((2*S*, 3*R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl) butan-2-yl)-2-(1-oxo-2, 5-diazaspiro[3.4] octan-2-yl)acetamide (7)

[00150] To a stirring solution of **6** (0.8 g, 1.69 mmol) in CH_3OH (60 mL) was added Pd/C (0.4 g) under N_2 atmosphere. The reaction mixture was stirred at RT for 4 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with MeOH. Obtained filtrate was concentrated under reduced pressure to afford **7** (0.5 g) as crude. This material was directly used for the next step without further purification.

LCMS (m/z): 339.3 [M^++1]

Synthesis of 1-Methyl-1*H*-1,2,4-triazole-5-carboxylic acid (Int-C)

[00151] A solution of 1-methyl-1H-1,2,4-triazole **SM 1** (1 g, 12.0 mmol) in dry THF (10 mL) was cooled to -78°C and *n*-BuLi (7.5 mL, 12.0 mmol) was slowly added under N_2 atmosphere. The reaction mixture was stirred for 1 h, quenched with dry ice and stirred for 30 min and then diluted with water and EtOAc (10 mL). The separated organic layer was concentrated under reduced pressure to afford **Int-C** (0.8 g, 53%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.80 (s, 1H), 4.09 (s, 3H).

LCMS (m/z): 128.1 [M^++1]

Synthesis of *N*-((2*S*, 3*R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl) butan-2-yl)-2-(5-(1-methyl-1*H*-1, 2, 4-triazole-5-carbonyl)-1-oxo-2, 5-diazaspiro[3.4] octan-2-yl) acetamide (Compound D)

[00152] To a stirring solution of **7** (0.315 g, 2.48 mmol) in CH_2Cl_2 (60 mL) was added EDCI.HCl (336 mg, 1.76 mmol), HOBt (297 mg, 2.20 mmol), DIPEA (0.67 mL, 3.67 mmol) and **Int-C** (0.5 g, 1.47 mmol) 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 DCM and washed with water. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. This material was purified by

column chromatography followed by prep-HPLC purification to afford **Compound D** (80 mg, 12%).

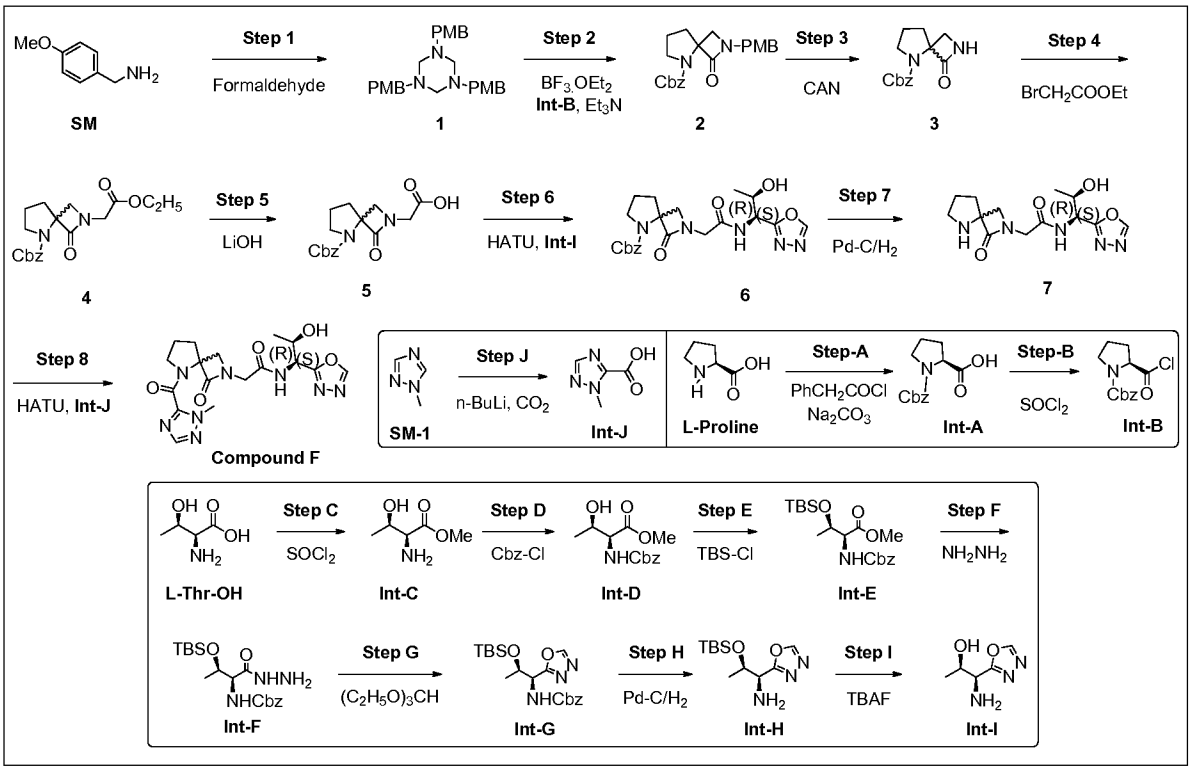
^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 4.55-4.51 (m, 1H), 4.08 (d, 2H), 3.97 (s, 2H), 3.87-3.84 (m, 3H), 3.70-3.55 (m, 2H), 3.45 (t, 1H), 3.35-3.31 (m, 2H), 2.75 (s, 3H), 2.27-2.24 (m, 2H), 1.98-1.92 (m, 4H), 1.85-1.84 (m, 2H), 1.19 (d, 3H).

LCMS (m/z): 448 [M^++1]

HPLC Purity: 94%

Example 5 – Synthesis of Compound F

Scheme 5.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00153] To a stirring solution of **SM** (200 g, 1.46 mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtained

crude; which was triturated with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, *J* = 8.0 Hz, 6H), 6.81 (d, *J* = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00154] To a stirring solution of **1** (45 g, 100 mmol) in CH_2Cl_2 (150 mL) was added $BF_3.OEt_2$ (37 mL, 301 mmol) drop wise at -40 °C. To above stirring solution **Int-B** (95 g, 342 mmol) in dry CH_2Cl_2 (500 mL) followed by Et_3N (210.2 mL, 1.50 mol) was added drop wise. The reaction mixture was stirred at -40 °C for 45 min. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution (1 x 150 mL) followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc (50 mL) and dried under vacuum to afford **2** (90g, 65%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): 7.36-7.30 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, *J* = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, *J* = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m, 2H), 1.20-1.15 (m, 2H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00155] To a stirring solution of **2** (46 g, 121 mmol) in MeCN (460 mL) and H_2O (200 mL) were cooled to 0 °C and added a solution of CAN (199 g, 0.23 mol) in H_2O (460 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water (100 mL) and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 x 150 mL) followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by silica gel column chromatography eluting with EtOAc to obtain **3** (12 g, 38%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, *J* = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00156] To a stirred solution of **3** (12 g, 46.1 mmol) in acetonitrile (120 mL) was added Cs_2CO_3 (37.6 g, 115.2 mmol) and ethyl 2-bromoacetate (7.7 mL, 69.2 mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/hexane to afford **4** (12.5 g, 78.6%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H)

LCMS m/z: 369.3 [M^++Na]

Synthesis of 2-(5-((benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00157] To a stirred solution of **4** (9.0 g, 26.0 mmol) in THF/ H_2O (80 mL/30 mL) were added LiOH.H_2O (2.73 g, 65.0 mmol) at RT and stirred for 3 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with EtOAc (2x50 mL). The separated aqueous layer was acidified to pH~3 using 2N HCl and extracted with EtOAc (3x50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (7.0 g, 85.3%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H)

Synthesis of benzyl 2-(2-(((1S, 2R)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00158] To a stirring solution of compound **5** (600 mg, 4.19 mmol) in DCM (20 mL) were added *N, N*-diisopropylethylamine (1.93 mL, 10.4 mmol), **Int-I** (1.60 g, 5.02 mmol), followed by HATU (1.91 g, 5.02 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 saturated $NaHCO_3$ solution (1x30 mL) followed by brine solution (1x20 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6** (600 mg, 33.3%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.21 (s, 1H), 7.35-7.32 (m, 5H), 5.13 (d, J = 4.5 Hz, 1H), 5.13 (s, 2H), 5.09-5.00 (m, 1H), 4.12-3.94 (m, 2H), 3.70-3.33 (m, 6H), 2.16-2.11 (m, 4H), 1.08 (d, J = 6.5 Hz, 3H)

LCMS m/z: 444.5 [M^++1]

Synthesis of *N*-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (7)

[00159] To a stirring solution of **6** (600 mg, 1.35 mmol) in MeOH (10 mL) were added (50% wet) 10% Pd/C (200 mg) and stirred under H_2 atmosphere (balloon pressure) for 3 h at RT. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc/MeOH (10 mL/10 mL). The filtrate was concentrated under reduced pressure to afford **7** (400 mg, crude) as yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.68 (s, 1H), 5.29-5.07 (m, 1H), 4.10-3.91 (m, 2H), 3.61 (d, J = 16.5 Hz, 1H), 3.40-3.31 (m, 1H), 3.16-2.93 (m, 2H), 2.02-1.91 (m, 2H), 1.80-1.76 (m, 2H), 1.32-1.28 (m, 1H), 1.24 (d, J = 6.5 Hz, 1H), 1.09 (d, J = 6.5 Hz, 3H)

LCMS m/z: 310.2 [M^++1];

Synthesis of *N*-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(5-(1-methyl-1H-1, 2, 4-triazole-5-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (Compound F)

[00160] To a stirring solution of **7** (300 mg, 0.97 mmol) in DCM (30 mL) were added *N, N*-diisopropylethyl amine (0.44 mL, 2.42 mmol), Int-J (147 mg, 1.16 mmol), followed by HATU (442 mg, 1.10 mmol) 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 give crude product, which was purified by column chromatography by 4% MeOH/DCM to

afford yellow syrup which was further purified by preparative HPLC to afford **Compound F** (80 mg, 19.7%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.52 (t, J = 8.0 Hz, 1H), 8.08 (s, 1H), 5.19-5.16 (m, 1H), 4.04 (s, 2H), 4.02 (s, 3H), 3.94-3.84 (m, 5H), 3.44-3.41 (m, 1H), 2.27-2.21 (m, 2H), 1.93-1.85 (m, 2H), 1.10-1.08 (m, 3H)

LCMS m/z: 419 [M^++1]

HPLC: 96.64%

Synthesis of 1-methyl-1H-1, 2, 4-triazole-5-carboxylic acid (Int-J)

[00161] To a stirred solution of **SM-1** (2.0 g, 24.0 mmol) in THF (20 mL) was added n-butyl lithium (19 mL, 12.0 mmol) at -78 °C dropwise and stirred for 2 h. Then solid CO_2 (2 g) was added and stirred at -78 °C for 1 h. The reaction mass was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was quenched with water (3 mL) and the obtained solid was filtered. The solid was triturated with diethylether/n-pentane (10 mL/10 mL). The white color solid was dried under vaccum to afford **Int-J** (2.0 g, 65.7%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.70 (s, 1H), 4.01 (s, 3H)

LCMS m/z: 128.3 [M^++1]

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00162] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61 mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified with 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as pale yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00163] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of (2*S*, 3*R*)-methyl 2-amino-3-hydroxybutanoate (Int-C)

[00164] To a stirring solution of L-Thr-OH (60 g, 504 mmol) in CH_3OH (400 mL) was added thionyl chloride (70 mL, 972 mmol) at 0 °C and stirred at 75 °C for 6 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-C** (60 g, crude). This material was directly used for the next step without further purification.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.45 (s, 2H), 5.70 (s, 1H), 4.12-4.10 (m, 1H), 3.90 (s, 1H), 3.73 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H).

Synthesis of (2*S*, 3*R*)-methyl 2-(((benzyloxy) carbonyl) amino)-3-hydroxybutanoate (Int-D)

[00165] To a stirring solution of $NaHCO_3$ (89 g, 1.065 mol) in water/1, 4 dioxane (150 mL/450 mL) were added **Int-C** (60 g, 355 mmol) at RT and stirred for 30 min. The reaction mixture was cooled to 0 °C. Cbz-Cl (60.7 mL, 426 mmol) was added drop wise and stirred for 1 h. The reaction mixture was stirred to RT and stirred for 16 h. After completion of starting material (by TLC), the reaction mass was diluted with EtOAc (300 ml). The separated organic layer was washed with (2x200 mL) of saturated $NaHCO_3$ solution followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was triturated with *n*-hexane and diethylether (50mL/50 mL) to afford **Int-D** (60 g, 63.8%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.37-7.30 (m, 5H), 7.20 (d, J = 8.4 Hz, 1H), 5.06 (s, 2H), 4.78 (d, J = 6.8 Hz, 1H), 4.09-4.05 (m, 2H), 3.64 (s, 3H), 1.09 (d, J = 6.0 Hz, 3H)

LCMS m/z: 268.2[M^++1]

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

[00166] To a stirring solution of **Int-D** (40 g, 149 mmol) in DMF (300 mL) were added DIPEA (69 mL, 374 mmol) TBDMS-Cl (30.91 mL, 179 mmol) at 0 °C and stirred at RT for 16 h. After completion of starting material (by TLC), the reaction mass was diluted with ether (200 ml). The separated organic layer was washed with (2x200 mL) of saturated $NaHCO_3$ solution followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 10% EtOAc/hexane to afford **Int-E** (40 g, 70.1%) as colorless syrup.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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^++1]

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

[00167] A solution of **Int-E** (20 g, 52.4 mmol) in EtOH (200 mL) was added hydrazine hydrate (13.12 mL, 262 mmol), at RT and stirred at 90 °C for 16 h. After completion of starting material (by TLC), ethanol was evaporated under reduced pressure. The crude residue was diluted with water (100 mL) and diethyl ether (200 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 15% EtOAc/hexane to afford **Int-F** (4.0 g, 20%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 ((1S, 2R)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamate (Int-G)

[00168] A solution of **Int-F** (4 g, 10.4 mmol) in triethyl orthoformate (40 mL) was added *p*-TSA (catalytic, 40 mg) at RT and after stirred at 120 °C for 3 h. After completion of starting material (by TLC), triethylorthoformate was evaporated under reduced pressure. The crude residue was purified by column chromatography eluting 10% EtOAc/hexane to afford **Int-G** (2.8 g, 68%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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)

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

Synthesis of (1*S*, 2*R*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propan-1-amine (Int-H)

[00169] To a stirring solution of **Int-G** (2.8 g, 7.16 mmol) in methanol (30 mL) was added 50% wet 10% Pd/C (1.4 g) and stirred under H_2 atmosphere (balloon pressure) for 2 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (10 mL). The filtrate was concentrated under reduced pressure to afford **Int-H** (1.7g, 92%) as colorless syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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]

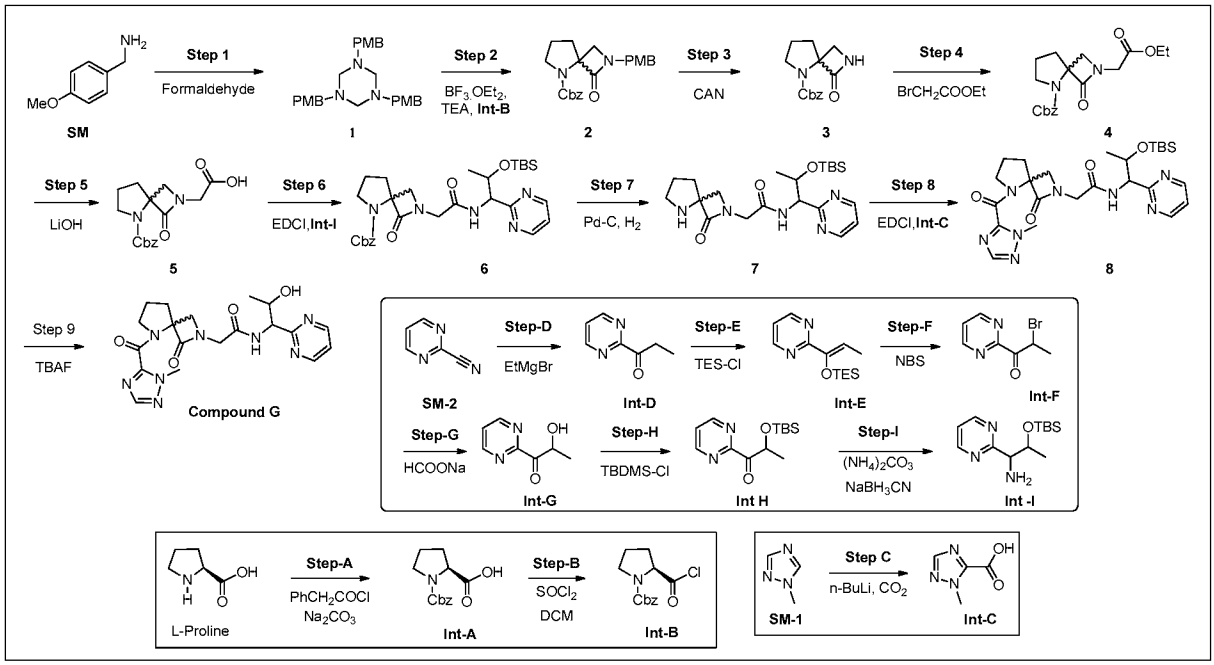
Synthesis of (1*S*, 2*R*)-1-amino-1-(1, 3, 4-oxadiazol-2-yl) propan-2-ol (Int-I)

[00170] To a stirring solution of **Int-H** (500 mg, 1.94 mmol) in THF (6 mL) was added TBAF (1.01 mL) slowly at 0° C and stirred at RT for 3 h. After completion of reaction (by TLC), the reaction mixture was evaporated and diluted with EtOAc/H_2O (10 mL/2 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-I** (120 mg, crude) as colorless thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.12 (s, 1H), 3.94 (d, J = 4.5 Hz, 1H), 3.85 (t, J = 5.5 Hz, 1H), 3.17-3.13 (m, 3H), 1.05 (d, J = 6.0 Hz, 3H).

Example 6 - Synthesis of Compound G

Scheme 7.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00171] To a stirring solution of **SM** (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtained crude; which was triturated with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00172] To a stirring solution of **1** (45 g, 100mmol) in CH_2Cl_2 (150 mL) was added $BF_3.OEt_2$ (37 mL, 301 mmol) drop wise at -40 °C. To above stirring solution **Int-B** (95 g, 342 mmol) in dry CH_2Cl_2 (500 mL) followed by Et_3N (210.2 mL, 1.50 mol) was drop wise. The reaction mixture was stirred at -40 °C for 45 min. The resulting reaction mixture was allowed to warm to RT and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution (1 x 150mL) followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc (50 mL) and dried under vacuum to afford **2** (90 g, 65%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): 7.36-7.30 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, J = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, J = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m, 2H), 1.20-1.15 (m, 2H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00173] To a stirring solution of **2** (46 g, 121 mmol) in MeCN (460 mL) and H_2O (200 mL) were cooled to 0 °C and added a solution of CAN (199 g, 0.23 mol) in H_2O (460 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water (100 mL) and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 x 150 mL) followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by silica gel column chromatography eluting with EtOAc to obtained **3** (12 g, 38%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, J = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, J = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00174] To a stirred solution of **3** (12 g, 46.1 mmol) in acetonitrile (120 mL) was added Cs_2CO_3 (37.6 g, 115.2 mmol) and ethyl 2-bromoacetate (7.7 mL, 69.2 mmol) at RT and stirred for 16 h at RT. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/hexane to afford **4** (12.5 g, 78.6%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H)

LCMS m/z: 369.3 [M^++Na]

Synthesis of 2-(5-((benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (5)

[00175] To a stirred solution of **4** (9.0 g, 26.0 mmol) in THF/ H_2O (80 mL/30 mL) were added LiOH.H_2O (2.73 g, 65.0 mmol) at RT and stirred for 3 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with EtOAc (2x50 mL). The separated aqueous layer was acidified to pH~3 using 2N HCl and extracted with EtOAc (3x50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (7.0 g, 85.3%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H)

Synthesis of benzyl 2-(2-((2-((*tert*-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00176] To a stirring solution of **5** (1.3 g, 4.08 mmol) in DCM (30 mL) were added *N, N*-diisopropylethylamine (2.1 mL, 12.2 mmol), **Int J** (1.09 g, 4.08 mmol), followed by HOBt (938 mg, 6.13 mmol), EDCI.HCl (1.1 g, 6.13 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 (30 mL). The separated organic layer was washed with brine solution (1 x 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude which was purified by column chromatography by eluting 4% MeOH/DCM to obtained **6** (1.5 g, 65%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.80-8.74 (m, 2H), 7.39-7.34 (m, 6H), 5.09 (s, 2H), 4.93 (t, J = 4.8 Hz, 1H), 4.38-4.19 (m, 1H), 4.05-3.68 (m, 2H), 3.49-3.39 (m, 4H), 2.20-2.11 (m, 2H), 1.86-1.85 (m, 2H), 1.19-1.10 (m, 4H), 0.65 (s, 9H), -0.07 (s, 3H), -0.03 (s, 3H)

LCMS m/z: 568 [M^++1]

Synthesis of *N*-(2-((*tert*-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)-2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (7)

[00177] To a stirring solution of **6** (500 mg, 0.88mmol) in EtOAc (25 mL) was added (50% wet) 10% Pd/C (250 mg) and stirred under H_2 atmosphere (balloon pressure) at RT for 7 h. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford **7** (320 mg, crude) as yellow thick syrup. This compound was used directly for next step without any purification.

LCMS m/z: 434.5 [M^++1]

Synthesis of *N*-(2-((*tert*-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl)-2-(5-(1-methyl-1H-1, 2, 4-triazole-5-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (8)

[00178] To a stirring solution of **Int-C** (93 mg, 0.73 mmol) in DCM (20 mL) were added *N, N*-diisopropylethylamine (0.4 mL, 2.21 mmol), compound **7** (320 mg, 0.73 mmol), followed by EDCI.HCl (211 mg, 1.10 mmol), HOBt (170 mg, 1.10 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 4% MeOH/DCM to afford **8** (210 mg, crude) as yellow thick syrup. This compound was used directly for next step without any purification.

LCMS m/z: 543.5 [M^++1]

Synthesis of *N*-(2-hydroxy-1-(pyrimidin-2-yl) propyl)-2-(5-(1-methyl-1H-1, 2, 4-triazole-5-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (Compound G)

[00179] To a stirring solution of compound **8** (210 mg, 0.38 mmol) in THF (5 mL) was added TBAF in THF (0.77 ml, 0.76 mmol) at 0 °C and stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 4% MeOH/DCM followed by preparative TLC to afford **Compound G** (70 mg, 42%) as yellow thick syrup. ^{1}H-NMR: (400 MHz, CD_3OD): δ 8.75-8.70 (m, 2H), 7.95 (s, 1H), 7.36-7.30 (m,1H), 5.16-5.13 (m, 1H), 4.53 (s, 1H), 4.41-4.43 (m, 2H), 4.29-4.03 (m, 1H), 3.99 (s, 3H), 3.96-3.81 (m, 2H), 3.58-3.54 (m, 1H), 2.37-2.34 (m, 2H), 2.09-2.00 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H)

LCMS m/z: 429 [M^++1]

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00180] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified with 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as pale yellow syrup. ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H).

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00181] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of 1-(pyrimidin-2-yl) propan-1-one (Int-D)

[00182] To a stirring solution of **SM-2** (20 g, 190 mmol) in THF (200 mL) was added ethyl magnesium bromide (1M in THF, 227 mL, 228 mmol) at 0 °C for 1 h. 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 (2x100 mL). The extracted organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 20% EtOAc/hexane to afford **Int-D** (15 g, 57%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^++1]

Synthesis of (*Z*)-2-(1-((triethylsilyl) oxy) prop-1-en-1-yl) pyrimidine (Int-E)

[00183] To a stirring solution of **Int-D** (15 g, 110 mmol) in THF (100 mL) was added LiHMDS (1M in THF, 220 mL, 220 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 (50 mL) and EtOAc (150 mL). The separated organic layer was extracted with brine solution (2x100 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 5% EtOAc/hexane to afford **Int-E** (20 g, 74%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 (Int-F)

[00184] To a stirring solution of **Int-E** (20 g, 80 mmol) in THF/H_2O (160 mL/40 mL) were added N-bromosuccinimide (10.2 g, 88mmol) slowly at RT and stirred for 2 h. After completion of starting material (by TLC), the reaction mixture was diluted with H_2O and EtOAc (100 ml/150 mL). The separated organic layer was washed with brine solution (2x100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **Int-F** (15 g, 87%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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)

Synthesis of 2-hydroxy-1-(pyrimidin-2-yl) propan-1-one (Int-G)

[00185] To a stirring solution of **Int-F** (15 g, 69 mmol) in MeOH (240 mL) was added sodium formate (18.9 g, 279 mmol) and stirred the reaction mass at 70 °C for 8 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 5% MeOH/DCM to afford **Int-G** (5.5 g, 51%) as colorless liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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).

Synthesis of (2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propan-1-one (Int-H)

[00186] To a stirring solution of **Int-G** (5.5 g, 36 mmol) in DCM (150 mL) were added imidazole (4.9 g, 72 mmol), DMAP (880 mg, 0.72 mmol) at 0 °C and stirred for 10 min. After added TBDMS-Cl (8.1 g, 54 mmol) at 0 °C and stirred at RT for 6 h. After completion of starting material (by TLC), diluted the reaction mass with H_2O (50 ml). The separated organic layer was washed with brine solution (2x50mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **Int-H** (3 g, 31%) as an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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 (Int-I)

[00187] To a stirring solution of **Int-H** (3 g, 11.2 mmol) in MeOH (50 mL) were added sodium acetate (1.8 g, 22.5 mmol), ammonium carbonate (8.8 g, 56.3 mmol), AcOH (0.6 mL, 11.2 mmol) at RT and stirred at 70 °C for 2 h. The reaction mixture was cooled to RT and sodium cyanoborohydride (1.39 g, 22.5 mmol) was added and stirred at 70 °C for 6 h. After completion of starting material (by TLC), MeOH was evaporated and the crude residue was diluted with DCM/H_2O (50 ml/50 mL). The separated organic layer was washed with brine (2x50mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 5% MeOH/DCM to afford **Int-I** (2.4 g, 80%) as semi solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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).

Synthesis of 1-methyl-1H-1, 2, 4-triazole-5-carboxylic acid (C)

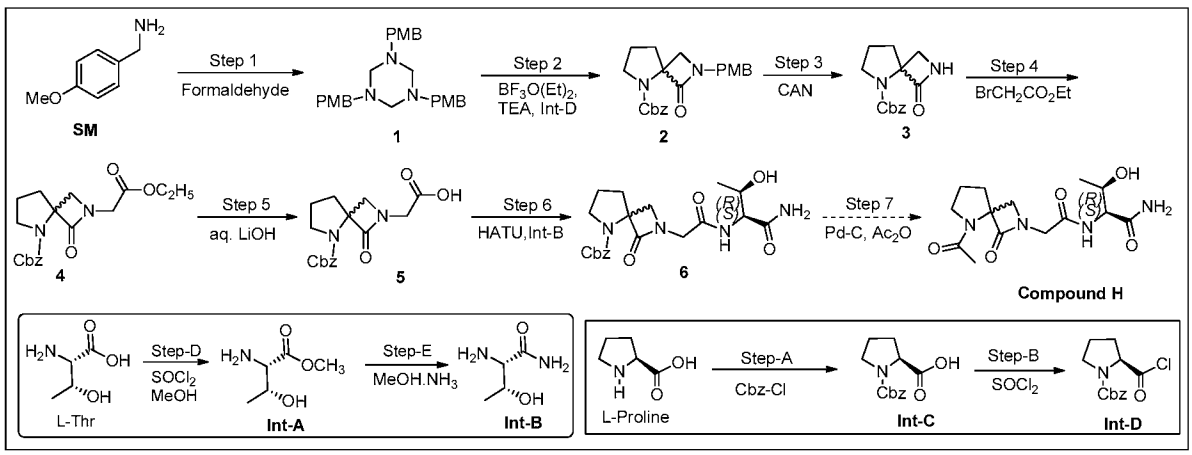
[00188] To a stirred solution of **SM-1** (2.0 g, 24.0 mmol) in THF (20 mL) was added n-butyl lithium (19 mL, 12.0 mmol) at -78 °C dropwise and stirred for 2 h and then quenched by addition of solid CO_2 (2 g) at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After consumption of the starting material (by TLC), the reaction mixture was treated with water (3 mL) and the obtained solid was filtered. The solid was triturated with diethylether/n-pentane (10 mL/10 mL), dried under vacuum to afford **Int-C** (2.0 g, 65.7%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.70 (s, 1H), 4.01 (s, 3H).

LCMS m/z: 128.3 [M^++1]

Example 7 – Synthesis of Compound H

Scheme 7.



Synthesis of 1,3,5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00189] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, 6H), 6.84 (d, 6H), 3.73 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00190] To a stirring solution of **Int-D** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) cooled to -40 °C was added Et_3N (210.2 mL, 1.50 mol) drop wise. The reaction mixture was stirred at -40 °C for 45 min. To this, a mixture of compound 1 (50 g, 0.12 mol) in CH_2Cl_2 (150 mL) and $BF_3.OEt_2$ (47.6 g, 0.33 mol) was added drop wise at -40 °C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic

layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.35 (d, 5H), 7.20 (d, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 5.15-5.10 (m, 2H), 4.29 (d, 1H), 3.79 (d, 3H), 3.59 (d, 1H), 3.57-3.49 (m, 2H), 3.10 (dd, 1H), 2.41-2.30 (m, 1H), 2.09-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.37 (t, 1H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00191] A stirring solution of **2** (60 g, 0.16 mol) in MeCN (200 mL) and H_2O (30 mL) was cooled to 0 °C and a solution of CAN (86.5 g, 0.48 mol) in H_2O (30 mL) was added. The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. Obtained material was purified by silica gel column chromatography eluting with 70% EtOAc/hexane; obtained material was triturated with 10% EtOAc/hexane to afford **3** (15 g, 36.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 1H), 7.42-7.30 (m, 5H), 5.19-5.00 (m, 2H), 3.55 (d, 1H), 3.50-3.32 (m, 2H), 3.19 (dd, 1H), 2.18-2.00 (m, 2H), 1.91-1.79 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00192] To a stirred solution of **3** (5 g, 19.23 mmol) in acetonitrile (100 mL) was added Cs_2CO_3 (15.6 g, 48 mmol) and ethyl 2-bromoacetate (3.2 mL, 28.84 mmol) at RT and stirring was continued at RT for 10 h. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 50 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexane to afford **4** (3.7 g, 56%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.38 (d, 5H, 5.19-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.47-2.39 (m, 1H), 2.25-2.21 (m, 1H), 2.05-2.01 (m, 1H), 1.95-1.92 (m, 1H), 1.30-1.25 (m, 3H)

LCMS (m/z): 345 [M^++1].

Synthesis of 2-(5-((benzyloxy)carbonyl)-1-oxo-2,5-diazaspiro [3.4] octan-2-yl)acetic acid (5)

[00193] To a stirred solution of **4** (2 g, 5.783 mmol) in THF: H_2O (24 mL, 5:1) was added LiOH.H_2O (606 mg, 14.4 mmol) at RT and stirred for 4h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~3-4 using citric acid and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (1.5 g, 83%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.41 (d, 5H), 5.07-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.21-2.09 (m, 2H), 1.95-1.92 (m, 2H)

LCMS (m/z): 319.4 [M^++1]

Synthesis of Benzyl 2-(2-(((2S, 3R)-1-amino-3-hydroxy-1-oxobutan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00194] To a stirring solution of **5** (1 g, 3.13 mmol) in CH_2Cl_2 (50 mL) was added HATU (1.4 g, 3.70 mmol) followed by DIPEA (1.5 mL, 7.82 mmol) and **Int-B** (443 mg, 3.76 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water and extracted with CH_2Cl_2 (2x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography to afford **6** (0.6 g, 46%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.82-7.65 (m, 1H), 7.41-7.38 (m, 5H), 7.27 (d, 1H), 7.12 (d, 1H), 5.10-5.01 (m, 2H), 4.89-4.85 (m, 1H), 4.25-3.99 (m, 3H), 3.94-3.90 (m, 1H), 3.74-3.69 (m, 1H), 3.52-3.45 (m, 2H), 2.22-2.09 (m, 2H), 1.92-1.79 (m, 2H), 1.27-1.25 (m, 1H), 1.09-1.01 (m, 3H)

LCMS m/z: 419.3 [M^++1]

Synthesis of (2S,3R)-2-(2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-3-hydroxy butanamide (Compound H)

[00195] To a stirring solution of 6 (1 g, 2.39 mmol) in EtOAc (50 mL) was added acetic anhydride (0.48 g, 4.78 mmol) followed by Pd/C (0.5 g) under N_2 atmosphere. The reaction

mixture was stirred at RT for 16 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with EtOAc (20 mL). Obtained filtrate was concentrated under reduced pressure to afford crude compound was purified by column chromatography. The obtained mixture of compound was purified by chiral preparative HPLC to afford **Compound H** fraction-I (0.075 g), fraction-II (0.062 g) as off-white solids.

^{1}H-NMR (Fr-I): (400 MHz, DMSO-d_6): δ 7.87 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 4.84 (d, J = 7.2 Hz, 1H), 4.10-4.03 (m, 2H), 3.96 (s, 2H), 3.79 (d, J = 5.2 Hz, 1H), 3.61-3.56 (m, 1H), 3.51-3.45 (m, 2H), 2.19-2.15 (m, 2H), 2.00 (s, 3H), 1.92-1.87 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H)

LCMS m/z: 327.3 [M^++1]

HPLC Purity Fr-I (91.20%),

^{1}H-NMR (Fr-II): (400 MHz, DMSO-d_6): δ 7.85 (d, J = 8.4 Hz, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.09-4.06 (m, 2H), 3.97 (s, 2H), 3.70 (d, J = 4.8 Hz, 1H), 3.60-3.55 (m, 1H), 3.51-3.45 (m, 2H), 2.18-2.13 (m, 2H), 1.99 (s, 3H), 1.92-1.85 (m, 2H), 1.05 (d, J = 6.4Hz, 3H)

LCMS m/z: 327.4 [M^++1]

HPLC Purity Fr-II (97.03%)

Synthesis of (2S,3R)-methyl 2-amino-3-hydroxybutanoate (Int-A)

[00196] To a stirring solution of (2S, 3R)-2-amino-3-hydroxybutanoic acid (200 g, 1.68 mol) in methanol (1.2 L) was added $SOCl_2$ (244 mL, 3.36 mol) drop wise at 0 °C and stirred for 1 h. The resulting reaction mixture was refluxed for 24 h. After consumption of the starting material (by TLC), the reaction mixture was warmed to RT and concentrated under vacuum and decanted with *n*-hexane (2x 50 mL). The residue was dissolved in EtOH (1 L) and neutralized with Et_3N (471 mL, 3.36 mol) and again stirred for 2 h. The precipitated solid was filtered off; obtained filtrate was concentrated under vacuum to afford **Int-A** (195 g, 80%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.51 (br s, 3H), 4.13-4.10 (m, 1H), 3.91 (br s, 1H), 1.20 (d, 3H)

LCMS m/z: 134.1 [M^++1]

Synthesis of (2S, 3R)-2-amino-3-hydroxybutanamide (Int-B)

[00197] A solution of Int-A (190 g, 1.35 mol) in IPA (2 L) was taken in autoclave and purged NH_3 gas (7-8 kg) and stirred at 35 °C for 24 h. After completion of the reaction, NH_3 was expelled and reaction mixture was concentrated under reduced pressure and added CH_2Cl_2 and filtered. Obtained solid was refluxed in EtOH for 1 h at 78 °C. The reaction mass was filtered in heating condition and *n*-hexane was added to the filtrate and again stirred for another 4 h. Obtained precipitated solid was filtered and dried under vacuum to afford **Int-B** (160 g, 47%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.38 (br s, 1H), 7.02 (br s, 1H), 4.66 (br s, 1H), 3.77-3.70 (m, 1H), 2.93 (d, 1H), 2.72 (br m, 1H), 1.05 (d, 3H)

LCMS m/z: 119.1 [M^++1]

UPLC (ELSD purity): 99.9%

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-C)

[00198] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61 mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified using 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-C** (450 g, 84%) as light yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

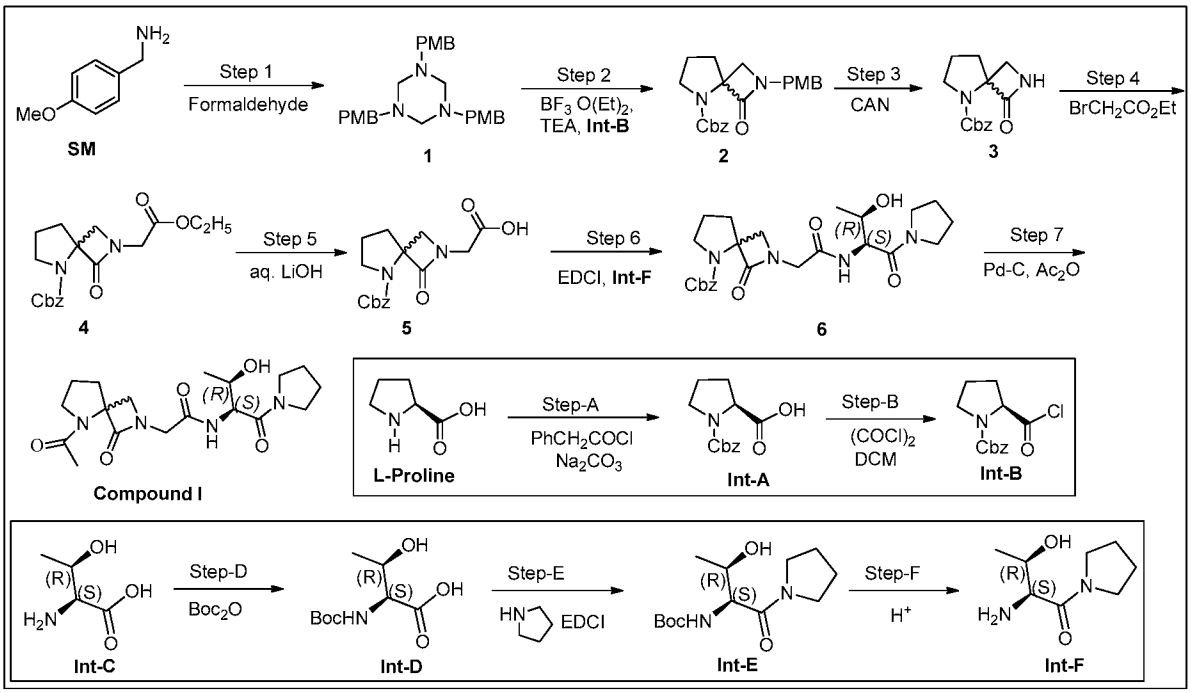
Benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (Int-D)

[00199] To a stirring solution of 1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (**Int-C**) (100 g, 0.40 mol) in CH_2Cl_2 (500 mL) was added catalytic amount of DMF (1 mL) and the reaction mixture was cooled to 0 °C. To this oxalyl chloride (112.3 mL, 0.60mol) was added drop wise and the reaction mixture was stirred at room temperature for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under

reduced pressure to afford **Int-D** (100 g) as crude. This material was directly used for the next step without further purification.

Example 8 – Synthesis of Compound I

Scheme 8.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00200] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was finally washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, 6H), 6.84 (d, 6H), 3.73 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00201] To a stirring solution of **Int-B** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) was cooled to -40 °C and Et_3N (210.2 mL, 1.50 mol) was added drop wise. The reaction mixture was stirred at -40 °C for 45 min. To this, a mixture of **1** (50 g, 0.12 mol) and BF_3OEt_2 (47.6 g, 0.33 mol) in CH_2Cl_2 (150 mL) was added drop wise at -40 °C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.35 (d, 5H), 7.20 (d, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 5.15-5.10 (m, 2H), 4.29 (d, 1H), 3.79 (d, 3H), 3.59 (d, 1H), 3.57-3.49 (m, 2H), 3.10 (dd, 1H), 2.41-2.30 (m, 1H), 2.09-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.37 (t, 1H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00202] To a stirring solution of **2** (60 g, 0.16 mol) in MeCN (200 mL) and H_2O (30 mL) was cooled to 0 °C and added a solution of CAN (86.5 g, 0.48 mol) in H_2O (30 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. Obtained material was purified by silica gel column chromatography eluting with 70% EtOAc/hexane; finally obtained material was triturated with 10% EtOAc/hexane to afford **3** (15 g, 36.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 1H), 7.42-7.30 (m, 5H), 5.19-5.00 (m, 2H), 3.55 (d, 1H), 3.50-3.32 (m, 2H), 3.19 (dd, 1H), 2.18-2.00 (m, 2H), 1.91-1.79 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00203] To a stirred solution of **3** (5 g, 19.23 mmol) in acetonitrile (100 mL) was added CS_2CO_3 (15.6 g, 48 mmol) and ethyl 2-bromoacetate (3.2 mL, 28.84 mmol) at RT and stirring was continued for 10 h at RT. The volatiles were evaporated under reduced pressure. The

residue was diluted with water and extracted with EtOAc (2 x 50 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 30% EtOAc/hexane to afford **4** (3.7 g, 56%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.38 (d, 5H), 5.19-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.47-2.39 (m, 1H), 2.25-2.21 (m, 1H), 2.05-2.01 (m, 1H), 1.95-1.92 (m, 1H), 1.30-1.25 (m, 3H)

LCMS (m/z): 345 [M^++1]

Synthesis of 2-(5-((benzyloxy)carbonyl)-1-oxo-2,5-diazaspiro [3.4] octan-2-yl)acetic acid (5)

[00204] To a stirred solution of **4** (2 g, 5.783 mmol) in THF: H_2O (24 mL, 5:1) was added LiOH.H_2O (606 mg, 14.4 mmol) at RT and stirred for 4 h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~3-4 using Citric acid and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **5** (1.5 g, 83%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.41 (d, 5H), 5.07-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.21-2.09 (m, 2H), 1.95-1.92 (m, 2H). LCMS (m/z):319.4 [M^++1]

Synthesis of Benzyl 2-(2-(((2S, 3R)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl) butan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6)

[00205] To a stirring solution of **5** (1 g, 3.14 mmol) in CH_2Cl_2 (50 mL) was added EDCI (719 mg, 3.76 mmol), DIPEA (2.8 mL, 15.7 mmol) followed by HOBt (635 mg, 3.76 mmol) and **Int-F** (784 mg, 3.77 mmol) and at 0 °C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water and extracted with CH_2Cl_2 (2x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography to afford **6** (0.8 g, 57%).

LCMS m/z: 473.4 [M^++1]

Synthesis of 2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)-N-((2S,3R)-3-hydroxy-1-oxo-1-pyrrolidin-1-yl)butan-2-yl)acetamide (Compound I)

[00206] To a stirring solution of **6** (0.3 g, 0.63 mmol) in EtOAc (50 mL) was added acetic anhydride (0.13 g, 1.27 mmol) followed by Pd/C (0.15 g) under N_2 atmosphere. The reaction mixture was stirred at RT for 16 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with EtOAc (10 mL). Obtained filtrate was concentrated under reduced pressure to afford crude compound was purified by column chromatography by eluting 2% MeOH:DCM to afford **Compound I** (0.09 g, 37%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.08 (t, J = 8.4 Hz, 1H), 4.83-4.75 (m, 1H), 4.44-4.38 (m, 1H), 3.93-3.83 (m, 3H), 3.72-3.67 (m, 1H), 3.64-3.61 (m, 4H), 3.60-3.58 (m, 1H), 3.57-3.46 (m, 2H), 2.13-2.10 (m, 2H), 2.09 (s, 3H), 2.07-1.97 (m, 4H), 1.91-1.87 (m, 2H), 1.04 (d, J = 10.8 Hz, 3H)

LCMS m/z: 381.3 [M^++1]

HPLC Purity: 46.41 & 47.86 (isomers).

Synthesis of (2S,3R)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoic acid (Int-D)

[00207] To a stirring solution of (2S,3R)-2-amino-3-hydroxybutanoic acid (**Int-C**) (10 g, 83.9 mmol) in 1,4-dioxane/water (100 mL, 1: 1)) was added $NaHCO_3$ (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_2Cl_2 (2 x 150 mL). The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **Int-D** (15 g, crude). This material was directly used for the next step without further purification.

Synthesis of tert-butyl ((2S,3R)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)carbamate (Int-E)

[00208] To a stirring solution of **Int-D** (5 g, 22.8 mmol) in CH_2Cl_2 (50 mL) was added, EDCI.HCl (5.2 g, 27.3 mmol) HOBt (4.6 g, 34.2 mmol), followed by DIPEA (10.5 mL, 57 mmol) and pyrrolidine (1.945 g, 27.3 mmol) under N_2 atmosphere 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 DCM and washed with water followed by saturated $NaHCO_3$ and citric acid. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography eluting with 2% MeOH/DCM to afford **Int-E** (3 g, 48%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 6.41 (d, 1H), 4.71 (d, 1H), 4.15 (t, 1H), 3.94 (q, 1H), 3.63-3.42 (m, 2H), 3.24 (q, 1H), 1.90-1.81 (m, 4H), 1.38 (s, 9H), 1.04 (s, 3H)

LCMS m/z: 273.2 [M^++1]

Synthesis of (2S,3R)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (Int-F):

[00209] To a stirring solution of **Int-E** (3 g, 11.0 mmol) in DCM (10 mL) was added ether-HCl (20 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure to get crude product, which was washed with ether to afford **Int-F** (2.0 g, 87%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.19 (br s, 3H), 3.98-3.91 (m, 2H), 3.62-3.59 (m, 1H), 3.49-3.42 (m, 1H), 3.39-3.35 (m, 2H), 1.96-1.90 (m, 4H), 1.17 (d, 3H)

LCMS m/z: 173.3 [M^++1]

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00210] To a stirring solution of L-Proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified using 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as light yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

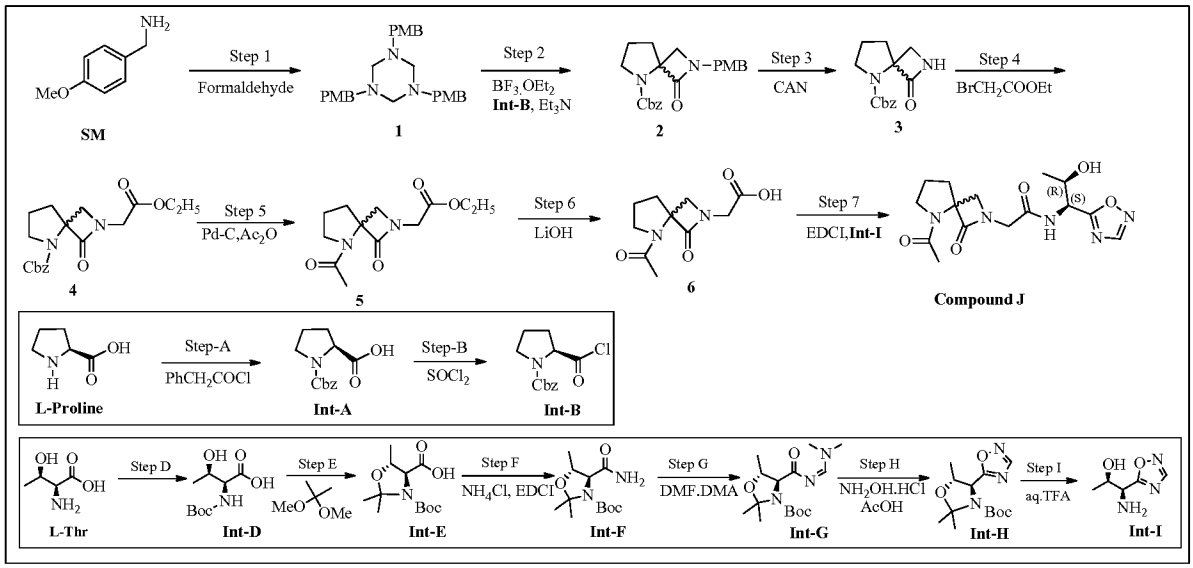
Synthesis of Benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (Int-B)

[00211] To a stirring solution of **Int-A** (100 g, 0.40 mol) in CH_2Cl_2 (500 mL) was added catalytic amount of DMF (1 mL) and the reaction mixture was cooled to 0 °C. To this oxalyl chloride (112.3 mL, 0.60 mol) was added drop wise and the reaction mixture was stirred at

room temperature for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-B** (100 g) as crude. This material was directly used for the next step without further purification.

Example 9 – Synthesis of Compound J

Scheme 9.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00212] To a stirring solution of (4-methoxyphenyl) methanamine (**SM**) (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid. ^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, 6H), 6.84 (d, 6H), 3.73 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H).

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00213] To a stirring solution of **Int-B** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) cooled to -40 °C was added Et_3N (210.2 mL, 1.50 mol) drop wise. The reaction mixture was stirred at -40 °C for 45 min. To this, a mixture of compound **1** (50 g, 0.12 mol) and BF_3.OEt_2 (47.6 g,

0.33 mol) in CH_2Cl_2 (150 mL) was added drop wise at -40 °C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.35 (d, 5H), 7.20 (d, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 5.15-5.10 (m, 2H), 4.29 (d, 1H), 3.79 (d, 3H), 3.59 (d, 1H), 3.57-3.49 (m, 2H), 3.10 (dd, 1H), 2.41-2.30 (m, 1H), 2.09-2.00 (m, 2H), 1.70-1.65 (m, 1H), 1.37 (t, 1H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00214] To a stirring solution of **2** (60 g, 0.16 mol) in MeCN (200 mL) and H_2O (30 mL) was cooled to 0 °C and added a solution of CAN (86.5 g, 0.48 mol) in H_2O (30 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. Obtained material was purified by silica gel column chromatography eluting with 70% EtOAc/hexane; obtained material was triturated with 10% EtOAc/hexane to afford **3** (15 g, 36.5%) as a liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 1H), 7.42-7.30 (m, 5H), 5.19-5.00 (m, 2H), 3.55 (d, 1H), 3.50-3.32 (m, 2H), 3.19 (dd, 1H), 2.18-2.00 (m, 2H), 1.91-1.79 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00215] To a stirred solution of **3** (5 g, 19.23 mmol) in acetonitrile (100 mL) was added Cs_2CO_3 (8.1 g, 24.99 mmol) and ethyl 2-bromoacetate (3.2 mL, 28.84 mmol) at RT and stirring was continued for 10 h at RT. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 50 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The obtained crude material was purified by silica gel column chromatography eluting with 20% EtOAc/hexane to afford **4** (4.4 g, 66%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.38 (d, 5H), 5.19-5.04 (m, 2H), 4.49-3.17 (m, 8H), 2.47-2.39 (m, 1H), 2.25-2.21 (m, 1H), 2.05-2.01 (m, 1H), 1.95-1.92 (m, 1H), 1.30-1.25 (m, 3H)

LCMS (m/z): 345 [M^++1]

Synthesis of Ethyl 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)acetate (5)

[00216] To a stirring solution of **4** (3.2 g, 9.24 mmol) in EtoAc (20 mL) was added acetic anhydride (1.8 g, 17.64 mmol) followed by Pd/C (1.2 g) under N_2 atmosphere. The reaction mixture was stirred at RT for 12 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with EtoAc (20 mL). Obtained filtrate was concentrated under reduced pressure to afford crude compound was purified by column chromatography by eluting EtOAc to **5** (2.0 g, 86%) as yellow liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 4.21 (s, 1H), 4.17-4.08 (m, 2H), 3.82 (s, 1H), 3.78 (s, 1H), 3.57-3.41 (m, 2H), 3.30-3.29 (m, 1H), 2.12-2.09 (m, 2H), 2.07 (s, 3H), 1.92-1.87 (m, 2H), 1.19 (t, J = 14.0 Hz, 3H)

LCMS m/z: 255.2 [M^++1]

Synthesis of 2-(5-Acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)acetic acid (6)

[00217] To a stirred solution of **5** (0.65 g, 2.55 mmol) in THF: H_2O (10 mL, 1:1) was added $LiOH.H_2O$ (0.268 g, 6.38 mmol) at RT and stirred for 5 h. After complete consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~2 using 2N HCl and extracted with EtOAc (2 x 20 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6** (0.58 g, 51%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.50 (br s, 1H), 4.12 (s, 1H), 3.72 (s, 1H), 3.65 (d, J = 4.8 Hz, 1H), 3.55-3.42 (m, 2H), 3.30 (d, J = 4.4 Hz, 1H), 2.11-2.08 (m, 2H), 1.99 (s, 3H), 1.89-1.86 (m, 2H)

LCMS m/z: 225.1[M^+-1]

Synthesis of 2-(5-Acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-N-((1S, 2R)-2-hydroxy-1-(1, 2, 4-oxadiazol-5-yl) propyl) acetamide (Compound J)

[00218] To a stirring solution of **6** (0.5 g, 2.21 mmol) in CH_2Cl_2 (20 mL) was added EDCI (0.63 g, 3.31 mmol), HOBt (0.44 g, 3.31 mmol) followed by DIPEA (1.4 g, 10.85 mmol) and Int-I (0.37 g, 2.65 mmol) at 0 °C. The reaction mixture was stirred at RT for 12 h. After consumption of the starting material (by TLC), the reaction was diluted with water and extracted with CH_2Cl_2 (2x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography by eluting 2% MeOH:DCM to afford **Compound J** (0.09 g, 12%) as yellow liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.61 (t, J = 8.4 Hz, 1H), 5.23-5.20 (m, 1H), 5.16-5.09 (m, 1H), 4.20-4.01 (m, 1H), 3.91-3.85 (m, 1H), 3.73-3.71 (m, 1H), 3.65 (s, 1H), 3.59-3.57 (m, 1H), 3.49-3.34 (m, 1H), 2.16-2.09 (m, 2H), 2.05 (s, 3H), 1.98-1.89 (m, 3H), 1.13-1.11 (m, 3H)

LCMS m/z: 352.2 [M^++1]

Synthesis of (S)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00219] To a stirring solution of (S)-pyrrolidine-2-carboxylic acid (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (444 g, 2.61 mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer acidified using 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L); Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **Int A** (450 g, 84%) as light yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.40-7.30 (m, 5H), 5.19-5.01 (m, 2H), 4.25 (dd, 1H), 3.51-3.50 (m, 2H), 2.29-2.15 (m, 1H), 1.89-1.80 (m, 3H)

LCMS m/z: 250 [M^++1]

Synthesis of (S)-benzyl 2-(chlorocarbonyl)pyrrolidine-1-carboxylate (Int-B)

[00220] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated

under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of 2-((*tert*-butoxycarbonyl) amino)-3-hydroxybutanoic acid (Int-D)

[00221] To a stirring solution of 2-amino-3-hydroxybutanoic acid (10 g, 83.9 mmol) in 1,4-dioxane/water (100 mL, 1: 1) was added $NaHCO_3$ (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_2Cl_2 (2 x 150 mL). The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **Int-D** (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 (Int-E)

[00222] To a stirring solution of **Int-D** (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_2 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 $NaHCO_3$ solution and washed with EtOAc. Aqueous layer was acidified using citric acid solution (pH~2) and extracted with CH_2Cl_2 (2x 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford **Int-E** (18 g, crude).

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 (Int-F)

[00223] To a stirring solution of **Int-E** (18 g, 69.4 mmol) in CH_2Cl_2 (180 mL) was added, EDCI.HCl (19.88 g, 0.104 mol) HOBt (14.16 g, 0.104 mol), followed by NH_4Cl (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, $NaHCO_3$ followed by brine. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude; which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford **Int-F** (13 g, 72.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^++1)-Boc]

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

[00224] A solution of **Int-F** (13 g, 50.3 mmol) in DMF.DMA (130 mL) was stirred at reflux temperature for 3 h under N_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-G** (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 (Int-H)

[00225] To a stirring solution of **Int-G** (15.7 g, 50.09 mmol) in ethanol (157 mL) was added hydroxylamine hydrochloride (6.96 g, 0.10 mol) under N_2 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 at RT, 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 **Int-H** (4.5 g, 32%).

^{1}H-NMR: (400 MHz, DMSO-d_6): 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]

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

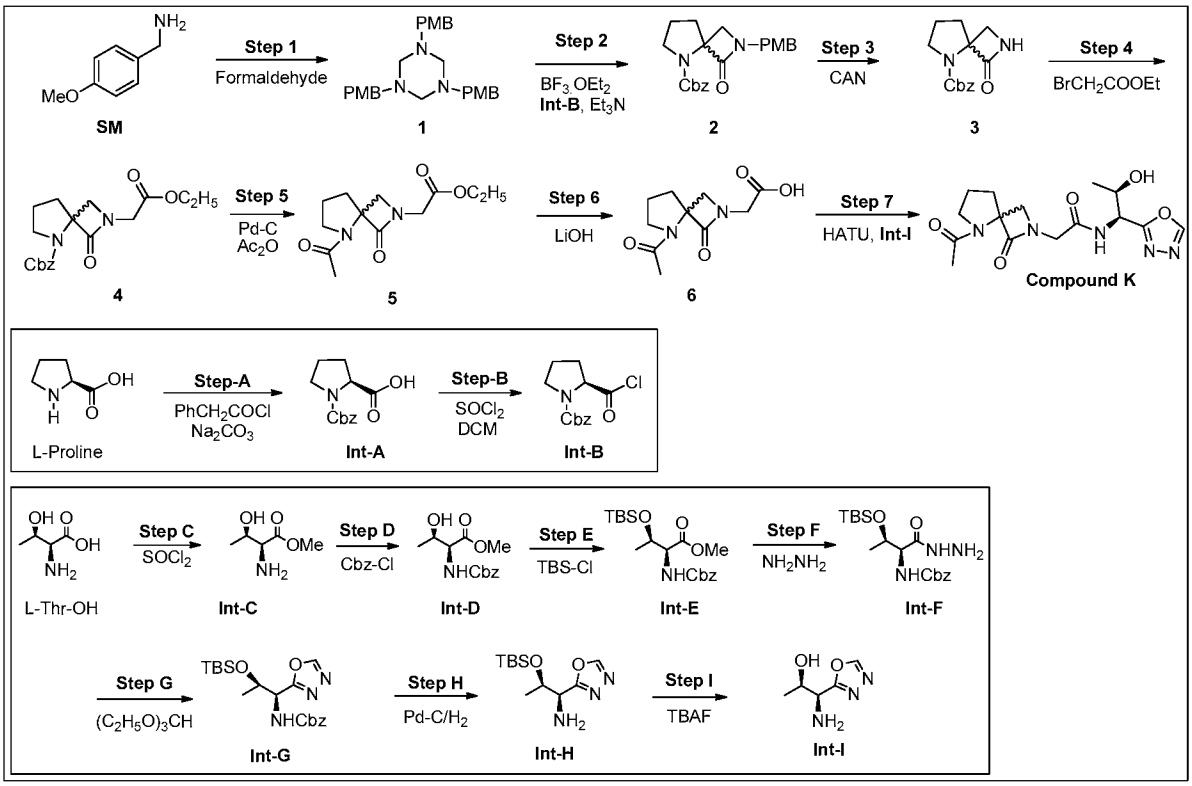
[00226] To a stirring solution of **Int-H** (5 g, 17.6 mmol) in water (25 mL) was added trifluoroacetic acid (25 mL). The reaction mixture was stirred at RT for 5 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under vacuum. The residue was dissolved in water and neutralized with aqueous $NaHCO_3$. The solvents from the reaction mixture was evaporated under vacuum and extracted with 5% $MeOH/CH_2Cl_2$ (4x 150 mL). The organic layer was concentrated under reduced pressure to afford **Int-I** (2.5 g, crude).

^{1}H-NMR: (400 MHz, D_2O): 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].

Example 10 – Synthesis of Compound K

Scheme 10.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00227] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200 g, 1.46mol) in EtOH (600 mL) at room temperature was added formaldehyde (33% aq, 105 mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H)

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00228] To a stirring solution of **1** (45 g, 100 mmol) in CH_2Cl_2 (150 mL) was added $BF_3.OEt_2$ (37 mL, 301 mmol) drop wise at -40 °C. To above stirring solution **Int-B** (95 g, 342

mmol) in dry CH_2Cl_2 (500 mL) followed by Et_3N (210.2 mL, 1.50 mol) was drop wise. The reaction mixture was stirred at -40 °C for 45 min. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (90g, 65%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): 7.36-7.30 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, J = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, J = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m,2H), 1.20-1.15 (m, 2H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00229] A stirring solution of **2** (46 g, 121 mmol) in MeCN (460 mL) and H_2O (200 mL) were cooled to 0 °C and added a solution of CAN (199 g, 0.23 mol) in H_2O (460 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water (100 mL) and the aqueous layer was extracted with EtOAc (2x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by silica gel column chromatography eluting with EtOAc to obtained **3** (12 g, 38%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, J = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, J = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00230] To a stirred solution of **3** (12 g, 46.1 mmol) in acetonitrile (120 mL) was added Cs_2CO_3 (37.6 g, 115.2 mmol) and ethyl 2-bromoacetate (7.7 mL, 69.2 mmol) at RT and stirred for 16 h at RT. After completion of reaction (by TLC), the volatiles were evaporated under

reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/hexane to afford **4** (12.5 g, 78.6%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, J = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, J = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H)

LCMS m/z: 369.3 [M^++Na]

Synthesis of ethyl 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetate (5)

[00231] To a stirring solution of **4** (12.5 g, 36 mmol) in EtOAc (100 mL) were added acetic anhydride (7.36 g, 72.2 mmol), 50% wet 10% Pd/C (5.0 g) and stirred under H_2 atmosphere (balloon pressure) for 4 h at RT. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to afford **5** (8.0 g, 87.9%) as yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 4.21 (s, 1H), 4.17 (s, 1H), 4.14-4.12 (m, 1H), 3.82 (s, 1H), 3.68 (d, J = 4.8 Hz, 1H), 3.56-3.51 (m, 1H), 3.46-3.43 (m, 1H), 3.29 (d, J = 4.8 Hz, 2H), 2.11-2.09 (m, 1H), 1.97 (s, 2H), 1.90-1.89 (m, 3H), 1.20 (t, J = 7.2 Hz, 3H).

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (6)

[00232] To a stirred solution of **5** (8.0 g, 31.49 mmol) in THF: H_2O (80 mL/30 mL) were added LiOH.H_2O (3.30 g, 78.7 mmol) at RT and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with ether (2x50 mL). The separated aqueous layer was acidified to pH~2 using 2N HCl and extracted with 5% MeOH/DCM (3x50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6** (6.5 g, 91.5%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 4.12 (s, 1H), 3.70 (s, 1H), 3.66-3.64 (m, 2H), 3.53-3.51 (m, 2H), 3.53-3.51 (m, 2H), 3.42 (d, J = 7.0 Hz, 1H), 2.73, 2.63 (dd, J = 16.0 Hz, J = 15 Hz, 2H), 2.10-2.07 (m, 1H)

LCMS m/z: 227.2 [M^++1]

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-N-((1S, 2R)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl) acetamide (Compound K)

[00233] To a stirring solution of **6** (200 mg, 1.39 mmol) in DCM (10 mL) were added *N, N*-diisopropylethylamine (0.64 mL, 3.47 mmol), Int-I (5.95 g, 1.68 mmol), followed by HATU (637 mg, 1.68 mmol) 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 give crude product, which was purified by column chromatography by 8% MeOH/DCM to afford yellow syrup which was further purified by preparative HPLC to afford **Compound K** (100 mg, 20.4%) as colorless liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 9.18 (d, J = 3.6 Hz, 1H), 8.54 (t, J = 7.6 Hz, 1H), 5.15-5.06 (m, 2H), 4.16-4.12 (m, 1H), 4.05, 4.00 (dd, J = 4.4 Hz, 4.4 Hz, 1H), 3.89-3.82 (m, 1H), 3.72 (t, J = 5.6 Hz, 1H), 3.61-3.56 (m, 1H), 3.51-3.45 (m, 1H), 3.37-3.33 (m, 1H), 2.18-2.08 (m, 2H), 2.02 (s, 3H), 1.93-1.90 (m, 2H), 1.10 (t, J = 6.4 Hz, 3H)

LCMS m/z: 352.3 [M^++1]

UPLC: 47.2% & 44.3%

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A)

[00234] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified with 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as pale yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00235] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B** as crude. This material was directly used for the next step without further purification.

Synthesis of (2*S*, 3*R*)-methyl 2-amino-3-hydroxybutanoate (Int-C)

[00236] To a stirring solution of L-Thr-OH (60 g, 504 mmol) in CH_3OH (400 mL) was added thionyl chloride (70 mL, 972 mmol) at 0 °C and stirred at 75 °C for 6 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **Int-C** (60 g, crude). This material was directly used for the next step without further purification.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.45 (s, 2H), 5.70 (s, 1H), 4.12-4.10 (m, 1H), 3.90 (s, 1H), 3.73 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H).

Synthesis of (2*S*, 3*R*)-methyl 2-(((benzyloxy) carbonyl) amino)-3-hydroxybutanoate (Int-D)

[00237] To a stirring solution of $NaHCO_3$ (89 g, 1.065 mol) in water/1,4-dioxane (150 mL/450 mL) were added **Int-C** (60 g, 355 mmol) at RT and stirred for 30 min. The reaction mixture was cooled to 0 °C. Cbz-Cl (60.7 mL, 426 mmol) was added drop wise and stirred for 1 h. The reaction mixture was stirred to RT and stirred for 16 h. After completion of starting material (by TLC), the reaction mass was diluted with EtOAc (300 ml). The separated organic layer was washed with (2x200 mL) of saturated $NaHCO_3$ solution followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was triturated with *n*-hexane and diethylether (50mL/50 mL) to afford **Int-D** (60 g, 63.8%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.37-7.30 (m, 5H), 7.20 (d, J = 8.4 Hz, 1H), 5.06 (s, 2H), 4.78 (d, J = 6.8 Hz, 1H), 4.09-4.05 (m, 2H), 3.64 (s, 3H), 1.09 (d, J = 6.0 Hz, 3H)

LCMS m/z: 268.2[M^++1]

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

[00238] To a stirring solution of **Int-D** (40 g, 149 mmol) in DMF (300 mL) were added DIPEA (69 mL, 374 mmol), TBDMS-Cl (30.91 mL, 179 mmol) at 0 °C and stirred at RT for 16 h. After completion of starting material (by TLC), the reaction mass was diluted with ether

(200 ml). The separated organic layer was washed with (2x200 mL) of saturated $NaHCO_3$ solution followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 10% EtOAc/hexane to afford **Int-E** (40 g, 70.1%) as colorless syrup.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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^++1].

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

[00239] A solution of **Int-E** (20 g, 52.4 mmol) in EtOH (200 mL) was added hydrazine hydrate (13.12 mL, 262 mmol), at RT and stirred at 90 °C for 16 h. After completion of starting material (by TLC), ethanol was evaporated under reduced pressure. The crude residue was diluted with water (100 mL) and diethyl ether (200 mL). After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 15% EtOAc/hexane to afford **Int-F** (4.0 g, 20%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 ((1S, 2R)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamate (Int-G)

[00240] A solution of **Int-F** (4 g, 10.4 mmol) in triethyl orthoformate (40 mL) was added *p*-TSA (catalytic, 40 mg) at RT and after stirred at 120 °C for 3 h. After completion of starting material (by TLC), triethylorthoformate was evaporated under reduced pressure. The crude residue was purified by column chromatography eluting 10% EtOAc/hexane to afford **Int-G** (2.8 g, 68%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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)

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

Synthesis of (1*S*, 2*R*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propan-1-amine (Int-H)

[00241] To a stirring solution of **Int-G** (2.8 g, 7.16 mmol) in methanol (30 mL) was added 50% wet 10% Pd/C (1.4 g) and stirred under H_2 atmosphere (balloon pressure) for 2 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (10 mL). The filtrate was concentrated under reduced pressure to afford **Int-H** (1.7g, 92%) as colorless syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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]

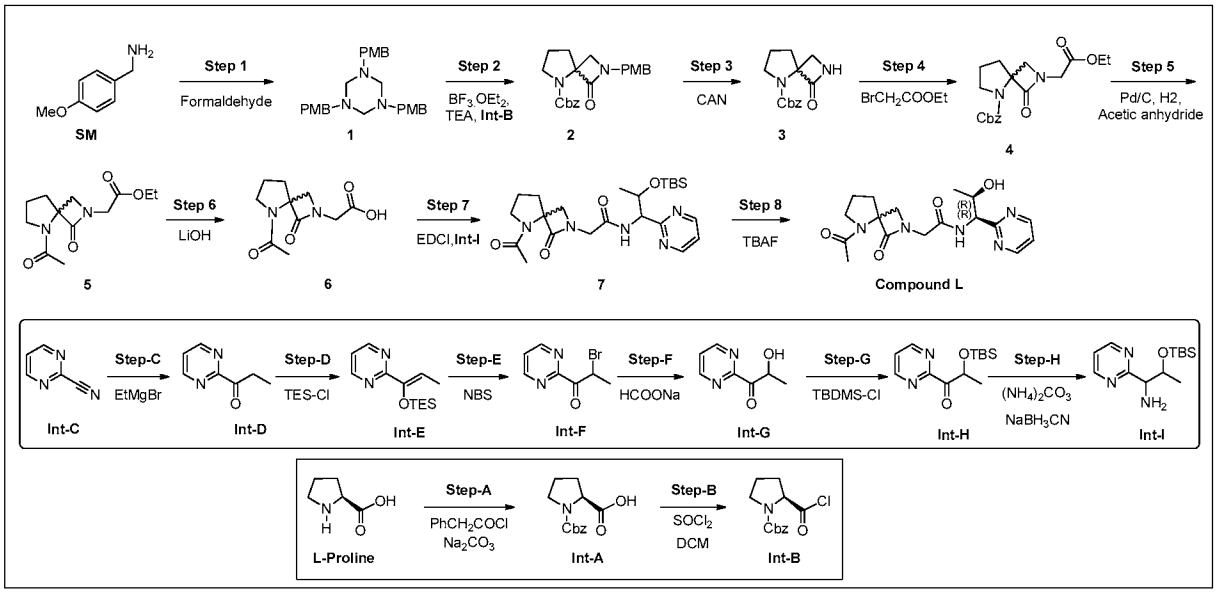
Synthesis of (1*S*, 2*R*)-1-amino-1-(1, 3, 4-oxadiazol-2-yl) propan-2-ol (Int-I)

[00242] To a stirring solution of **Int-H** (500 mg, 1.94 mmol) in THF (6 mL) was added TBAF (1.01 mL) slowly at 0° C and stirred at RT for 3 h. After completion of reaction (by TLC), the reaction mixture was evaporated and diluted with EtOAc/H_2O (10 mL/2 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-I** (120 mg, crude) as colorless thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.12 (s, 1H), 3.94 (d, J = 4.5 Hz, 1H), 3.85 (t, J = 5.5 Hz, 1H), 3.17-3.13 (m, 3H), 1.05 (d, J = 6.0 Hz, 3H).

Example 11 – Synthesis of Compound L

Scheme 11.



Synthesis of 1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (1)

[00243] To a stirring solution of (4-methoxyphenyl) methanamine **SM** (200g, 1.46mol) in EtOH (600mL) at room temperature was added formaldehyde (33% aq, 105mL) drop wise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was washed with *n*-hexane to afford **1** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H), 3.29 (s, 6H)

Synthesis of Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (2)

[00244] To a stirring solution of **1** (45 g, 100mmol) in CH_2Cl_2 (150 mL) was added $BF_3.OEt_2$ (37mL, 301mmol) drop wise at -40 °C. **Int-B** (95 g, 342 mmol) in dry CH_2Cl_2 (500 mL) was added, followed by Et_3N (210.2 mL, 1.50 mol) drop wise. The reaction mixture was stirred at -40 °C for 45 min. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved

in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **2** (90g, 65%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): 7.36-7.30 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13, 3.96 (dd, J = 15.5 Hz, 15.0 Hz, 1H), 3.73 (s, 3H), 3.11 (t, J = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m,2H), 1.20-1.15 (m, 2H)

LCMS m/z: 381 [M^++1]

Synthesis of Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (3)

[00245] To a stirring solution of **2** (46 g, 121 mmol) in MeCN (460 mL) and H_2O (200 mL) were cooled to 0 °C and added a solution of CAN (199 g, 0.23 mol) in H_2O (460 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water (100 mL) and the aqueous layer was extracted with EtOAc (2x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by silica gel column chromatography eluting with EtOAc to obtain **3** (12 g, 38%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, J = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17, 3.13 (dd, J = 5.0 Hz, 5.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H)

LCMS m/z: 261 [M^++1]

Synthesis of Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (4)

[00246] To a stirred solution of **3** (12 g, 46.1mmol) in acetonitrile (120 mL) was added CS_2CO_3 (37.6 g, 115.2 mmol) and ethyl 2-bromoacetate (7.7 mL, 69.2 mmol) at RT and stirred for 16 h at RT. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/hexane to afford **4** (12.5 g, 78.6%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H)

LCMS m/z: 369.3 [M^++Na].

Synthesis of ethyl 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetate (5)

[00247] To a stirring solution of **4** (12.5 g, 36 mmol) in EtOAc (100 mL) were added acetic anhydride (7.36 g, 72.2mmol), 50% wet 10% Pd/C (5.0g) and stirred under H_2 atmosphere (balloon pressure) for 4 h at RT. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to afford **5** (8.0 g, 87.9%) as yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 4.21 (s, 1H), 4.17 (s, 1H), 4.14-4.12 (m, 1H), 3.82 (s, 1H), 3.68 (d, *J* = 4.8 Hz, 1H), 3.56-3.51 (m, 1H), 3.46-3.43 (m, 1H), 3.29 (d, *J* = 4.8 Hz, 2H), 2.11-2.09 (m, 1H), 1.97 (s, 2H), 1.90-1.89 (m, 3H), 1.20 (t, *J* = 7.2 Hz, 3H)

LCMS m/z: 255 [M^+-1]

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (6)

[00248] To a stirred solution of **5** (8.0 g, 31.49 mmol) in THF: H_2O (80 mL/30 mL) were added LiOH.H_2O (3.30 g, 78.7 mmol) at RT and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with ether (2x50 mL). The separated aqueous layer was acidified to pH~2 using 2N HCl and extracted with 5% MeOH/DCM (3x50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6** (6.5 g, 91.5%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 4.12 (s, 1H), 3.70 (s, 1H), 3.66-3.64 (m, 2H), 3.53-3.51 (m, 2H), 3.53-3.51 (m, 2H), 3.42 (d, *J* = 7.0 Hz, 1H), 2.73, 2.63 (dd, *J* = 16.0 Hz, *J* = 15 Hz, 2H), 2.10-2.07 (m, 1H)

LCMS m/z: 227.2 [M^++1]

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-*N*-(2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) acetamide (7)

[00249] To a stirring solution of **6** (400 mg, 1.77 mmol) in DCM (20 mL) were added *N*, *N*-diisopropylethylamine (0.9 mL, 5.32mmol), **Int-I** (474 mg, 1.77mmol), HOBt (410 mg,

2.66mmol), EDCI.HCl (509 mg, 2.66mmol) 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 give crude product, which was purified by column chromatography by 4% MeOH/DCM to afford **7** (300 mg, 35%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.78 (d, J = 16.0 Hz, 2H), 8.35 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 16.0 Hz, 1H), 4.88 (t, J = 8.0 Hz, 1H), 4.37 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.85 (s, 2H), 3.76 (d, J = 10.0 Hz, 1H), 3.63-3.57 (m, 1H), 3.49-3.43 (m, 1H), 3.13 (d, J = 9.0 Hz, 1H), 2.13-2.10 (m, 2H), 2.01 (s, 3H), 1.16 (d, J = 5.5 Hz, 3H), 0.64 (s, 9H), 0.06 (s, 6H)

LCMS m/z: 474.6 [M^+-1]

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-*N*-((1*R*, 2*R*)-2-hydroxy-1-(pyrimidin-2-yl) propyl) acetamide (Compound L)

[00250] To a stirring solution of **7** (300 mg, 0.63 mmol) in THF (20 mL) was added TBAF (1.26 mL) slowly at 0° C and stirred at RT for 2 h. After completion of reaction (by TLC), the reaction mixture was evaporated to give crude product, which was purified by column chromatography eluting 4% MeOH/DCM to afford mixture (110 mg) of isomers again purified by chiral preparative HPLC method purification to afford **Compound L** (60 mg, 26%) as colorless liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.76 (t, J = 6.0 Hz, 2H), 8.28 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 4.8 Hz, 1H), 4.91-4.79 (m, 2H), 4.15-4.10 (m, 1H), 3.92-3.78 (m, 2H), 3.67 (d, J = 4.8 Hz, 1H), 3.60-3.54 (m, 1H), 3.49-3.31 (m, 2H), 2.13-2.11 (m, 2H), 2.09 (s, 3H), 2.08-1.87 (m, 2H), 1.09 (d, J = 6.4 Hz, 3H)

LCMS m/z: 362.4 [M^++1]

HPLC: 97.5%

Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (Int-A):

[00251] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified with 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts

were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Int-A** (450 g, 84%) as pale yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H)

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (Int-B)

[00252] To a stirring solution of **Int-A** (2.5 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (2.7 g, 0.02 mol) at 0 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford **Int-B**. This material was directly used for the next step without further purification.

Synthesis of 1-(pyrimidin-2-yl) propan-1-one (Int-D)

[00253] To a stirring solution of **Int-C** (20 g, 190mmol) in THF (200 mL) was added ethyl magnesium bromide (1M in THF, 227 mL, 228mmol) at 0 °C for 1 h. After completion of starting material (by TLC), the reaction mixture was diluted with saturated ammonium chloride solution and EtOAc (150mL). The separated organic layer was washed with brine solution (2x100 mL). The extracted organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 20% EtOAc/hexane to afford **Int-D** (15g, 57%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^++1]

Synthesis of (*Z*)-2-(1-((triethylsilyl) oxy) prop-1-en-1-yl) pyrimidine (Int-E)

[00254] To a stirring solution of **Int-D** (15 g, 110 mmol) in THF (100 mL) was added LiHMDS (1M in THF, 220 mL, 220mmol) slowly at 0 °C and stirred for 30 min. Then chloro triethylsilane (24.8 g, 165mmol) in THF (50 mL) was added 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 (50mL) and EtOAc (150mL). The separated organic layer was extracted with brine solution (2x100 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material

which was purified by column chromatography eluting 5% EtOAc/hexane to afford **Int-E** (20 g, 74%) as yellow thick syrup.

^{1}**H-NMR:** (400 MHz, DMSO-d_6): 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 (Int-F)

[00255] To a stirring solution of **Int-E** (20 g, 80 mmol) in THF/H_2O (160 mL/40 mL) were added N-bromosuccinimide (10.2 g, 88 mmol) slowly at RT and stirred for 2 h. After completion of starting material (by TLC), the reaction mixture was diluted with H_2O and EtOAc (100 ml/150 mL). The separated organic layer was extracted with brine solution (2x100 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **Int-F** (15 g, 87%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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).

Synthesis of 2-hydroxy-1-(pyrimidin-2-yl) propan-1-one (Int-G)

[00256] To a stirring solution of **Int-F** (15 g, 69mmol) in MeOH (240 mL) was added sodium formate (18.9 g, 279 mmol) and stirred the reaction mass at 70 °C for 8 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 5% MeOH/DCM to afford Int G (5.5 g, 51%) as colorless liquid.

^{1}**H-NMR:** (400 MHz, DMSO-d_6): 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)

Synthesis of (2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propan-1-one (Int-H)

[00257] To a stirring solution of **Int-G** (5.5 g, 36 mmol) in DCM (150 mL) were added imidazole (4.9 g, 72 mmol), DMAP (880 mg, 0.72 mmol) at 0 °C and stirred for 10 min. After added TBDMS-Cl (8.1 g, 54 mmol) at 0 °C and stirred at RT for 6 h. After completion of starting material (by TLC) reaction mixture was diluted with H_2O (50 ml). The separated organic layer was washed with brine solution (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **Int-H** (3g, 31%) as an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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)

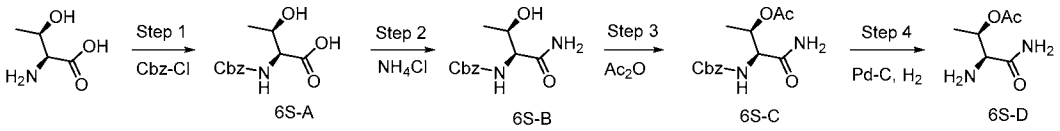
Synthesis of (2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propan-1-amine (Int-I)

[00258] To a stirring solution of **Int-H** (3 g, 11.2mmol) in MeOH (50mL) were added sodium acetate (1.8 g, 22.5mmol), ammonium carbonate (8.8 g, 56.3mmol), AcOH (0.6 mL, 11.2 mmol) at RT and then stirred the reaction mixture at 70 °C for 2 h. The temperature of the reaction was cooled to RT and sodium cyanoborohydride (1.39 g, 22.5 mmol) was added and stirred at 70 °C for 6 h. After completion of starting material (by TLC), MeOH was evaporated and the crude residue was diluted with DCM/H_2O (50 ml/50 mL). The separated organic layer was extracted with brine solution (2x50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 5% MeOH/DCM to afford **Int-I** (2.4 g, 80%) as semi solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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)

LCMS m/z: 268[M^++1]

Scheme 6S- I-1



Synthesis of (2*S*, 3*R*)-2-(((benzyloxy) carbonyl) amino)-3-hydroxybutanoic acid (6S-A):

[00259] To a stirring solution of $NaHCO_3$ (529 g, 6.30 mol) in water (1 L) was added L-threonine (250 g, 2.10 mol) at RT and stirred for 30 min. The reaction mixture was cooled to 0 °C. Cbz-Cl (850 mL, 2.52 mol, 50% of $PhCH_3$) was added drop wise and stirred for 1 h. The reaction mixture was warmed to RT and again stirred for 28 h. To this MTBE (1L) was added and stirred for 20 min. Separated aqueous layer in toluene was stirred for 20 min. Aqueous layer was acidified with 1N HCl (pH~1-2) and extracted with EtOAc (3x 1.5 L). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was stirred with dicyclohexylamine (819 mL,4.20 mol) for 4 h to get white solid, filtered and dried. Obtained solid was refluxed with EtOAc (1.5 L) for 1h and then filtered. The solid material was dissolved in water (1 L) and acidified with dil.H_2SO_4 and again stirred for 30 min. The aqueous layer was extracted with EtOAc (3x 1 L). The separated

organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was triturated with *n*-hexane to afford **6S-A** (230 g, 43%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.55 (br m, 1H), 7.37-7.30 (m, 5H), 6.94 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H), 4.08-3.94 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H).

ELSD purity: 84.66%

Synthesis of benzyl ((2S, 3R)-1-amino-3-hydroxy-1-oxobutan-2-yl) carbamate (6S-B):

[00260] A solution of **6S-A** (25 g, 98.8 mmol) in DCM (250 mL) was added ammonium chloride (7.86 g, 147 mmol), HATU (45 g, 118 mmol), *N, N*-diisopropylamene (45.5 mL, 261 mmol) and stirred at RT for 16 h. After completion of starting material (by TLC), the organic layer was washed by saturated sodium bicarbonate solution (1x150 mL) followed by 2N HCl (1x100 mL). After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 2% MeOH/DCM to afford **6S-B** (16 g, 66%) as an off- white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.36-7.32 (m, 5H), 7.04 (s, 1H), 7.25 (s, 1H), 5.03 (s, 2H), 4.75 (d, J = 6.0 Hz, 1H), 3.95-3.92 (m, 1H), 3.86-3.83 (m, 1H), 1.27-1.23 (m, 1H), 1.04 (d, J = 6.5 Hz, 3H).

LCMS m/z: 253.3[M^++1]

Synthesis of (2R, 3S)-4-amino-3-(((benzyloxy) carbonyl) amino)-4-oxobutan-2-yl acetate (6S-C):

[00261] To a stirring solution of **6S-B** (16 g, 63.4 mmol) in CH_2Cl_2 (250 mL) were added Et_3N (10.5 mL, 76.0 mmol) and DMAP (773 mg, 6.34 mmol), Ac_2O (7.12 mL, 76.0 mmol) at 0 °C and stirred at RT for 2 h. After completion of starting material (by TLC), the organic layer was washed with water (1x150 mL) followed by brine (1x100 mL) washing. After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 1% MeOH/DCM to afford **6S-C** (15 g, 80.3%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.45 (s, 1H), 7.35-7.30 (m, 5H), 7.24 (d, J = 9.2 Hz, 1H), 7.17 (s, 1H), 5.09-5.05 (m, 1H), 5.01 (s, 2H), 4.14-4.10 (m, 1H), 1.93 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H)

LCMS m/z: 295.1 [M^++1]

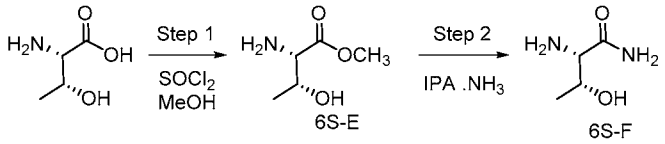
Synthesis of (2R, 3S)-3, 4-diamino-4-oxobutan-2-yl acetate (6S-D):

[00262] To a stirring solution of **6S-C** (15 g, 51 mmol) in methanol (500 mL) was added 50% wet 10% Pd/C (4 g) and stirred under H_2 atmosphere (balloon pressure) for 4 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (50 mL). The filtrate was concentrated under reduced pressure to afford **6S-D** (7.5 g, 91.9%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.59 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 4.78 (d, J = 5.2 Hz, 1H), 4.10 (m, 1H), 4.00-3.96 (m, 1H), 1.89 (s, 3H), 1.01 (d, J = 6.4 Hz, 3H)

LCMS m/z: 161.5 [M^++1]

Scheme 6S- I-2



Synthesis of (2S,3R)-methyl 2-amino-3-hydroxybutanoate (6S-E):

[00263] To a stirring solution of (2S, 3R)-2-amino-3-hydroxybutanoic acid (200 g, 1.68 mol) in methanol (1.2 L) was added $SOCl_2$ (244 mL, 3.36 mol) dropwise at 0 °C and stirred for 1 h. The resulting reaction mixture was refluxed for 24 h. After consumption of the starting material (by TLC), the reaction mixture was warmed to RT and concentrated under vacuum and decanted with *n*-hexane (2x 50 mL). The residue was dissolved in EtOH (1 L) and neutralized with Et_3N (471 mL, 3.36 mol) and again stirred for 2 h. The precipitated solid was filtered off; obtained filtrate was concentrated under vacuum to afford **6S-E** (195 g, 80%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.51 (br s, 3H), 4.13-4.10 (m, 1H), 3.91 (br s, 1H), 1.20 (d, 3H).

LCMS m/z: 134.1 [M^++1]

Synthesis of (2S, 3R)-2-amino-3-hydroxybutanamide (6S-F):

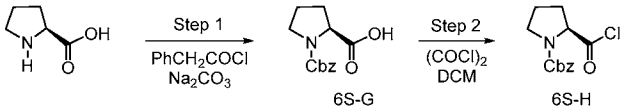
[00264] A solution of **6S-E** (190 g, 1.35 mol) in IPA (2 L) was taken in autoclave and purged NH_3 gas (7-8 kg) and stirred at 35 °C for 24 h. After completion of the reaction, $NH_3$was expelled and reaction mixture was concentrated under reduced pressure and added CH_2Cl_2 and filtered. Obtained solid was refluxed in EtOH for 1 h at 78 °C. The reaction mass was filtered in heating condition and *n*-hexane was added to the filtrate and again stirred for

another 4 h. Obtained precipitated solid was filtered and dried under vacuum to afford **6S-F** (160 g, 47%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.38 (br s, 1H), 7.02 (br s, 1H), 4.66 (br s, 1H), 3.77-3.70 (m, 1H), 2.93 (d, 1H), 2.72 (br m, 1H), 1.05 (d, 3H).

LCMS m/z: 119.1[M^++1].

Scheme 6S-I-3



Synthesis of (*S*)-1-((benzyloxy) carbonyl) pyrrolidine-2-carboxylic acid (6S-G):

[00265] To a stirring solution of L-proline (250 g, 2.17 mol) in water (1 L) was added Na_2CO_3 (576 g, 5.43 mol) and stirred for 1 h. After being cooled to 0 °C, benzylchloroformate (50% in $PhCH_3$) (444 g, 2.61mol) was added drop wise to the reaction mixture and again stirred for 1 h. The resulting reaction mixture was warmed to RT and further stirred for 24 h. After consumption of the starting material (by TLC), the reaction was diluted with water (1 L) and ether (1.5 L). The separated aqueous layer was treated with $PhCH_3$ (1.5 L) and acidified using 6N HCl. The aqueous layer was extracted with EtOAc (3x 1.5 L), combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-G** (450 g, 84%) as light yellow syrup.

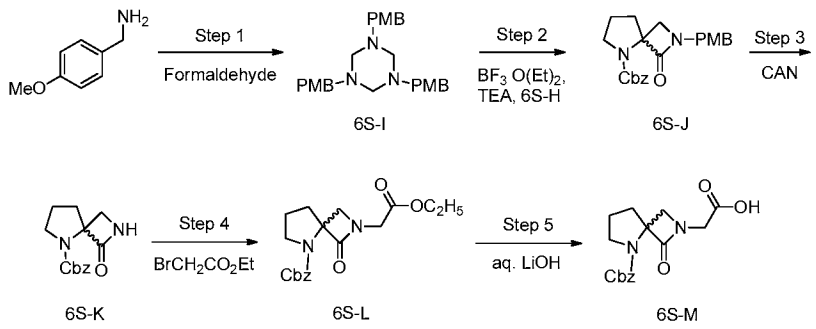
^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.71 (br s, 1H), 7.37-7.26 (m, 5H), 5.07-4.99 (m, 2H), 4.25-4.15 (m, 1H), 3.45-3.34 (m, 2H), 2.25-2.14 (m, 1H), 1.94-1.79 (m, 3H).

LCMS m/z: 250.4 [M^++1]

Synthesis of (*S*)-benzyl 2-(chlorocarbonyl) pyrrolidine-1-carboxylate (6S-H):

[00266] To a stirring solution of **6S-G** (90 g, 361 mmol) in CH_2Cl_2 (400 mL) was added oxalyl chloride (42 mL, 542 mmol) at 0 °C and stirred for 2 h. After complete formation of acid chloride, the reaction mixture was concentrated under reduced pressure to afford **6S-H** (95 g, crude). This material was directly used for the next step without further purification.

Scheme 6S-I-4



1, 3, 5-Tris (4-methoxybenzyl)-1, 3, 5-triazinane (6S-I):

[00267] To a stirring solution of (4-methoxyphenyl) methanamine (200 g, 1.46 mol) in EtOH (600 mL) at room temperature was added formaldehyde (33%aq, 105 mL) dropwise. The reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with EtOAc (100 mL) and washed with water (100 mL) followed by brine. The separated organic layer was concentrated under reduced pressure to obtain crude; which was finally washed with *n*-hexane to afford compound **6S-I** (200 g, 30.6%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.18 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 8.0 Hz, 6H), 3.71 (s, 9H), 3.50 (s, 6H) , 3.29 (s, 6H).

Benzyl 2-(4-methoxybenzyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-J):

[00268] To a stirring solution of **6S-H** (100 g, 0.37 mol) in dry CH_2Cl_2 (500 mL) was cooled to -40 °C and added Et_3N (210.2 mL, 1.50 mol) dropwise. The reaction mixture was stirred at -40 °C for 45 min. To this a mixture of **6S-I** (50 g, 0.12 mol) in CH_2Cl_2 (150 mL) and $BF_3.OEt_2$ (47.6 g, 0.33 mol) was added drop wise at -40 °C. The resulting reaction mixture was allowed to stir at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in EtOAc and kept in the refrigerator for crystallization. Obtained crystals were filtered and washed with cold EtOAc and dried under vacuum to afford **6S-J** (82 g, 58%) as white crystalline solid.

^{1}H-NMR: (500 MHz, DMSO-d6): δ 7.36-7.30 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.09 (s, 2H), 4.29 (s, 1H), 4.13-3.96 (m, 1H), 3.73 (s, 3H), 3.11 (t, J = 5.0 Hz, 2H), 2.16-2.09 (m, 2H), 1.83-1.77 (m, 2H), 1.20-1.15 (m, 2H).

LCMS m/z: 381 [M^++1]

Benzyl 1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-K):

[00269] To a stirring solution of **6S-J** (30 g, 78.94mmol) in MeCN (300 mL) and H_2O (150 mL) were cooled to 0 °C and added a solution of CAN (129 g, 0.23 mol) in H_2O (300 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mass was poured into ice cold water and the aqueous layer was extracted with EtOAc (2x 150mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude. Obtained material was purified by silica gel column chromatography eluting with EtOAc to afford **6S-K** (8 g, 40%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.36-7.29 (m, 5H), 5.10 (s, 2H), 3.53 (d, *J* = 4.5 Hz, 2H), 3.36-3.30 (m, 1H), 3.17-3.13 (m, 1H), 2.17-2.10 (m, 2H), 1.82-1.76 (m, 2H).

LCMS m/z: 261 [M^++1]

Benzyl 2-(2-ethoxy-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-L)

[00270] To a stirred solution of **6S-K** (10.0 g, 38.46 mmol) in acetonitrile (100 mL) were added CS_2CO_3 (31.34 g, 96.19 mmol) and ethyl 2-bromoacetate (6.42 mL, 57.60 mmol) at RT and stirred for 16 h at RT. The volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 100 mL). The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude material was purified by silica gel column chromatography eluting with 80% EtOAc/Hexane to afford **6S-L** (10.0 g, 75%) as pale brown syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.13-4.10 (m, 2H), 3.69 (d, *J* = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, *J* = 6.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.21-1.14 (m, 3H).

LCMS m/z: 261 [M^++1]

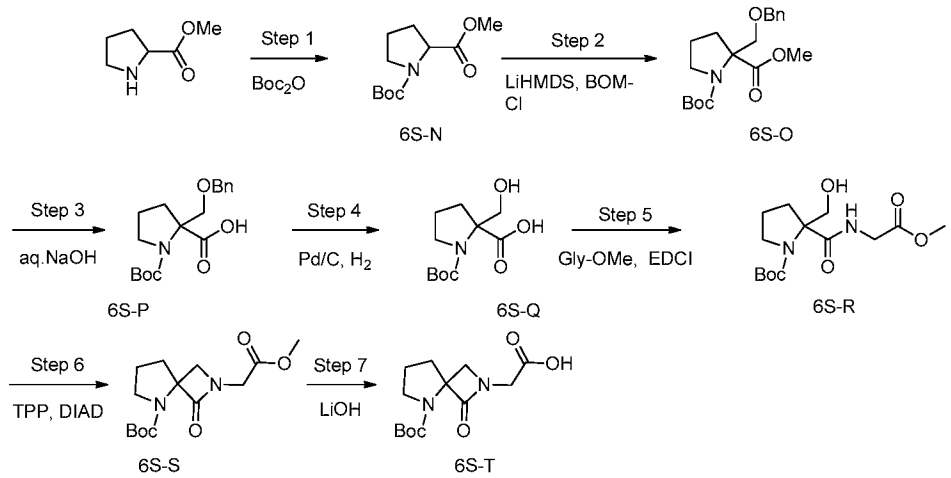
2-(5-((benzyloxy) carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (6S-M):

[00271] To a stirred solution of **6S-L** (6.0 g, 17.34 mmol) in THF: H_2O (75mL/40 mL) were added LiOH.H_2O (1.82 g, 43.33 mmol) at RT and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water, washed with ether, the aqueous layer was acidified to pH~2 using 2N HCl and extracted with EtOAc (2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford compound to afford **6S-M** (4.5 g, 88.2%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 7.35-7.30 (m, 5H), 5.06 (s, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 3.69 (d, J = 4.5 Hz, 1H), 3.47-3.44 (m, 3H), 2.16 (t, J = 6.0 Hz, 2H),1.87-1.80 (m, 2H)

LCMS m/z: 319 [M^++1]

Scheme 6S-I-5:



Synthesis of 1-tert-butyl 2-methyl pyrrolidine-1,2-dicarboxylate (6S-N):

[00272] To a stirring solution of proline methyl ester (70 g, 422 mmol) in CH_2Cl_2 (700 mL) were added Et_3N (183 mL, 1.26 mol) at 0 °C and stirred for 10 min. After added Boc-anhydride (184 mL, 845 mmol) at 0 °C and the reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was diluted with water (200 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layer was washed with citric acid (1 x 150 mL), brine (1 x 200 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 50% EtOAc/*n*-hexane to obtain **6S-N** (80 g, 83%) as thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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);

LCMS (m/z): 129 [(M^++1)-Boc];

Synthesis of 1-tert-butyl 2-methyl 2-((benzyloxy)methyl)pyrrolidine-1,2-dicarboxylate (6S-O):

[00273] To a stirring solution of **6S-N** (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_4Cl 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_2SO_4 and concentrated to obtain crude compound which was purified by column chromatography by eluting 10% EtOAc/*n*-hexane to afford **6S-O** (30 g, 79%) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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^++1)-Boc]

Synthesis of 2-((benzyloxy)methyl)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (6S-P):

[00274] To a stirring solution of **6S-O** (30 g, 86 mmol) in methanol (70 mL) was added NaOH solution (6.88 g in 70 mL H_2O) 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 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_2SO_4 and concentrated to afford crude was triturated with n-hexane to obtain **6S-P** (25 g, 86.8%) as off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ12.35 (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^++1]

Synthesis of 1-(tert-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine-2-carboxylic acid (6S-Q):

[00275] To a stirring solution of **6S-P** (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_2 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 **6S-Q** (15 g, 82.8%) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ4.66 (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).

Synthesis of tert-butyl2-(hydroxymethyl)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (6S-R):

[00276] To a stirring solution of **6S-Q** (25 g, 102 mmol) in CH_2Cl_2 (250 mL) were added DIPEA (54.3 mL, 303 mmol), EDCI (23.2 g, 122 mmol), HOBT (16.5 g, 122 mmol), glycine methyl ester.HCl (15.3 g, 122 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 (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with citric acid (1 x 100 mL) followed by bicarbonate solution (1 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 20% EtOAc/*n*-hexane to afford **6S-R** (20 g, 62.5%) as yellow thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.02 (d, J = 19.5 Hz, 1H), 5.01 (t, J = 5.0 Hz, 1H), 4.03-4.00 (m, 3H), 3.84-3.76 (m, 2H), 3.71-3.68 (m, 1H), 3.61 (s, 3H), 2.27-2.23 (m, 2H), 1.98-1.75 (m, 2H), 1.38 (s, 9H);

Mass (ESI): *m/z*217.2 [M^--Boc+1]

Synthesis of tert-butyl 2-(2-methoxy-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-S):

[00277] To a stirring solution of triphenylphosphine (72.5 g, 276 mmol) in THF (200 mL) was added DIAD (54.5 g, 276 mmol) at RT and stirred for 30 min. After added **6S-R** (35 g, 110 mmol) in (60 mL) THF slowly and 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 triturated with 30% diethyl ether/*n*-hexane (2 x 500 mL). The filtered organic solvent was concentrated and crude residue was purified by column chromatography by eluting 30% EtOAc/*n*-hexane to afford **6S-S** (30 g, crude) as semi solid.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ4.50-4.37 (m, 1H), 3.86 (s, 3H), 3.74-3.63 (m, 2H), 3.47-3.31 (m,1H), 3.69-3.60 (m, 1H), 3.42-3.33 (m, 2H), 3.28-3.23 (m, 1H), 2.18-2.14 (m, 2H), 1.90-1.76 (m, 2H), 1.40 (s, 9H)

Mass (ESI): *m/z*319.3 [M^++1]

Synthesis of 2-(5-(tert-butoxycarbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetic acid (6S-T):

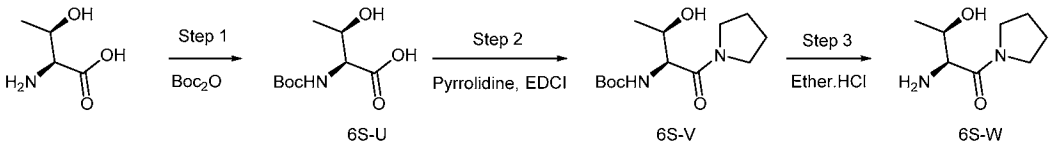
[00278] To a stirring solution of **6S-S** (10 g, 33.5 mmol) in THF/H_2O (100 mL) were added LiOH.H_2O (2.11 g, 50.2 mmol) at RT and stirred for 16 h. After consumption of the starting material (by TLC), reaction mass was evaporated under reduced pressure. The crude was washed with diethyl ether (2 x 200 mL). The separated aqueous layer was acidified by using citric acid solution (pH~3) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to afford **6S-T** (5 g, 52.6%)

^{1}H-NMR: (500 MHz, DMSO-d_6): δ12.80 (br s, 1H), 4.14-4.10 (m, 1H), 3.74-3.54 (m, 2H), 3.38-3.33 (m, 2H), 3.30-3.23 (m, 1H), 2.14-2.08 (m, 2H), 1.83-1.76 (m, 2H), 1.39 (s, 9H);

LCMS (m/z): 283.3 [M$^-$-1],

HPLC: 97.6%

Scheme 6S-I-6



6S-U 6S-V 6S-W

(*2S, 3R*)-2-((tert-butoxycarbonyl) amino)-3-hydroxybutanoic acid (6S-U)

[00279] To a stirring solution of (*2S, 3R*)-2-amino-3-hydroxybutanoic acid (10 g, 83.9 mmol) in 1, 4-dioxane/water (100 mL, 1: 1)) was added $NaHCO_3$ (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_2Cl_2 (2 x 150 mL). The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-U** (15 g, crude). This material was directly used for the next step without further purification.

***tert*-butyl ((*2S,3R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)carbamate (6S-V):**

[00280] To a stirring solution of **6S-U** (5 g, 22.8 mmol) in CH_2Cl_2 (50 mL) was added EDCI.HCl (5.2 g, 27.3 mmol), HOBt (4.6 g, 34.2 mmol)followed by DIPEA (10.5 mL, 57 mmol) and pyrrolidine (1.945 g, 27.3 mmol) under N_2 atmosphere 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 DCM and washed with water followed by saturated $NaHCO_3$ and citric acid. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography eluting with 2% MeOH/DCM to afford **6S-V** (3 g, 48%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 6.41 (d, 1H), 4.71 (d, 1H), 4.15 (t, 1H), 3.94 (q, 1H), 3.63-3.42 (m, 2H), 3.24 (q, 1H), 1.90-1.81 (m, 4H), 1.38 (s, 9H), 1.04 (s, 3H).

LCMS (m/z):273.2[M^++1]

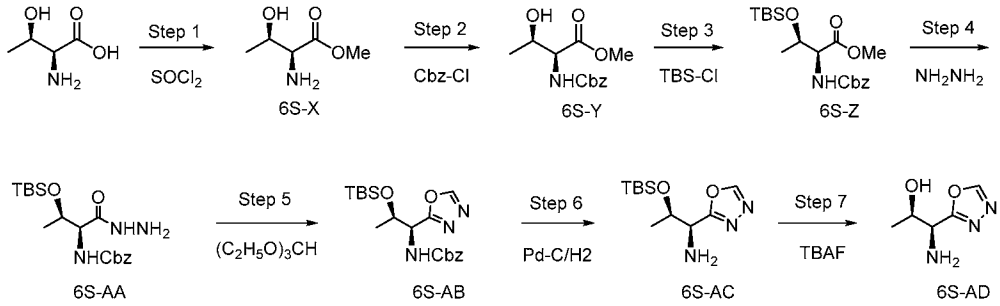
(*2S,3R*)-2-amino-3-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (6S-W):

[00281] To a stirred solution of **6S-V** (3 g, 11.0 mmol) in DCM (10 mL) was added diethyl ether saturated with HCl (20 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure to get crude product, which was washed with ether to afford **6S-W** (2.0 g, 87%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.19 (br s, 3H), 3.98-3.91 (m, 2H), 3.62-3.59 (m, 1H), 3.49-3.42 (m, 1H), 3.39-3.35 (m, 2H), 1.96-1.90 (m, 4H), 1.17 (d, 3H).

LCMS (m/z):173.3[M^++1]

Scheme 6S-I-7



Synthesis of (2*S*, 3*R*)-methyl 2-amino-3-hydroxybutanoate (6S-X):

[00282] To a stirring solution of L-threonine (50 g, 420 mmol) in CH_3OH (250 mL) was added thionyl chloride (62.4 mL, 840mmol) at 0 °C and stirred at 75 °C for 6 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **6S-X** (60 g, crude). This material was directly used for the next step without further purification.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.45 (s, 2H), 5.70 (s, 1H), 4.12-4.10 (m, 1H), 3.90 (s, 1H), 3.73 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H).

Synthesis of (2*S*, 3*R*)-methyl 2-(((benzyloxy) carbonyl) amino)-3-hydroxybutanoate (6S-Y):

[00283] To a stirring solution of **6S-X** (60 g, 353 mmol) in water/1,4 dioxane (150 mL/300 mL) The reaction mixture was cooled to 0 °C added $NaHCO_3$ (88.9 g, 1.059 mol) at 0 C and stirred for 15 min.. Cbz-Cl (60.7 mL, 426 mmol) was added drop wise and stirred for 1

h. The reaction mixture was stirred to RT and stirred for 12 h. After completion of starting material (by TLC), diluted the reaction mass with EtOAc (300 ml). The separated organic layer was washed with (2x200 mL) of saturated $NaHCO_3$ solution followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was triturated with *n*-hexane (500mL) to afford **6S-Y** (70 g, 74 %) as white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.37-7.30 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 2H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.09-4.05 (m, 2H), 3.64 (s, 3H), 1.09 (d, *J* = 6.0 Hz, 3H).

LCMS m/z: 268.2[M^++1]

Synthesis of (2*S*, 3*R*)-methyl 2-(((benzyloxy) carbonyl) amino)-3-((tert-butyldimethylsilyl) oxy) butanoate (6S-Z):

[00284] To a stirring solution of **6S-Y** (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 mass with EtOAc (500 ml). The separated organic layer was washed with (2x200 mL) of H_2O followed by brine solution (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 10% EtOAc/hexane to afford **6S-Z** (50 g, 70.1%) as colorless syrup.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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^++1]

Synthesis of benzyl ((2*S*, 3*R*)-3-((tert-butyldimethylsilyl) oxy)-1-hydrazinyl-1-oxobutan-2-yl) carbamate (6S-AA):

[00285] A solution of **6S-Z** (50 g, 131 mmol) in EtOH (400mL) 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), ethanol was evaporated 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_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by column chromatography by eluting with 20% EtOAc/hexane to afford **6S-AA** (25 g, 50%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 ((1S, 2R)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propyl) carbamate (6S-AB):

[00286] A solution of **6S-AA** (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), triethyl orthoformate was evaporated under reduced pressure. The crude residue was purified by column chromatography eluting 10% EtOAc/hexane to afford **6S-AB** (15 g, 58%) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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);

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

Synthesis of (1*S*, 2*R*)-2-((tert-butyldimethylsilyl) oxy)-1-(1, 3, 4-oxadiazol-2-yl) propan-1-amine (6S-AC):

[00287] To a stirring solution of **6S-AB** (15 g, 38.3 mmol) in methanol (200 mL) was added 50% wet 10% Pd/C (5 g) and stirred under H_2 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 **6S-AC** (10 g, crude) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): 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]

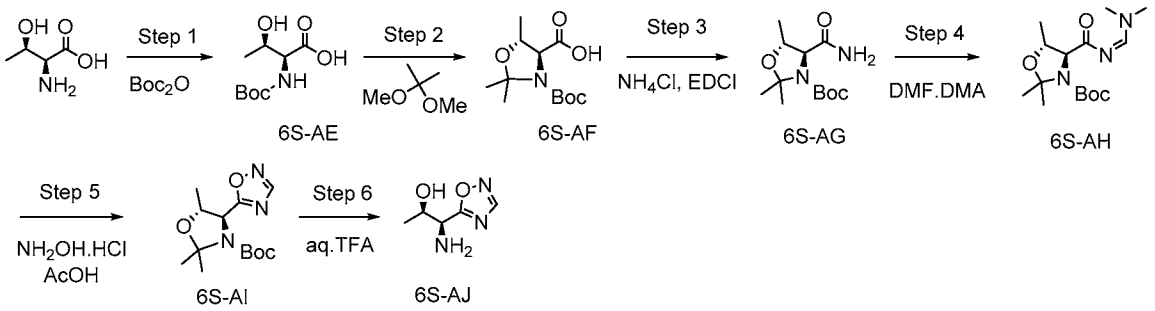
Synthesis of (1*S*, 2*R*)-1-amino-1-(1, 3, 4-oxadiazol-2-yl) propan-2-ol (6S-AD):

[00288] To a stirring solution of **6S-AC** (10 g, 38.9 mmol) in THF (100 mL) was added TBAF (20.3 g, 77.8 mmol) slowly at 0° C and stirred at RT for 3 h. After completion of reaction (by TLC), the reaction mixture was evaporated and diluted with EtOAc/H_2O (200 mL/50 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting 5% MeOH/DCM to afford **6S-AD** (5 g, crude) as thick syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.12 (s, 1H), 3.94 (d, J = 4.5 Hz, 1H), 3.85 (t, J = 5.5 Hz, 1H), 3.17-3.13 (m, 3H), 1.05 (d, J = 6.0 Hz, 3H).

LCMS m/z: 144 [M^++1]

Scheme 6S-I-8:



Synthesis of 2-((*tert*-butoxycarbonyl) amino)-3-hydroxybutanoic acid (6S-AE):

[00289] To a stirring solution of 2-amino-3-hydroxybutanoic acid (10 g, 83.9 mmol) in 1,4-dioxane/water (100 mL, 1: 1)) were added $NaHCO_3$ (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_2Cl_2 (2 x 150 mL). The separated organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **6S-AE** (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 (6S-AF):

[00290] To a stirring solution of **6S-AE** (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_2 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 $NaHCO_3$ solution and washed with EtOAc (1x100 mL). Aqueous layer was acidified using citric acid solution (pH~2) and extracted with CH_2Cl_2 (2x100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford **6S-AF** (18 g, crude).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ13.25 (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 (6S-AG):

[00291] To a stirring solution of **6S-AF** (18 g, 69.4 mmol) in CH_2Cl_2 (180 mL) was added HOBt (14.16 g, 0.104 mol), EDCI.HCl (19.88 g, 0.104 mol) followed by NH_4Cl (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, $NaHCO_3$ followed by brine. Organic layer was dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure to give crude; which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford **6S-AG** (13 g, 72.5%).

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^++1)-Boc]

Synthesis of (Z)-*tert*-butyl 4-(((dimethylamino) methylene) carbamoyl)-2, 2, 5-trimethyloxazolidine-3-carboxylate (6S-AH):

[00292] A solution of **6S-AG** (13 g, 50.3 mmol) in DMF.DMA (130 mL) was stirred at reflux temperature for 3 h under N_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to afford **6S-AH** (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 (6S-AI):

[00293] To a stirring solution of **6S-AH** (15.7 g, 50.09 mmol) in ethanol (157 mL) was added hydroxylamine hydrochloride (6.96 g, 0.10 mol) under N_2 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. 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 **6S-AI** (4.5 g, 32%).

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^+]

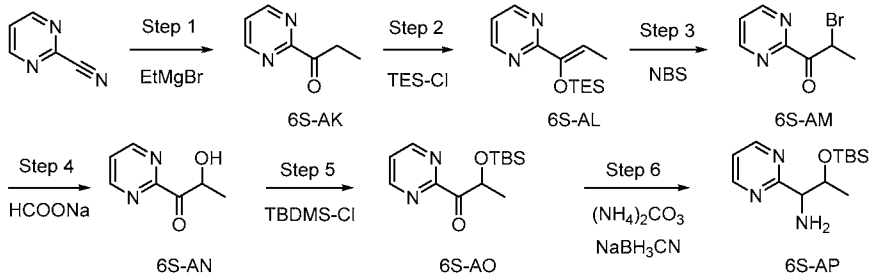
Synthesis of 1-amino-1-(1, 2, 4-oxadiazol-5-yl) propan-2-ol (6S-AJ):

[00294] To a stirring solution of **6S-AI** (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 $NaHCO_3$. The solvent from the reaction mixture was evaporated under vacuum and extracted with 5% $MeOH/CH_2Cl_2$ (3x 100 mL). The organic layer was concentrated under reduced pressure to afford **6S-AJ** (2.5 g, crude).

^{1}H-NMR: (400 MHz, D_2O): 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]

Scheme 6S-I-9



Synthesis of 1-(pyrimidin-2-yl) propan-1-one (6S-AK):

[00295] To a stirring solution of pyrimidine-2-carbonitrile (20 g, 190 mmol) in THF (200 mL) was added ethyl magnesium bromide (1M in THF, 227 mL, 228 mmol) at 0 °C for 1 h. 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 (2x100 mL). The extracted organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 20% EtOAc/hexane to afford **6S-AK** (15 g, 57%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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^++1]

Synthesis of (*Z*)-2-(1-((triethylsilyl) oxy) prop-1-en-1-yl) pyrimidine (6S-AL):

[00296] To a stirring solution of **6S-AK** (15 g, 110 mmol) in THF (100 mL) was added LiHMDS (1M in THF, 220 mL, 220 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 (50 mL) and EtOAc (150 mL). The separated organic layer was extracted with brine solution (2x100 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 5% EtOAc/hexane to afford **6S-AL** (20 g, 74%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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 (6S-AM):

[00297] To a stirring solution of **6S-AL** (20 g, 80 mmol) in THF/H_2O (160 mL/40 mL) were added N-bromosuccinamide (10.2 g, 88 mmol) slowly at RT and stirred for 2 h. After completion of starting material (by TLC), the reaction mixture was diluted with H_2O and EtOAc (100 ml/150 mL). The separated organic layer was washed with brine solution (2x100 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **6S-AM** (15 g, 87%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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).

Synthesis of 2-hydroxy-1-(pyrimidin-2-yl) propan-1-one (6S-AN):

[00298] To a stirring solution of **6S-AM** (15 g, 69 mmol) in MeOH (240 mL) was added sodium formate (18.9 g, 279 mmol) and stirred the reaction mass at 70 °C for 8 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 5% MeOH/DCM to afford **6S-AN** (5.5 g, 51%) as colorless liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): 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)

Synthesis of (2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propan-1-one (6S-AO):

[00299] To a stirring solution of **6S-AN** (5.5 g, 36 mmol) in DCM (150 mL) were added imidazole (4.9 g, 72mmol), DMAP (880 mg, 0.72 mmol) at 0 °C and stirred for 10 min. After added TBDMS-Cl (8.1 g, 54 mmol) at 0 °C and stirred at RT for 6 h. After completion of starting material (by TLC), diluted the reaction mass with H_2O (50 ml). The separated organic

layer was washed with brine solution (2x50mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material which was purified by column chromatography eluting 30% EtOAc/hexane to afford **6S-AO** (3 g, 31%) as an off-white solid.

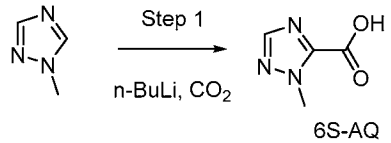
^{1}H-NMR: (400 MHz, $CDCl_3$): δ 9.00 (d, J = 5.2 Hz, 2H), 7.71 (t, J = 4.8 Hz, 1H), 5.47-5.42 (m, 1H), 1.35 (d, J = 6.8 Hz, 3H), 0.79 (s, 9H), 0.05 (s, 6H)

Synthesis of (2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propan-1-amine (6S-AP):

[00300] To a stirring solution of **6S-AO** (3 g, 11.2 mmol) in MeOH (50 mL) were added sodium acetate (1.8 g, 22.5 mmol), ammonium carbonate (8.8 g, 56.3 mmol), AcOH (0.6 mL, 11.2 mmol) at RT. The reaction mixture was then stirred at 70 °C for 2 h. The temperature of the reaction was cooled to RT and added sodium cyanoborohydride (1.39 g, 22.5 mmol) and stirred at 70 °C for 6 h. After consumption of starting material (by TLC), the MeOH was evaporated and the crude residue was diluted with DCM/H_2O (50 ml/50 mL). The separated organic layer was washed with brine (2x50mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude material was purified by column chromatography eluting 5% MeOH/DCM to afford **6S-AP** (2.4 g, 80%) as semi solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): 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).

Scheme 6S-I-10



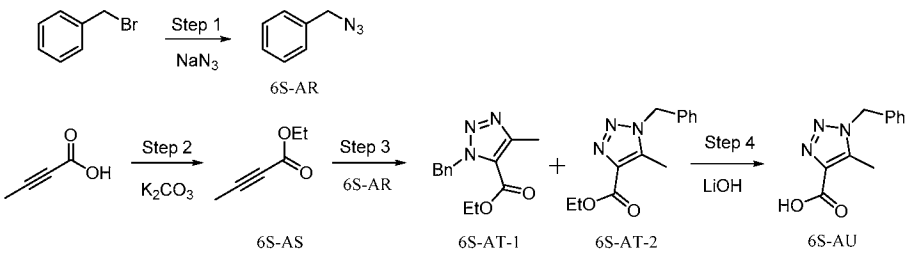
Synthesis of 1-methyl-1H-1, 2, 4-triazole-5-carboxylic acid (6S-AQ):

[00301] To a stirred solution of 1-methyl-1H-1, 2, 4-triazole (2.0 g, 24.0 mmol) in THF (20 mL) was added n-butyl lithium (19 mL, 12.0 mmol) at -78 °C dropwise and stirred for 2 h. Solid CO_2 (2 g) was the added and the reaction stirred at -78 °C for 1 h. The reaction mass was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water (3 mL) and the obtained solid was filtered. The solid was triturated with diethyl ether/n-pentane (10 mL/10 mL). The white color solid was dried on vacuum to afford **6S-AQ** (2.0 g, 65.7%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.70 (s, 1H), 4.01 (s, 3H);

LCMS m/z: 128.3 [M^++1]

Scheme 6S-I-11



Synthesis of (azidomethyl) benzene (6S-AR):

[00302] To a stirring solution of benzyl bromide (30 g, 175 mmol) in dimethyl formamide (300 mL) was added sodium azide (45.6 g, 701 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 70 °C for 16 h. After completion of reaction monitored (by TLC), the reaction mixture was allowed to RT; the volatiles were diluted with water (300 mL) and ether (200 mL). The separated organic layer was washed by (3x200 mL) of chilled water. After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-AR** (18 g, crude) as an off-white solid.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 4.32 (s, 2H).

Synthesis of ethyl but-2-ynoate (6S-AS):

[00303] To a stirring solution of but-2-ynoic acid (2 g, 23.8 mmol) in dimethyl formamide (20 mL) was added potassium carbonate (8.21 g, 59.5 mmol) slowly at 0 °C under inert atmosphere. After added ethyl iodide (2.85 mL, 35.7 mmol) dropwise and the resultant reaction mixture was stirred at RT for 12 h. After completion of reaction monitored (by TLC), the reaction mixture was diluted with water (50 mL) and EtOAc (100 mL). The separated organic layer was washed by (3 x 100 mL) of chilled water and organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-AS** (1.4 g, crude) as reddish syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 4.23 (q, J = 6.5 Hz, 2H), 2.06 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H);

Synthesis of ethyl 1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (6S-AT-1 & 6S-AT-2):

[00304] To a stirring solution of **6S-AS** (8.0 g, 71.3 mmol) in toluene (80 mL) was added **6S-AR** (12.0 g, 107 mmol) at RT under inert atmosphere. The resultant reaction mixture was

heated to 100 °C and stirred for 16 h. The reaction mixture was allowed to RT; the volatiles were evaporated under reduced pressure to which, crude residue was purified by column chromatography by eluting 40% EtOAc/hexane to afford two isomers **6S-AT-1** (8 g) & **6S-AT-2** (8.2 g).

^{1}H-NMR (6S-AH-1): (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 5H), 5.86 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H),LCMS m/z: 246.3 [M^++1].

^{1}H-NMR(6S-AH-2): (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 3H), 7.16 (t, *J* = 6.0 Hz, 2H), 5.53 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

LCMS m/z: 246.3 [M^++1].

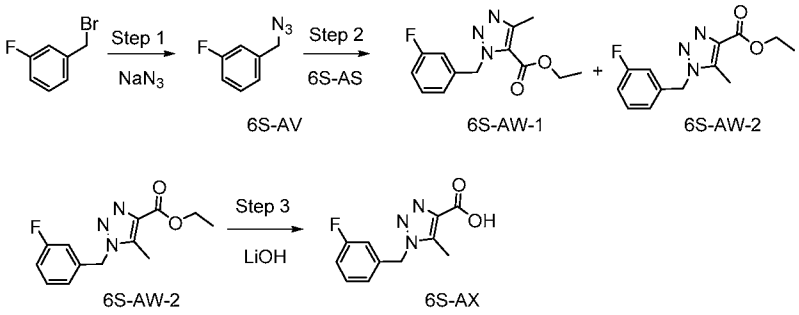
Synthesis of 1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-AU):

[00305] To a stirring solution of compound **6S-AT-2** (8.2 g, 33.4 mmol) in THF/H_2O (82 mL/82 mL, 1:1) was added LiOH.H_2O (4.2 g, 0.40 mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2N HCl and the precipitated solid was filtered and washed with water (25 mL), dried under reduced pressure to afford **6S-AU** (7.0 g, 97.2%) as an off-white solid.

^{1}H-NMR(H_2):(400 MHz, DMSO-d_6): δ 13.01 (br s, 1H), 7.40-7.32 (m, 5H), 5.63 (s, 2H), 2.45 (s, 3H).

LCMS m/z: 218.3[M^++1]

Scheme 6S-I-12



Synthesis of 1-(azidomethyl)-3-fluorobenzene (6S-AV):

[00306] To a stirring solution of 1-(bromomethyl)-3-fluorobenzene (1 g, 5.29 mmol) in dimethyl formamide (10 mL) was added sodium azide (859 mg, 13.2 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 90 °C for 12 h. After completion of reaction monitored (by TLC), the reaction mixture was allowed to RT; the volatiles were diluted with water (100 mL) and ethyl acetate (100 mL). The separated organic layer was washed by (3 x 100 mL) of chilled water. After the separated organic layer was dried over

anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-AV** (700 mg, 87.7%) as yellow syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.18-7.10 (m, 1H), 7.08 (s, 1H), 4.40 (s, 2H)

IR: 2102cm^{-1}

Synthesis of ethyl 1-(3-fluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (6S-AW-1 & 6S-AW-2):

[00307] To a stirring solution of **6S-AV** (2.4 g, 15.8 mmol) in toluene (10 mL) was added **6S-AG** (1.78 g, 15.8 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was allowed to RT; the volatiles were evaporated under reduced pressure to which, crude residue was purified by column chromatography by eluting 20% EtOAc/hexane to afford **6S-AW-1** (1 g, 24%) and **6S-AW-2** (1.5 g, 36.1%) as an off-white solid.

^{1}H-NMR (6S-AW-2, confirmed by NOE)**:** (500 MHz, DMSO-d_6): δ 7.44-7.39 (m, 1H), 7.19-7.15 (m, 1H), 7.03 (dd, *J* = 10.5 Hz, 8.0 Hz, 2H), 5.67 (s, 2H), 4.29 (q, *J* = 7.5 Hz, 2H), 2.50 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H);

Mass m/z: 264.2 [M^++1]

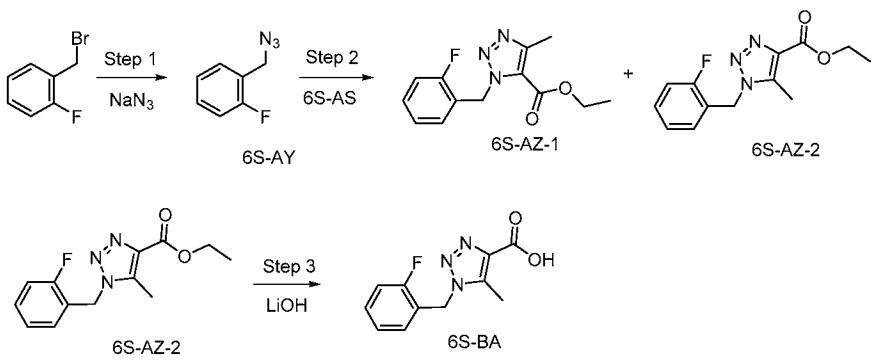
Synthesis of 1-(3-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-AX):

[00308] To a stirring solution of **6S-AW-2** (1.5 g, 5.7 mmol) in THF/H_2O (10 mL/5 mL, 1:1), EtOH (2 mL) were added LiOH.H_2O (490 mg, 11.4 mmol) at RT and stirred for 6 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N*HCl. The precipitated solid was filtered and co-distilled with toluene (20 mL x 2), dried under reduced pressure to afford **6S-AX** (1.34 g, 82%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 4.16 (d, *J* = 7.5 Hz, 2H), 2.50 (s, 3H), 1.84-1.79 (m, 1H), 1.68-1.49 (m, 5H), 1.21-0.96 (m, 5H);

Mass m/z: 236.2[M^++1]

Scheme 6S-I-13



Synthesis of 1-(azidomethyl)-2-fluorobenzene (6S-AY):

[00309] To a stirring solution of 1-(bromomethyl)-2-fluorobenzene (1 g, 5.29 mmol) in dimethyl formamide (10 mL) was added sodium azide (859 mg, 13.22 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 90 °C for 16 h. After completion of reaction monitored (by TLC), the reaction mixture was diluted with water (100 mL) and EtOAc (100 mL). The separated organic layer was washed by (3x100 mL) of chilled water and organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-AY** (700 mg, crude) as yellow syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.18-7.08 (m, 2H), 4.40 (s, 2H);

IR: 2102 (cm^{-1})

Synthesis of ethyl 1-(2-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (6S-AZ-1 & 6S-AZ-2):

[00310] To a stirring solution of **6S-AY** (1.5 g, 13.39 mmol) in toluene (15 mL) was added **6S-AS** (3.03 g, 20.08 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 16 h. After completion of the reaction, allowed to RT and the volatiles were evaporated under reduced pressure to afford crude residue was purified by column chromatography by eluting 15% EtOAc/hexane to afford and **6S-AZ-1** (500 mg, 14.2%) and **6S-AZ-2** (800 mg, 22.8%) as yellow solid.

^{1}H-NMR(6S-AZ-2, confirmed by NOESY1D**):** (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 1H), 7.12-7.05 (m, 3H), 5.58 (s, 2H), 4.42 (q, J = 7.0 Hz, 2H), 2.51 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H);

Synthesis of 1-(2-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BA):

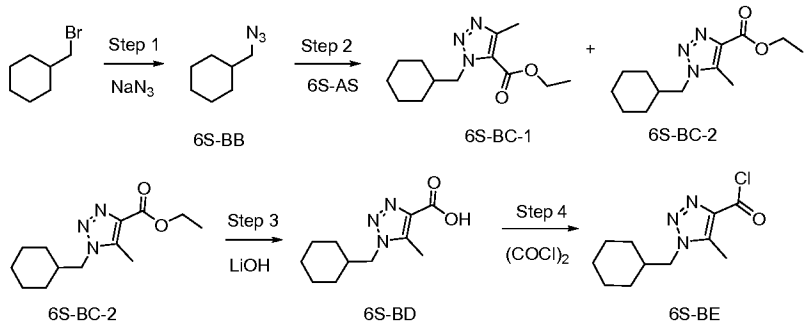
[00311] To a stirring solution of **6S-AZ-2** (800 mg, 3.04 mmol) in THF/H_2O (10 mL/10 mL, 1:1) were added LiOH.H_2O (318 mg, 7.60 mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N* HCl and the precipitated solid was filtered and washed

with water (5 mL) followed by *n*-pentane (5 mL) dried under reduced pressure to afford **6S-BA** (600 mg, 84%) as an off-white solid.

^{1}H-NMR(I_2): (400 MHz, DMSO-d_6): δ 13.03 (br s, 1H), 7.45-7.39 (m, 1H), 7.28-7.16 (m, 3H), 5.65 (s, 2H), 2.50 (s, 3H);

Mass m/z: 236.1[M^++1]

Scheme 6S- I-14



Synthesis of (azidomethyl) cyclohexane (6S-BB):

[00312] To a stirring solution of (bromomethyl) cyclohexane (2 g, 11.2 mmol) in dimethylformamide (10 mL) was added sodium azide (2.18 g, 33.8 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 90 °C for 12 h. After completion of reaction monitored (by TLC), the reaction mixture was allowed to RT; the volatiles were diluted with water (100 mL) and ethyl acetate (100 mL). The separated organic layer was washed by (3x100 mL) of chilled water. After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BB** (1.0 g, 64.5%) as brown syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 3.10 (t, J = 7.0 Hz, 2H), 2.15-1.98 (m, 4H), 1.77-1.66 (m, 4H), 1.56-1.53 (m, 1H), 1.00-0.95 (m,2H)

Synthesis of ethyl 1-(cyclohexylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (6S-BC-1 & 6S-BC-2):

[00313] To a stirring solution of **6S-BB** (1.0 g, 7.18 mmol) in toluene (10 mL) was added **6S-AS** (1.20 g, 10.7 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was allowed to RT; the volatiles were evaporated under reduced pressure and the crude residue was purified by column chromatography by eluting with 20% EtOAc/hexane to afford and **6S-BC-1** (400 mg, 22.1%) and **6S-BC-2** (700 mg, 38.8%) as an off-white solid.

^{1}H-NMR (6S-BC-2, confirmed by Noesy**):** (400 MHz, $CDCl_3$): δ 4.42 (q, *J* = 7.2 Hz, 2H), 4.10 (d, *J* = 7.6Hz, 2H), 2.56 (s, 3H), 1.95-1.88 (m, 1H), 1.76-1.69 (m, 3H), 1.68-1.61 (m, 2H), 1.41-1.33 (m, 3H), 1.03 (t, *J* = 11.6 Hz, 3H), 0.97-0.89 (m, 2H);

Mass m/z: 252.3 [M^++1]

Synthesis of 1-(cyclohexylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BD)

[00314] To a stirring solution of **6S-BC-2** (700 mg, 2.78 mmol) in THF/H_2O (10 mL/5 mL, 1:1), EtOH (1 mL) were added LiOH.H_2O (230 mg, 5.57 mmol) at RT and stirred for 6 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N* HCl. The precipitated solid was filtered and washed with water (2 mL), dried under reduced pressure to afford **6S-BD** (600 mg, 96.7%) as an off-white solid.

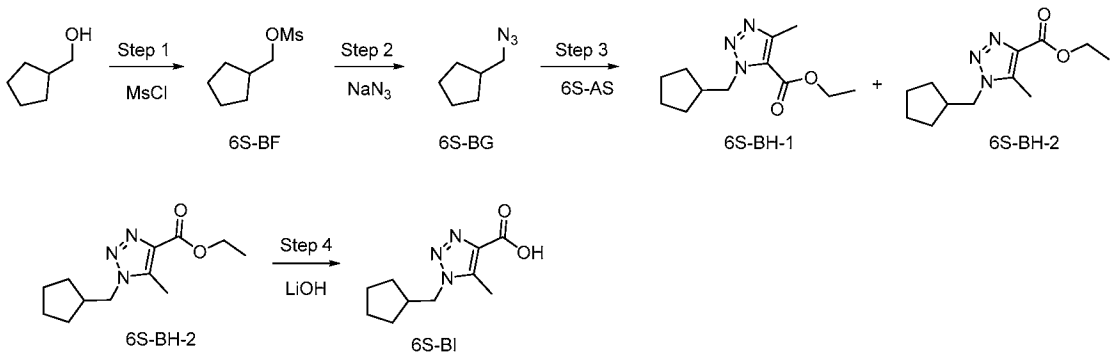
^{1}H-NMR(6S-BD): (500 MHz, DMSO-d_6): δ 12.5 (br s, 1H), 4.16 (d,*J* = 7.5 Hz, 2H), 2.50 (s, 3H), 1.84-1.79 (m, 1H), 1.68-1.49 (m, 5H), 1.21-0.96 (m, 5H);

Mass m/z: 224.2[M^++1]

Synthesis of 1-(cyclohexylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carbonyl chloride (6S-BE):

[00315] To a stirring solution of **6S-BD** (200 mg, 0.89 mmol) in CH_2Cl_2 (5 mL), DMF (0.1mL) were added oxalyl chloride (0.14 mL, 17.8 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 3 h. After formation of the acid chloride volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford **6S-BE** (210 mg, crude).

Scheme 6S-I-15



Synthesis of cyclopentylmethyl methanesulfonate (6S-BF):

[00316] To a stirring solution of cyclopentylmethanol (2 g, 20 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (7.21 mL, 50 mmol) and mesyl chloride (2.31 mL, 30 mmol) at -78 °C and

stirred at RT for 2 h. After completion of starting material (by TLC), the organic layer was washed with water (1x 30 mL) followed by brine solution (1x 50 mL). After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BF** (2 g, crude) as brown syrup. The obtained crude was used for next step without any further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ4.11 (d, J = 7.5 Hz, 2H), 3.00 (s, 3H), 2.33-2.27 (m, 1H), 1.83-1.77 (m, 2H), 1.65-1.57 (m, 4H), 1.32-1.25 (m, 2H)

Synthesis of (azidomethyl) cyclopentane (6S-BG):

[00317] To a stirring solution of **6S-BF** (2 g (crude), 11.2 mmol) in DMF (20 mL) was added sodium azide (2.19 g, 33.7 mmol) at RT and heated to 80 °C for 16 h. After completion of starting material (by TLC), the reaction mass was diluted with water (100 mL) and EtOAc (50 mL). The separated organic layer was washed with water (1x 100 mL) followed by brine solution (1x 100 mL). After the separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BG** (1.2 g, crude) as brown syrup. The obtained crude was used for next step without any further purification.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ3.20 (d, J = 7.2 Hz, 2H), 2.18-2.11 (m, 1H), 1.84-1.76 (m, 2H), 1.69-1.53 (m, 4H), 1.28-1.20 (m, 2H)

Synthesis of ethyl 1-(cyclopentylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (6S-BH-1 & 6S-BH-2):

[00318] To a stirring solution of **6S-BG** (1.2 g (crude), 9.6 mmol) in toluene (15 mL) was added **6S-AS** (1.29 g, 11.5 mmol) at RT and heated to 100 °C for 16 h. After completion of starting material (by TLC), evaporated reaction mass under reduced pressure to obtain crude which was purified by column chromatography by eluting 10% EtOAc/*n*-hexane to afford **6S-BH-1** (300 mg, 13.2%) and **6S-BH-2** (600 mg, 26.4%) as white solid.

^{1}H-NMR: (6S-BH-2, identified by NOESY): (400 MHz, $CDCl_3$): δ4.45-4.39 (m, 2H), 4.21 (d, J = 8.0 Hz, 2H), 2.57 (s, 3H), 2.46-2.42 (m, 1H), 1.73-1.56 (m, 6H), 1.43 (d, J = 7.2 Hz, 3H), 1.34-1.25 (m, 2H)

LCMS m/z: 238.2 [M^++1]

1-(cyclopentylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BI):

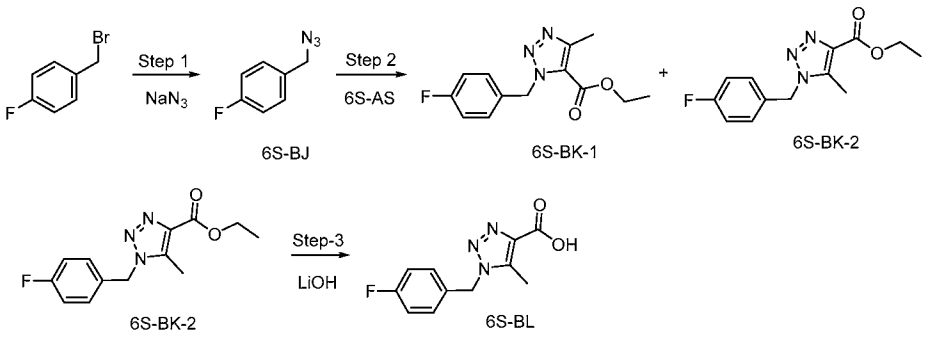
[00319] To a stirred solution of **6S-BH-2** (600 mg, 2.53 mmol) in THF: H_2O (10 mL/3 mL) were added LiOH.H_2O (265 mg, 6.30 mmol) at RT and stirred for 16 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The

residue was diluted with water (10 mL) and acidified to pH~2 using citric acid. The obtained precipitate was filtered and triturated with n-hexane (10 mL) to afford **6S-BI** (400 mg, 75.7%) as white solid.

^{1}**H-NMR**: (400 MHz, DMSO-d_6): δ 12.9 (br s, 1H), 4.24 (d, *J* = 7.6 Hz, 2H), 2.51 (s, 3H), 2.40-2.32 (m, 1H), 1.62-1.50 (m, 6H), 1.27-1.21 (m, 2H);

LCMS m/z: 210.2 [M^++1]

Scheme 6S- I-16



Synthesis of 1-(azidomethyl)-4-fluorobenzene (6S-BJ):

[00320] To a stirring solution of 1-(bromomethyl)-4-fluorobenzene (1 g, 5.29 mmol) in dimethylformamide (10 mL) was added sodium azide (859 mg, 13.22 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 80 °C for 12 h. After completion of reaction monitored (by TLC), the reaction mixture was diluted with water (100 mL) and EtOAc (100 mL). The separated organic layer was washed by (3x100 mL) of chilled water and organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BJ** (800mg, crude) as yellow syrup.

IR: (2100 cm^{-1})

Synthesis of ethyl 1-(4-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylate (6S-BK-1& 6S-BK-2):

[00321] To a stirring solution of **6S-AS** (500 mg, 4.46 mmol) in toluene (5 mL) was added **6S-BJ** (1.01 g, 6.69 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 12 h. After completion of the reaction, allowed to RT and the volatiles were evaporated under reduced pressure to afford crude residue was purified by column chromatography by eluting 30% EtOAc/hexane to afford **6S-BK-1** (250 mg, 21.3%) and **6S-BK-2** (400 mg, 34.1%) as yellow solid.

^{1}H-NMR(6S-BK-2, confirmed by NOESY1D**):** (500 MHz, $CDCl_3$): δ 7.18-7.15 (m, 2H), 7.04 (t, *J* = 8.5 Hz, 2H), 5.50 (s, 2H), 4.41 (q, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H);

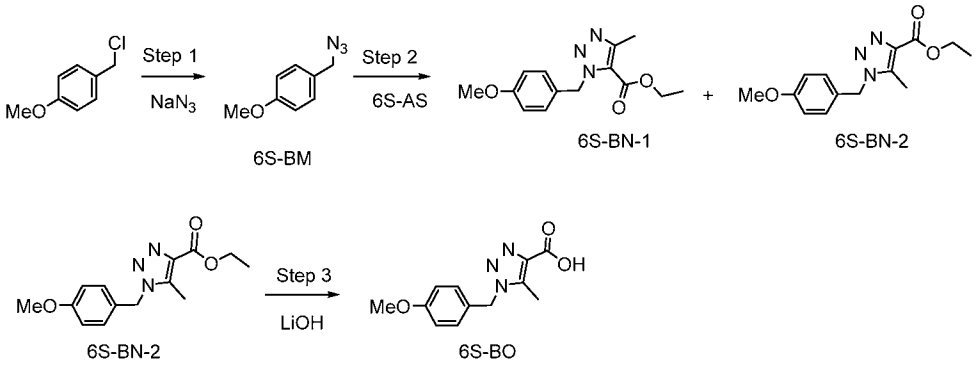
Synthesis of 1-(4-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BL):

[00322] To a stirring solution of **6S-BK-2** (800 mg, 3.04 mmol) in THF/H_2O (5 mL/5 mL, 1:1) were added LiOH.H_2O (318 mg, 7.60 mmol) at RT and stirred for 16 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N* HCl and the precipitated solid was filtered and washed with water (5 mL) followed by *n*-pentane (5 mL) dried under reduced pressure to afford **6S-BL** (400 mg, 56%) as white solid.

^{1}H-NMR(6S-BL): (500 MHz, DMSO-d_6): δ 13.02 (br s, 1H), 7.28 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 9.0 Hz, 2H), 5.61 (s, 2H), 2.51 (s, 3H);

Mass m/z: 236.1[M^++1]

Scheme 6S-I-17:



Synthesis of 1-(azidomethyl)-4-methoxybenzene (6S-BM):

[00323] To a stirring solution of 1-(chloromethyl)-4-methoxybenzene (2 g, 12.7 mmol) in dimethyl formamide (20 mL) was added sodium azide (2.07 g, 31.7 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 100 °C for 12 h. After completion of reaction as indicated by TLC, the reaction mixture was allowed to cool to RT; the volatiles were diluted with water (200 mL) and ethyl acetate (200 mL). The separated organic layer was washed by (3x200 mL) of chilled water and organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BM** (1.4 g, crude) as reddish syrup.

^{1}H-NMR: (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.26 (s, 2H), 3.81 (s, 3H);

IR: 2097cm^{-1}

Synthesis of 4-(ethoxymethyl)-1-(4-methoxybenzyl)-5-methyl-1H-1, 2, 3-triazole (6S-BN-1 & 6S-BN-2):

[00324] To a stirring solution of **6S-AS** (1 g, 8.92 mmol) in toluene (10 mL) was added **6S-BM** (2.18 g, 13.39 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was allowed to cool to RT; the volatiles were evaporated under reduced pressure to which, crude residue was purified by column chromatography by eluting 20% EtOAc/hexane to afford **6S-BN-1** (200 mg, 8.1%) and **6S-BN-2** (300 mg, 12.2%)

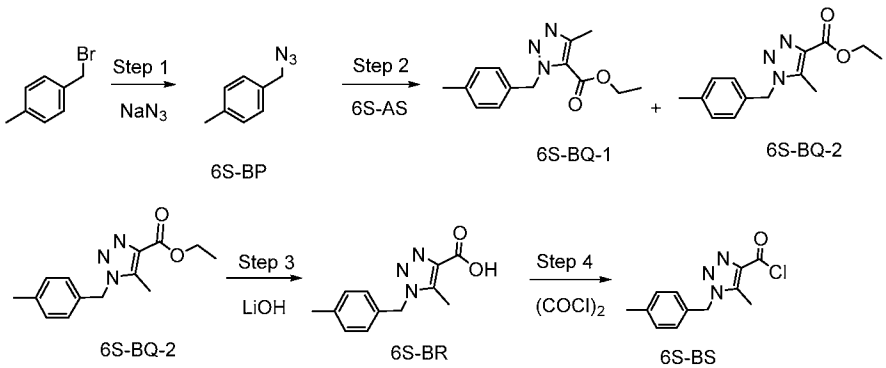
^{1}H-NMR(6S-BN-2, confirmed by NOESY**):** (500 MHz, $CDCl_3$): δ 7.12 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5Hz, 2H), 5.46 (s, 2H), 4.41 (q, J = 7.5 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H)

Synthesis of 1-(4-methoxybenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BO):

[00325] To a stirring solution of **6S-BN-2** (300 mg, 1.09 mmol) in THF/H_2O (2 mL/2 mL, 1:1) were added LiOH.H_2O (114 mg, 2.72 mmol) at RT and stirred for 6 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N* HCl and the precipitated solid was filtered. The obtained solid was triturated with *n*-pentane (2 mL), dried under reduced pressure to afford **6S-BO** (130 mg, 48%) as a white solid.

^{1}H-NMR(6S-BO): (500 MHz, DMSO-d_6): δ 12.85 (br s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.53 (s, 2H), 3.72 (s, 3H), 2.50 (s, 3H)

Scheme 6S- I-18:



Synthesis of 1-(azidomethyl)-4-methylbenzene (6S-BP):

[00326] To a stirring solution of 1-(bromomethyl)-4-methylbenzene (1 g, 5.40 mmol) in dimethyl formamide (15 mL) was added sodium azide (878 mg, 13.51 mmol) at RT under inert atmosphere. The resultant reaction mixture was stirred at 100 °C for 12 h. After completion of reaction monitored (by TLC), the reaction mixture was allowed to RT; the volatiles were

diluted with water (100 mL) and ethyl acetate (2 x 100 mL). The separated organic layer was washed by (3x200 mL) of chilled water and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **6S-BP** (700 mg, crude) as brown syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.26-7.20 (m, 4H), 4.37 (s, 2H), 2.30 (s, 3H);

IR: 2097cm^{-1}

Synthesis of ethyl 5-methyl-1-(4-methylbenzyl)-1H-1, 2, 3-triazole-4-carboxylate (6S-BQ-1 & 6S-BQ-2):

[00327] To a stirring solution of **6S-AS** (4.72 g, 42.5 mmol) in toluene (30 mL) was added **6S-BP** (2.5 g, 17.0 mmol) at RT under inert atmosphere. The resultant reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was allowed to RT; the volatiles were evaporated under reduced pressure to which, crude residue was purified by column chromatography by eluting 50% EtOAc/hexane to afford **6S-BQ-1** (1.5 g, 33.7%) and **6S-BQ-2** (2 g, 45%) as a yellow sticky solid.

^{1}H-NMR(6S-BQ-2, confirmed by NOESY**):** (500 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.5 Hz, 2H), 7.05 (d, *J* = 8.0Hz, 2H), 5.48 (s, 2H), 4.40 (q, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H)

Synthesis of 5-methyl-1-(4-methylbenzyl)-1H-1, 2, 3-triazole-4-carboxylic acid (6S-BR):

[00328] To a stirring solution of **6S-BQ-2** (500 mg, 1.92 mmol) in THF/H_2O (10 mL/10 mL, 1:1) were added LiOH.H_2O (201 mg, 4.80 mmol) at RT and stirred for 6 h. After completion of reaction (by TLC), the volatiles were evaporated under reduced pressure. The residue was acidified with aqueous 2*N* HCl (pH~2) and the precipitated solid was filtered. The obtained solid was triturated with *n*-pentane (2 mL), dried under reduced pressure to afford **6S-BR** (350 mg, 78.8%) as a white solid.

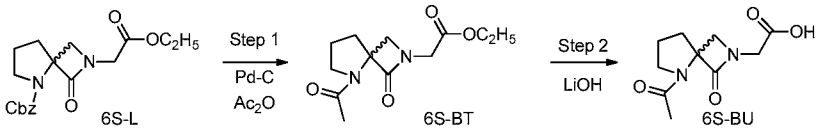
^{1}H-NMR(6S-BR): (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 2H), 2.48 (s, 3H), 2.33 (s, 3H);

LCMS m/z: 232.1 [M^++1]

Synthesis of 5-methyl-1-(4-methylbenzyl)-1H-1, 2, 3-triazole-4-carbonyl chloride (6S-BS):

[00329] To a stirring solution of **6S-BR** (250 mg, 1.08 mmol) in CH_2Cl_2 (10 mL), DMF (0.1 mL) were added oxalyl chloride (0.18 mL, 2.16 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride **6S-BS** (250 mg, crude).

Scheme 6S- I-19:



Synthesis of ethyl 2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetate (6S-BT):

[00330] To a stirring solution of 6S-L (12.5 g, 36 mmol) in EtOAc (100 mL) were added acetic anhydride (7.36 g, 72.2 mmol), 50% wet 10% Pd/C (5.0 g) and stirred under H_2 atmosphere (balloon pressure) for 4 h at RT. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to afford 6S-BT (8.0 g, 87.9%) as yellow syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ4.21 (s, 1H), 4.17 (s, 1H), 4.14-4.12 (m, 1H), 3.82 (s, 1H), 3.68 (d, J = 4.8 Hz, 1H), 3.56-3.51 (m, 1H), 3.46-3.43 (m, 1H), 3.29 (d, J = 4.8 Hz, 2H), 2.11-2.09 (m, 1H), 1.97 (s, 2H), 1.90-1.89 (m, 3H), 1.20 (t, J = 7.2 Hz, 3H).

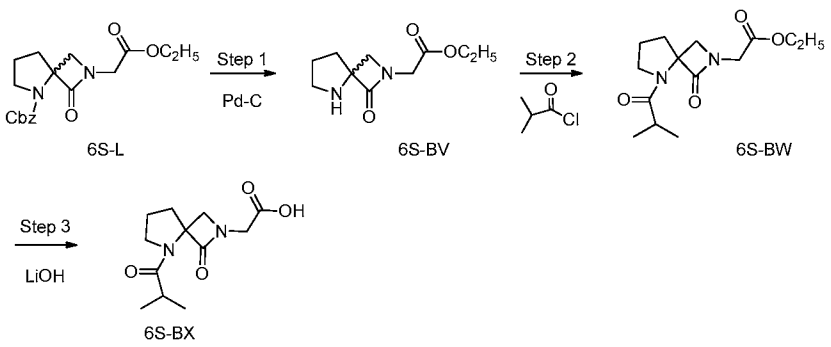
2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetic acid (6S-BU):

[00331] To a stirred solution of **6S-BT** (8.0 g, 31.49 mmol) in THF: H_2O (80 mL/30 mL) were added LiOH.H_2O (3.30 g, 78.7 mmol) at RT and stirred for 2 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (25 mL), extracted with ether (2x50 mL).The separated aqueous layer was acidified to pH~2 using 2N HCl and extracted with 5% MeOH/DCM (3x50 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6S-BU** (6.5 g, 91.5%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ12.5 (br s, 1H), 4.12 (s, 1H), 3.70 (s, 1H), 3.66-3.64 (m, 2H), 3.53-3.51 (m, 2H), 3.53-3.51 (m, 2H), 3.42 (d, J = 7.0 Hz, 1H), 2.73- 2.63 (m,2H), 2.10-2.07 (m, 1H);

LCMS m/z: 227.2 [M^++1]

Scheme 6S- I-20:



Synthesis of ethyl 2-(1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetate (6S-BV):

[00332] To a stirring solution of 6S-L (3.8 g, 10.98 mmol) in methanol (50 mL) was added 50% wet 10% Pd/C (800 mg) and stirred under H_2 atmosphere (balloon pressure) for 2 h at RT. The reaction mixture was filtered through a pad of celite and triturated with methanol (50 mL). The filtrate was concentrated under reduced pressure to afford 6S-BV (2 g, 86.2%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ4.11-3.92 (m, 4H), 3.40-3.26 (m, 4H), 1.94-1.91 (m, 2H), 1.75-1.67 (m, 2H), 1.91 (t, J = 7.5 Hz, 3H);

Synthesis of ethyl 2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetate (6S-BW):

[00333] To a stirring solution of **6S-BV** (2.0 g, 9.43 mmol) in CH_2Cl_2 (20 mL) was added TEA (3.25 mL, 23.58 mmol) followed by isobutyryl chloride (1.07 mL, 14.14 mmol) at 0 °C and stirred for 3 h at RT. After the reaction was completed, the reaction mass was diluted with water (30 mL). The separated organic layer was washed by brine solution (1 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6S-BW** (2.4 g, crude) as thick syrup. This material was directly used for the next step without further purification.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 4.20 (s, 2H), 4.14-4.08 (m, 1H), 3.80-3.76 (m, 1H), 3.62-3.57 (m, 2H), 3.51-3.46 (m, 2H), 2.68-2.63 (m, 1H), 2.09-2.05 (m, 2H), 1.89-1.85 (m, 2H), 1.21-1.16 (m, 3H), 1.03-0.95 (m, 6H);

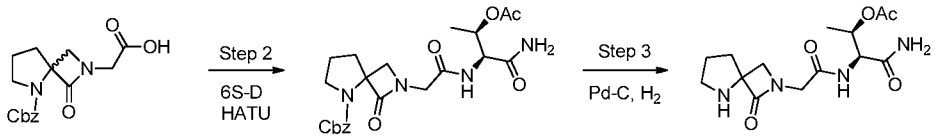
Synthesis of 2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetic acid (6S-BX):

[00334] To a stirred solution of **6S-BW** (2.4 g (crude), 8.51 mmol) in THF: H_2O (20 mL/20 mL) were added LiOH.H_2O (893 mg, 21.27 mmol) at RT and stirred for 4 h. After consumption of the starting material (by TLC), the volatiles were evaporated under reduced pressure. The residue was diluted with water (20 mL) and washed with EtOAc (1 x 50 mL). The separated aqueous layer was acidified to pH~4 using citric acid and extracted with EtOAc

(2 x 50 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6S-BX** (1.2 g, 57%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.83 (br s, 1H), 4.13(s, 2H), 3.70-3.46 (m, 4H), 2.70-2.64 (m, 1H), 2.10-2.06 (m, 2H), 1.91-1.85 (m, 2H), 1.01-0.96 (m, 6H)

Scheme 6S-1:



Synthesis of benzyl 2-(2-(((2R, 3S)-3-acetoxy-1-amino-1-oxobutan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-FNL-2):

[00335] To a stirred solution of **6S-M** (0.1 g, 0.31 mmol) in DMF (2 mL) was added HATU (141 mg, 0.37 mmol) followed by **6S-D** (59 mg, 0.37 mmol) and DIPEA (0.14 mL, 0.37 mmol). The resultant reaction mixture was allowed to warm to RT and stirred for 10 h. It was quenched with water and extracted with EtOAc (2 x 20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography afforded **(6S-FNL-2)** (30 mg, 21%).

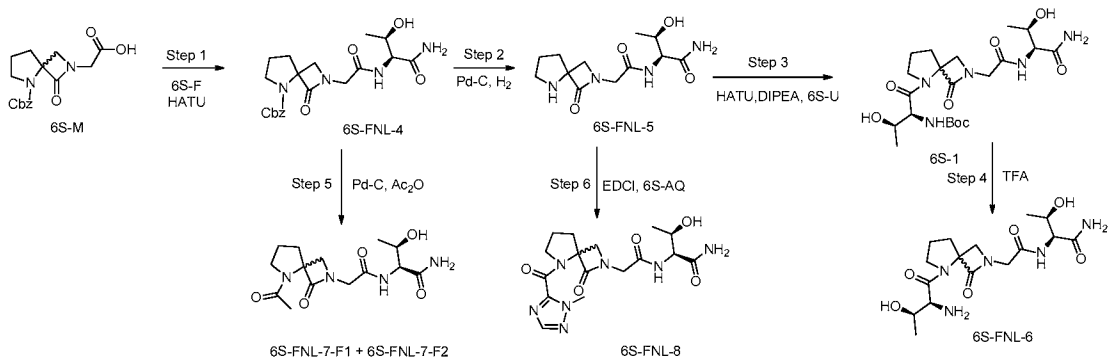
^{1}H-NMR: (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 2H), 5.55-5.49 (m, 1H), 5.43-5.39 (m, 1H), 5.34 (s, 2H), 4.79-4.76 (m, 1H), 4.39-4.11 (m, 1H), 3.94-3.89 (m, 2H), 3.84-3.70 (m, 1H), 3.62-3.53 (m, 1H), 2.41-2.36 (m, 1H), 2.23-2.15 (m, 1H), 2.08 (s, 3H), 2.02-1.88 (m, 2H), 1.35-1.22 (m, 3H)

Synthesis of (2*R*, 3*S*)-4-amino-4-oxo-3-(2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido) butan-2-yl acetate (6S-FNL-3):

[00336] To a stirred solution of **(6S-FNL-2)** (0.4 g, 0.86 mmol) in MeOH (20 mL) was added 10% Pd/C (0.1 g) under inert atmosphere. The resulting reaction mixture was agitated under H_2 atmosphere (balloon pressure) for 4 h at RT. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude was triturated with ether to afford **(6S-FNL-3)** (0.2 g, 70%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ8.04 (s, 1H), 7.54 (br s, 1H), 7.18 (s, 2H), 5.18-5.12 (m, 1H), 4.48-4.42 (m, 1H), 3.98-3.92 (m, 2H), 3.41-3.37 (m, 1H), 3.29-3.26 (m, 1H), 2.92-2.87 (m, 2H), 1.98-1.87 (m, 5H), 1.77-1.72 (m, 2H), 1.18-1.12 (m, 3H).

Scheme 6S-2:



Synthesis of Benzyl 2-(2-((1-amino-3-hydroxy-1-oxobutan-2-yl) amino)-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-FNL-4):

[00337] To a stirring solution of **6S-M** (0.1 g, 0.31 mmol) in DMF (2 mL) were added **6S-F** (55 mg, 0.47 mmol), DIPEA (96.87 mg, 0.78 mmol), HATU (143 mg, 0.37 mmol) at 0 °C and under inert atmosphere. The resultant reaction mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with ice cold water and extracted with EtOAc (2 x 20 mL). The organic layer was washed with water followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography affords **(6S-FNL-4)** (40 mg, 30%).

^{1}H-NMR: (400 MHz, $CDCl_3$): δ 8.09-7.36 (m, 1H), 7.35-7.33 (m, 5H), 6.60 (br s, 1H), 5.37 (br s, 1H), 5.09 (s, 2H), 4.56-4.39 (m, 3H), 4.13-3.99 (m, 1H), 3.70-3.51 (m, 4H), 3.48-3.39 (m, 1H), 2.43-2.39 (m, 1H), 2.27-2.21 (m, 1H), 2.07-1.91 (m, 1H), 1.59-1.42 (m, 1H), 1.28-1.20 (m, 3H)

Synthesis of (2*S*, 3*R*)-3-hydroxy-2-(2-(1-oxo-2,5-diazaspiro[3.4]octan-2-yl) acetamido) butanamide (6S-FNL-5):

[00338] To a stirring solution of **(6S-FNL-4)** (0.2 g, 0.47 mmol) in MeOH (10 mL) was added 10% Pd/C (40 mg) under inert atmosphere. The resulting reaction mixture was agitated under H_2 atmosphere (balloon pressure) for 4 h at RT. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude was triturated with ether to afford **(6S-FNL-5)** (0.11 g, 83%).

^{1}H-NMR: (400 MHz, CD_3OD): δ 4.23-4.21 (m, 1H), 4.20-4.10 (m, 1H), 4.05 (s, 2H), 3.53-3.47 (m, 2H), 3.12-3.00 (m, 2H), 2.22-2.07 (m, 2H), 2.01-1.82 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H)

UPLC (ELSD purity): 99.9%

Synthesis of *tert*-butyl ((2*S*, 3*R*)-1-(2-(2-(((2*S*, 3*R*)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octan-5-yl)-3-hydroxy-1-oxobutan-2-yl) carbamate (6S-1):

[00339] To a stirring solution of **(6S-FNL-5)** (300 mg, 1.05mmol) in DCM (25 mL), DMF (0.5 mL) were added *N, N*-diisopropylethylamine (0.58 mL, 3.15 mmol), **6S-U** (277 mg, 1.26mmol), followed by HATU (481 mg, 1.26mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 6% MeOH/DCM to afford crude (400mg, 70% pure by LCMS), further purified by preparative chromatography to yield pure **6S-1** (230 mg, 44.9% yield) as an off-white solid.

Preparative column: Kromasil 250x21.2, 10µm

Mobile phase: n-Hexane: [DCM: MeOH (80:20)]

^{1}H-NMR: (500 MHz, DMSO-d_6): δ7.83 (d, J = 8.5 Hz, 1H), 7.25 (s, 2H), 6.33 (d, J = 9.0 Hz, 1H), 4.80-4.75 (m, 2H), 4.24-3.98 (m, 4H), 3.71-3.60 (m, 3H), 3.39-3.33 (m, 1H), 2.14-1.89 (m, 4H), 1.41 (s, 9H), 1.14-1.05 (m, 6H);

LCMS m/z: 486.3 [M^++1]

Synthesis of (2*S*, 3*R*)-2-(2-(5-((2*S*, 3*R*)-2-amino-3-hydroxybutanoyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-3-hydroxybutanamide (6S-FNL-6):

[00340] To a stirring solution of compound **6S-1** (130 mg, 0.26 mmol) in DCM (3 mL) was added TFA (152 mg, 1.34 mmol) at 0 °C and stirred at RT for 2 h. After completion of starting material (by TLC), the reaction mixture was concentrated under reduced pressure and co-distilled with a mixture of solvents pentane (2 mL), diethyl ether (2 mL), DCM (1 mL) to afford **(6S-FNL-6)** (110 mg, 82.7% LCMS purity 93.32%) as white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ4.33-4.28 (m, 1H), 4.23-4.19 (m, 4H), 4.05-4.01 (m, 1H), 3.91-3.87 (m, 1H), 3.71-3.65 (m, 2H), 3.55-3.49 (m, 1H), 2.30-2.24 (m, 2H), 2.02-1.97 (m, 2H), 1.27 (t, J = 4.0 Hz, 3H), 1.15 (t, J = 5.5 Hz, 3H);

LCMS m/z: 386.3 [M^++1]

(2S,3R)-2-(2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-3-hydroxy butanamide (6S-FNL-7):

[00341] To a stirring solution of **(6S-FNL-4)** (1 g, 2.39 mmol) in EtOAc (50 mL) was added acetic anhydride (0.48 g, 4.78 mmol) followed by Pd/C (0.5 g) under N_2 atmosphere.

The reaction mixture was stirred at RT for 16 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with EtOAc (20mL). Obtained filtrate was concentrated under reduced pressure to afford crude compound was purified by column chromatography. The obtained mixture of compound was purified by chiral preparative HPLC to afford **(6S-FNL-7-F1)** in fraction-I (0.075 g), **(6S-FNL-7-F2)** in fraction-II (0.062 g) as off-white solids.

^{1}H-NMR (Fr-I): (400 MHz, DMSO-d_6): δ7.87 (d,J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 4.84 (d, J = 7.2 Hz, 1H), 4.10-4.03 (m, 2H), 3.96 (s, 2H), 3.79 (d, J = 5.2 Hz, 1H), 3.61-3.56 (m, 1H), 3.51-3.45 (m, 2H), 2.19-2.15 (m, 2H), 2.00 (s, 3H), 1.92-1.87 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H).

LCMS m/z: 327.3 [M^++1].

HPLC Purity: Fr-I (91.20%), Fr-II (97.03%)

^{1}H-NMR (Fr-II): (400 MHz, DMSO-d_6): δ7.85 (d,J = 8.4 Hz, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.09-4.06 (m, 2H), 3.97 (s, 2H), 3.70 (d, J = 4.8 Hz, 1H), 3.60-3.55 (m, 1H), 3.51-3.45 (m, 2H), 2.18-2.13 (m, 2H), 1.99 (s, 3H), 1.92-1.85 (m, 2H), 1.05 (d, J = 6.4Hz, 3H);

LCMS m/z: 327.4 [M^++1]

HPLC Purity: Fr-II 97.03%

(*2S,3R*)-3-hydroxy-2-(2-(5-(1-methyl-1*H*-1,2,4-triazole-5-carbonyl)-1-oxo-2,5-diazaspiro [3.4]octan-2-yl)acetamido)butanamide (6S-FNL-8):

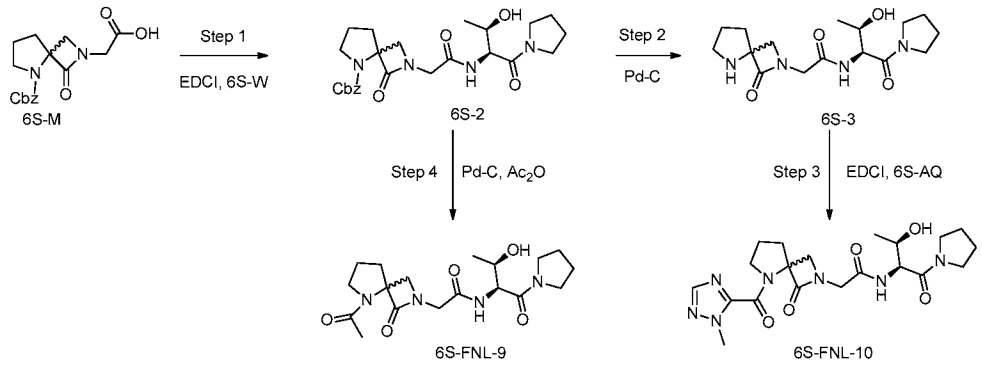
[00342] To a stirring solution of (NRX-2079) (6S-FNL-5) (0.25 g, 0.88 mmol) in CH_2Cl_2 (20 mL) was added HOBt (178 mg, 1.32 mmol), EDCI.HCl (0.2 g, 1.00 mmol) followed by DIPEA (0.4 mL, 2.20 mmol) and 6S-AQ (134mg, 1.05 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography followed by prep-HPLC purification to afford NRX-2310 (6S-FNL-8) (0.07 g, 21%).

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.89 (t, 1H), 7.25 (d, 1H), 7.12 (t, 1H), 4.93 (s, 1H), 4.19-4.15 (m, 2H), 4.03 (s, 3H), 3.96-3.91 (m, 4H), 3.44 (d, 1H), 2.25-2.20 (m, 3H), 1.97-1.91 (m, 2H), 1.07 (s, 3H).

LCMS (m/z):394.2[M^++1]

HPLC Purity: 93%

Scheme 6S-3:



Benzyl 2-(2-(((*2S, 3R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl) butan-2-yl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-2):

[00343] To a stirring solution of **6S-M** (1 g, 3.14 mmol) in CH_2Cl_2 (50 mL) was added EDCI (719 mg, 3.76 mmol), HOBt (635 mg, 4.71 mmol) followed by DIPEA (2.8 mL, 15.7 mmol) and 6S-W (784 mg, 3.77 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction was quenched with water and extracted with CH_2Cl_2 (2x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography to afford **6S-2** (0.8 g, 54%).

LCMS (m/z):473.4 [M^++1]

***N*-((2*S*,3*R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)-2-(1-oxo-2,5-diazaspiro[3.4] octan-2-yl)acetamide (6S-3):**

[00344] To a stirring solution of **6S-2** (0.8 g, 1.69 mmol) in CH_3OH (60 mL) was added Pd/C (0.4 g) under N_2 atmosphere. The reaction mixture was stirred at RT for 4 h under H_2atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with MeOH. Obtained filtrate was concentrated under reduced pressure to afford **6S-3** (0.5 g) as crude. This material was directly used for the next step without further purification.

LCMS (m/z):339.3 [M^++1]

***N*-((2*S*,3*R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)-2-(5-(1-methyl-1*H*-1,2,4-triazole-5-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-FNL-9):**

[00345] To a stirring solution of 6S-3 (0.315 g, 2.48 mmol) in CH_2Cl_2 (60 mL) was added EDCI.HCl (336 mg, 1.76 mmol), HOBt (297 mg, 2.20 mmol), DIPEA (0.67 mL, 3.67 mmol) and 6S-AQ (0.5 g, 1.47 mmol) 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 DCM and washed with water. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. This material was purified by column chromatography followed by prep-HPLC purification to afford **(6S-FNL-9)**: (80 mg, 12%).

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.09 (s, 1H), 4.55-4.51 (m, 1H), 4.08 (d, 2H), 3.97 (s, 2H), 3.87-3.84 (m, 3H), 3.70-3.55 (m, 2H), 3.45 (t, 1H), 3.35-3.31 (m, 2H), 2.75 (s, 3H), 2.27-2.24 (m, 2H), 1.98-1.92 (m, 4H), 1.85-1.84 (m, 2H), 1.19 (d, 3H).

LCMS (m/z):448[M^++1]

HPLC Purity: 94%

Synthesis of 2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)-N-((2*S*,3*R*)-3-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)acetamide (6S-FNL-10):

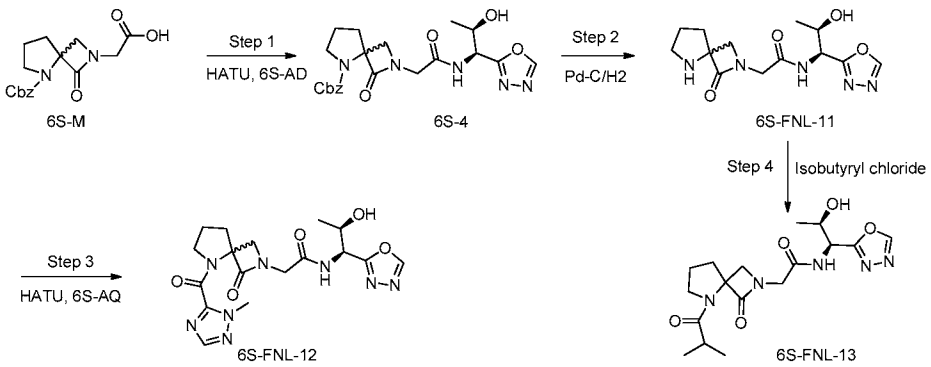
[00346] To a stirring solution of **6S-2** (300 mg, 0.63 mmol) in EtOAc (20 mL) was added acetic anhydride (0.13 g, 1.27 mmol) followed by Pd/C (150 mg) under N_2 atmosphere. The reaction mixture was stirred at RT for 16 h under H_2 atmosphere. After consumption of the starting material (by TLC), the reaction mixture was filtered through a pad of celite and washed with EtOAc (20 mL). Obtained filtrate was concentrated under reduced pressure to afford crude compound was purified by column chromatography by eluting with 2% MeOH/DCM to afford **(6S-FNL-10)** (90 mg, 37.5%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.08 (t, J = 8.4 Hz, 1H), 4.83-4.75 (m, 1H), 4.44-4.38 (m, 1H), 3.93-3.83 (m, 3H), 3.72-3.67 (m, 1H), 3.64-3.57 (m, 3H), 3.55-3.46 (m, 1H), 3.29-3.23 (m, 3H), 2.13-2.09 (m, 2H), 2.07 (s, 3H), 1.98-1.82 (m, 4H), 1.79-1.73 (m, 2H), 1.11-0.98 (m, 3H);

LCMS m/z: 381.3 [M^++1];

HPLC Purity: 94.2%

Scheme 6S-4:



Synthesis of benzyl 2-(2-(((1S, 2R)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-4):

[00347] To a stirring solution of **6S-M** (600 mg, 4.19 mmol) in DCM (20 mL) were added *N, N*-diisopropylethylamine (1.93 mL, 10.4 mmol), **6S-AD** (1.60 g, 5.02 mmol), followed by HATU (1.91 g, 5.02 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 saturated $NaHCO_3$ solution (1x30 mL) followed by brine solution (1x20 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **6S-4** (600 mg, 33.3%) as pale yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.21 (s, 1H), 7.35-7.32 (m, 5H), 5.13 (d, J = 4.5 Hz, 1H), 5.13 (s, 2H), 5.09-5.00 (m, 1H), 4.12-3.94 (m, 2H), 3.70-3.33 (m, 6H), 2.16-2.11 (m, 4H), 1.08 (d, J = 6.5 Hz, 3H);

LCMS m/z: 444.5 [M^++1]

Synthesis of *N*-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (6S-FNL-11):

[00348] To a stirring solution of **6S-4** (600 mg, 1.35 mmol) in MeOH (10 mL) were added (50% wet) 10% Pd/C (200 mg) and stirred under H_2 atmosphere (balloon pressure) for 3 h at RT. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc/MeOH (10 mL/10 mL). The filtrate was concentrated under reduced pressure to afford **(6S-FNL-11)** (400 mg, crude) as yellow syrup.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.68 (s, 1H), 5.29-5.07 (m, 1H), 4.10-3.91 (m, 2H), 3.61 (d, J = 16.5 Hz, 1H), 3.40-3.31 (m, 1H), 3.16-2.93 (m, 2H), 2.02-1.91 (m, 2H), 1.80-1.76 (m, 2H), 1.32-1.28 (m, 1H), 1.24 (d, J = 6.5 Hz, 1H), 1.09 (d, J = 6.5 Hz, 3H);

LCMS m/z: 310.2 [M^++1];

Synthesis of*N*-((1*S*, 2*R*)-2-hydroxy-1-(1, 3, 4-oxadiazol-2-yl) propyl)-2-(5-(1-methyl-1H-1, 2, 4-triazole-5-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamide (6S-FNL-12):

[00349] To a stirring solution of **(6S-FNL-11)** (300 mg, 0.97 mmol) in DCM (30 mL) were added *N, N*-diisopropylethylamine (0.44 mL, 2.42 mmol), **6S-AQ** (147 mg, 1.16 mmol), followed by HATU (442 mg, 1.10 mmol) 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 give crude product, which was purified by column chromatography by 4% MeOH/DCM to afford yellow syrup was purified by preparative HPLC method purification to afford **(6S-FNL-12)** (80 mg, 19.7%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.52 (t, J = 8.0 Hz, 1H), 8.08 (s, 1H), 5.19-5.16 (m, 1H), 4.04 (s, 2H), 4.02 (s, 3H), 3.94-3.84 (m, 5H), 3.44-3.41 (m, 1H), 2.27-2.21 (m, 2H), 1.93-1.85 (m, 2H), 1.10-1.08 (m, 3H);

LCMS m/z: 419 [M^++1];

HPLC: 96.64%

Synthesis of *N*-((1*S*,2*R*)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)-2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-FNL-13):

[00350] To a stirred solution of **(6S-FNL-11)** (250 mg, 0.8 mmol) in DCM (20 mL) was added TEA (242 mg, 2.4 mmol) at 0 °C. After added isobutyryl chloride (102 mg, 0.96 mmol) slowly and the resulting reaction mixture was stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL).The organic layer was washed by citric acid (1 x 20 mL) followed by brine solution (1x20 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2followed by preparative HPLC purification to afford compound **(6S-FNL-13)** (80 mg, 26.3%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ9.19 (s, 1H), 8.64-8.57 (m, 1H), 5.17-5.13 (m, 1H), 5.12-5.08 (m, 1H), 4.17-4.09 (m, 2H), 3.84-3.76 (m, 1H), 3.70-3.64 (m, 2H), 3.57-3.51 (m, 1H), 3.37-3.34 (m, 1H), 2.77-2.70 (m, 1H), 2.17-2.05 (m, 2H), 1.90-1.79 (m, 2H), 1.13 (d, J = 6.0 Hz, 3H), 1.03-0.97 (m, 6H);

LCMS m/z: 380.4 [M^++1];

HPLC: 98.5% (both enantiomers)

Scheme 6S-5:

2-(5-acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)-N-((1S,2R)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)acetamide (6S-FNL-14):

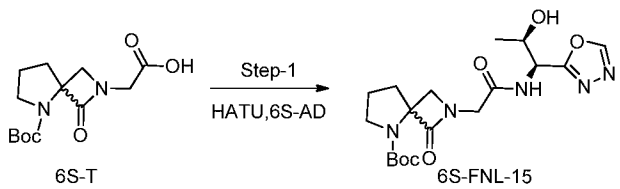
[00351] To a stirring solution of 6S-BU (200 mg, 1.39 mmol) in DCM (10 mL) were added *N,N*-diisopropylethylamine (0.64 mL, 3.47 mmol), **6S-AD** (5.95 g, 37.7 mmol), followed by HATU (637 mg, 1.68 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography by 8% MeOH/DCM to afford yellow syrup was purified by preparative HPLC method purification to afford **(6S-FNL-14)** (100 mg, 20.4%) as colorless liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ9.18 (d, J = 3.6 Hz, 1H), 8.54 (t, J = 7.6 Hz, 1H), 5.15-5.06 (m, 2H), 4.16-4.12 (m, 1H), 4.05 - 4.00 (m, 1H), 3.89-3.82 (m, 1H), 3.72 (t, J = 5.6 Hz, 1H), 3.61-3.56 (m, 1H), 3.51-3.45 (m, 1H), 3.37-3.33 (m, 1H), 2.18-2.08 (m, 2H), 2.02 (s, 3H), 1.93-1.90 (m, 2H), 1.10 (t, J = 6.4 Hz, 3H)

LCMS *m/z*: 352.3 [M^++1];

UPLC: 47.2%&44.3%

Scheme 6S-6:



Synthesis of tert-butyl 2-(2-(((1*S*,2*R*)-2-hydroxy-1-(1,3,4-oxadiazol-2-yl)propyl)amino)-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-FNL-15):

[00352] To a stirring solution of **6S-T** (500 mg, 1.76 mmol) in DCM (20 mL) were added DIPEA (0.88 mL, 5.1 mmol), **6S-AD** (302 mg, 2.11 mmol) followed by HATU (801 mg, 2.11 mmol)at 0 °C and stirred for 12 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 saturated $NaHCO_3$ solution (1 x 20 mL) followed by brine solution (1 x 20 mL).

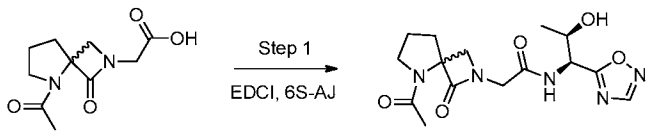
The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford **(6S-FNL-15)** (220 mg, 31.6%) as sticky syrup.

^{1}H-NMR: (400 MHz, D_2O): δ8.99 (s, 1H), 5.46-5.38 (m, 1H), 4.80 (s, 2H), 4.56-4.43 (m, 1H), 4.14-3.93 (m,1H), 3.64-3.46 (m, 3H), 2.38-2.34 (m, 2H), 2.00-1.96 (m, 2H), 1.50 (s, 9H), 1.34 (d, J = 6.0 Hz, 3H);

LCMS *(m/z):* 410.6 [M^++1];

HPLC: 92.4%

Scheme 6S-7:



6S-BU 6S-FNL-16

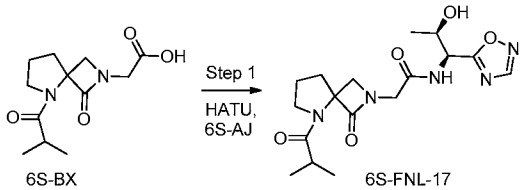
2-(5-Acetyl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)-N-((1S,2R)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl)propyl)acetamide (6S-FNL-16):

[00353] To a stirring solution of **6S-BU** (0.5 g, 2.21 mmol) in CH_2Cl_2 (20 mL) was added EDCI (0.63 g, 3.31 mmol), HOBT (0.44 g, 3.31 mmol) and 6S-AJ (0.37 g, 2.65 mmol) followed by DIPEA (1.4 g, 10.85 mmol) at 0 °C. The reaction mixture was stirred at RT for 12 h. After consumption of the starting material (by TLC), the reaction was diluted with water and extracted with CH_2Cl_2 (2x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography by eluting 2% MeOH: DCM to afford **(6S-FNL-16)** (0.09 g, 12%) as yellow liquid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.94 (s, 1H), 8.61 (t,J = 8.4 Hz, 1H), 5.23-5.20 (m, 1H), 5.16-5.09 (m, 1H), 4.20-4.01 (m, 1H), 3.91-3.85 (m, 1H), 3.73-3.71 (m, 1H), 3.65 (s, 1H), 3.59-3.57 (m, 1H), 3.49-3.34 (m, 1H), 2.16-2.09 (m, 2H), 2.05 (s, 3H), 1.98-1.89 (m, 3H), 1.13-1.11 (m, 3H).

LCMS *m/z*: 352.2 [M^++1]

Scheme 6S-8:



6S-BX 6S-FNL-17

Synthesis ofN-((1*S*,2*R*)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl)propyl)-2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-FNL-17):

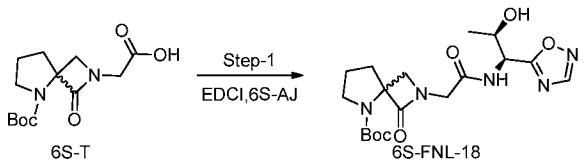
[00354] To a stirring solution of **6S-BX** (500 mg, 1.96 mmol) in DMF (5 mL) were added *N, N*-diisopropylethylamine (1.15 mL, 6.86 mmol), 6S-AJ (604 mg, 2.35 mmol) followed by HATU (893 mg, 2.35 mmol) at 0 °C and stirred at RT for 12 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (50 mL) and EtOAc (50 mL). The separated organic layer was washed with citric acid solution (1 x 100 mL), brine solution (2 x 50 mL) followed by water (2 x 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography by 2% MeOH/DCM to afford **(6S-FNL-17)** (128 mg, 17.2%) as sticky solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.94 (s, 1H), 8.68-8.60 (m, 1H), 5.22-5.10 (m, 2H), 4.20-4.07 (m, 2H), 3.86-3.79 (m, 1H), 3.71-3.65 (m, 2H), 3.58-3.51 (m, 1H), 3.38-3.34 (m, 1H), 2.77-2.66 (m, 1H), 2.15-1.91 (m, 4H), 1.14 (d, J = 4.0 Hz, 3H), 1.03-0.97 (m, 6H);

LCMS *m/z*: 380.4 [M^++1];

UPLC: 94.01%

Scheme 6S-9:



Synthesis of tert-butyl 2-(2-(((1*S*,2*R*)-2-hydroxy-1-(1,2,4-oxadiazol-5-yl)propyl)amino)-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-FNL-18):

[00355] To a stirring solution of **6S-T** (1 g, 3.51 mmol) in DMF (10 mL) were added DIPEA (1.75 mL, 10.53 mmol), EDCI (1.0 g, 5.26 mmol), HOBT (710 mg, 5.26 mmol) followed by **6S-AJ** (602 mg, 4.21 mmol) at 0 °C and stirred for 16 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (15 mL). The separated organic layer was washed with brine solution (1 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford **(6S-FNL-18)** (150mg, 10.5%) as thick syrup.

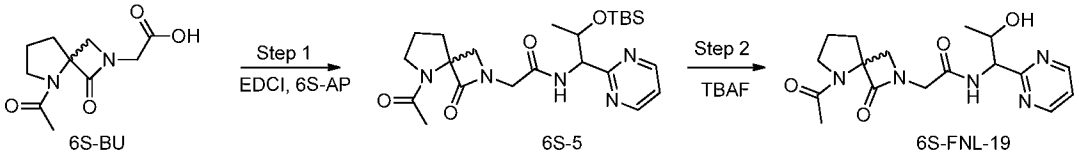
^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.95 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 5.25 (d, J = 4.8 Hz, 1H), 5.19-5.10 (m, 1H), 4.21-4.17 (m, 2H), 3.86-3.80 (m, 1H), 3.71-3.67 (m,1H), 3.55 (t, J =

4.4 Hz, 2H), 3.27-3.23 (m, 1H), 2.13-2.08 (m, 2H), 1.82-1.74 (m, 2H), 1.39 (s, 9H), 1.10 (d, *J* = 6.4 Hz, 3H);

Mass (ESI): *m/z* 432.4 [M^++Na];

HPLC:98.35% (both isomers)

Scheme 6S-10:



6S-BU 6S-5 6S-FNL-19

2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-*N*-(2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) acetamide (6S-5):

[00356] To a stirring solution of **6S-BU** (400 mg, 1.77 mmol) in DCM (20 mL) were added *N, N*-diisopropylethylamine (0.9 mL, 5.32 mmol), 6S-AP (474 mg, 1.77 mmol), EDCI.HCl (509 mg, 2.66 mmol), HOBT (410 mg, 2.66 mmol) 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 give crude product, which was purified by column chromatography by 4% MeOH/DCM to afford **6S-5** (300 mg, 35%) as colorless thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.78 (d, *J* = 16.0 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 16.0 Hz, 1H), 4.88 (t, *J* = 8.0 Hz, 1H), 4.37 (d, *J* = 8.0 Hz, 1H), 3.90 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 2H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.63-3.57 (m, 1H), 3.49-3.43 (m, 1H), 3.13 (d, *J* = 9.0 Hz, 1H), 2.13-2.10 (m, 2H), 2.01 (s, 3H), 1.16 (d, *J* = 5.5 Hz, 3H), 0.64 (s, 9H), 0.06 (s, 6H); **LCMS** m/z: 474.6 [M^+-1]

Synthesis of 2-(5-acetyl-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)-*N*-((1*R*, 2*R*)-2-hydroxy-1-(pyrimidin-2-yl) propyl) acetamide (6S-FNL-19):

[00357] To a stirring solution of **6S-5** (300 mg, 0.63 mmol) in THF (20 mL) was added TBAF (1.26 mL) slowly at 0° C and stirred at RT for 2 h. After completion of reaction (by TLC), the reaction mixture was evaporated to give crude product, which was purified by column chromatography eluting 4% MeOH/DCM to afford mixture (110 mg) of isomers again purified by chiral preparative HPLC method purification to afford **(6S-FNL-19)** (60 mg, 26%) as colorless liquid.

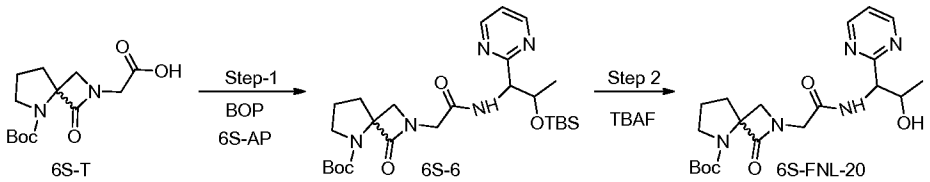
^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.76 (t, *J* = 6.0 Hz, 2H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 4.8 Hz, 1H), 4.91-4.79 (m, 2H), 4.15-4.10 (m, 1H), 3.92-3.78 (m, 2H), 3.67 (d, *J* = 4.8 Hz,

1H), 3.60-3.54 (m, 1H), 3.49-3.31 (m, 2H), 2.13-2.11 (m, 2H), 2.09 (s, 3H), 2.08-1.87 (m, 2H), 1.09 (d, J = 6.4 Hz, 3H);

LCMS *m/z*: 362.4 [M^++1];

HPLC: 97.5%

Scheme 6S-11:



Synthesis of tert-butyl 2-(2-((2-((tert-butyldimethylsilyl) oxy)-1-(pyrimidin-2-yl) propyl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-6):

[00358] To a stirring solution of **6S-T** (300 mg, 1.05 mmol) in DCM (20 mL) were added DIPEA (0.55 mL, 3.16 mmol), **6S-AP** (338 mg, 1.26 mmol) followed by BOP (696 mg, 1.57 mmol) at 0 °C and stirred for 12 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (15 mL). The separated organic layer was washed with brine solution (1 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford **6S-6** (150 mg, 26%) as sticky syrup.

LCMS ***(m/z):*** 534.7 [M^++1]

Synthesis of tert-butyl 2-(2-((2-hydroxy-1-(pyrimidin-2-yl) propyl) amino)-2-oxoethyl)-1-oxo-2, 5-diazaspiro [3.4] octane-5-carboxylate (6S-FNL-20):

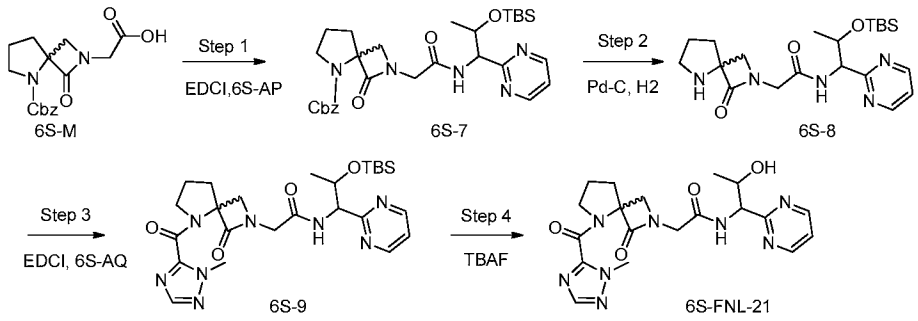
[00359] To a stirring solution of **6S-6** (300 mg, 0.56 mmol) in THF (10 mL) was added TBAF (1M in THF) (1.11 mL, 1.12 mmol) at 0 °C under N_2 atmosphere and stirred at RT for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to obtain crude residue which was diluted with water (10 mL) and EtOAc (20 mL). The separated organic layer was washed with brine solution (1 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude compound which was purified by preparative HPLC purification to obtained **(6S-FNL-20)** (40 mg, 17%) as white solid.

^{1}H-NMR: (400 MHz, CD_3OD): 8.79-8.72 (m, 2H), 7.39-7.34 (m, 1H), 5.13-5.08 (m, 1H), 4.81-4.70 (m, 1H), 4.50-4.40 (m, 1H), 4.35-4.21 (m, 1H), 3.91-3.75 (m, 2H), 3.48-3.37 (m, 3H), 2.33-2.22 (m, 2H), 1.97-1.85 (m, 2H), 1.41 (s, 9H), 1.18-1.16 (m, 3H);

LCMS *(m/z):* 420.5 [M^++1];

HPLC: 99.3%

Scheme 6S-12:



Synthesis of benzyl 2-(2-((2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)amino)-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-7):

[00360] To a stirring solution of **6S-M** (1.3 g, 4.08 mmol) in DCM (30 mL) were added *N, N*-diisopropylethylamine (2.1 mL, 12.2 mmol), **6S-AP** (1.09 g, 4.08 mmol) followed by EDCI.HCl (1.1 g, 6.13 mmol) HOBT (938 mg, 6.13 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 (30 mL). The separated organic layer was washed with brine solution (1 x 50 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude which was purified by column chromatography by eluting 4% MeOH/DCM to obtained **6S-7** (1.5 g, 65%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.80-8.74 (m, 2H), 7.39-7.34 (m, 6H), 5.09 (s, 2H), 4.93 (t, J = 4.8 Hz, 1H), 4.38-4.19 (m, 1H), 4.05-3.68 (m, 2H), 3.49-3.39 (m, 4H), 2.20-2.11 (m, 2H), 1.86-1.85 (m, 2H), 1.19-1.10 (m, 4H), 0.65 (s, 9H), -0.07 (s, 3H), -0.03 (s, 3H);

LCMS m/z: 568 [M^++1]

Synthesis of *N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-2-(1-oxo-2, 5-diazaspiro [3.4] octan-2-yl)acetamide (6S-8):

[00361] To a stirring solution of **6S-7** (500 mg, 0.88 mmol) in EtOAc (25 mL) was added (50% wet) 10% Pd/C (250 mg) and stirred under H_2 atmosphere (balloon pressure) at RT for 7 h. After completion of reaction (by TLC), the reaction mixture was filtered through a pad of celite and triturated with EtOAc (10 mL). The filtrate was concentrated under reduced pressure to afford **6S-8** (320 mg, crude) as yellow thick syrup. This compound was used directly for next step without any purification.

LCMS m/z: 434.5 [M^++1]

Synthesis of *N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-(pyrimidin-2-yl)propyl)-2-(5-(1-methyl-1H-1,2,4-triazole-5-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-9):

[00362] To a stirring solution of **6S-AQ** (93 mg, 0.73 mmol) in DCM (20 mL) were added *N, N*-diisopropylethylamine (0.4 mL, 2.21 mmol), **6S-8** (320 mg, 0.73 mmol), followed by EDCI.HCl (211 mg, 1.10 mmol), HOBT (170mg, 1.10 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 4% MeOH/DCM to afford **6S-9** (210 mg, crude) as yellow thick syrup. This compound was used directly for next step without any purification.

LCMS m/z: 543.5 [M^++1]

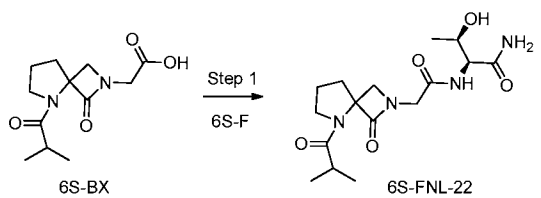
Synthesis of *N*-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-2-(5-(1-methyl-1H-1,2,4-triazole-5-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-FNL-21):

[00363] To a stirring solution of **6S-9** (210 mg crude, 0.38 mmol) in THF (5 mL) was added TBAF in THF (0.77 ml, 0.76 mmol) at 0 °C and stirred at RT for 3 h. After consumption of the starting material (by TLC), the reaction mixture was evaporated under reduced pressure and the obtained crude was purified by column chromatography by eluting 4% MeOH/DCM followed by preparative TLC to afford **(6S-FNL-21)** (70 mg, 42%) as yellow thick syrup.

^{1}H-NMR: (400 MHz, CD_3OD): δ8.75-8.70 (m, 2H), 7.95 (s, 1H), 7.36-7.30 (m,1H), 5.16-5.13 (m, 1H), 4.53 (s, 1H), 4.41-4.43 (m, 2H), 4.29-4.03 (m, 1H), 3.99 (s, 3H), 3.96-3.81 (m, 2H), 3.58-3.54 (m, 1H), 2.37-2.34 (m, 2H), 2.09-2.00 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H) ;

LCMS m/z: 429 [M^++1].

Scheme 6S-13:



Synthesis of (2*S*,3*R*)-3-hydroxy-2-(2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)butanamide (6S-FNL-22):

[00364] To a stirring solution of **6S-BX** (500 mg, 1.96 mmol) in DMF (3 mL) were added *N, N*-diisopropylethylamine (1.02 mL, 5.88 mmol), **6S-F** (277mg, 2.35 mmol) followed by HATU (893 mg, 2.35 mmol) at 0 °C and stirred at RT for 16 h. After consumption of the

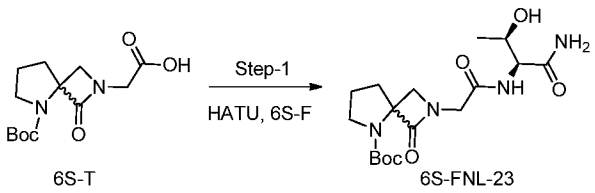
starting material (by TLC), the reaction mixture was quenched with brine solution (15 mL) and extracted with 10% MeOH/DCM (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography by 2% MeOH/DCM to afford **(6S-FNL-22)** (100mg, 14.4%) as white solid.

^{1}H-NMR: (400 MHz, D_2O): δ4.37-4.34 (m, 2H), 4.08-3.96 (m, 2H), 3.84-3.79 (m, 1H), 3.72-3.68 (m, 1H), 3.67-3.61 (m, 1H), 2.93-2.86 (m, 1H), 2.37-2.25 (m, 2H), 2.11-2.02 (m, 2H), 1.38-1.29 (m, 4H), 1.14-1.09 (m, 6H);

LCMS *m/z*: 355.5 [M^++1];

HPLC: 99.97%

Scheme 6S-14:



Synthesis of tert-butyl 2-(2-(((2*S*,3*R*)-1-amino-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1-oxo-2,5-diazaspiro[3.4]octane-5-carboxylate (6S-FNL-23):

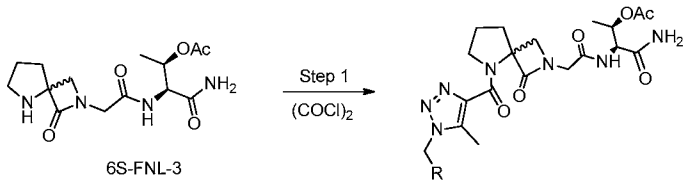
[00365] To a stirring solution of **6S-T** (2 g, 7.04 mmol) in DMF (10 mL) were added DIPEA (3.78 mL, 21.12 mmol), **6S-F** (997 mg, 8.44 mmol) followed by HATU (3.2 g, 8.44 mmol)at 0 °C and stirred for 16 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained crude material was purified by silica gel column chromatography eluting with 2% MeOH/DCM to afford **(6S-FNL-23)** (1.1 g, 40.7%) as white solid.

^{1}H-NMR: (400 MHz, D_2O): δ4.33-4.26 (m, 3H), 4.21-4.12 (m, 1H), 4.05-3.86 (m, 1H), 3.59-3.55 (m, 2H), 3.53-3.35 (m,1H), 2.33-2.27 (m, 2H), 1.97-1.90 (m, 2H), 1.46 (s, 9H), 1.25-1.22 (m, 3H);

Mass (ESI): *m/z* 383.4 [M^+-1];

HPLC:97.8% (both isomers)

Scheme 6S-15:



R=Ph : 6S-FNL-24 R=3-F Ph : 6S-FNL-28
R=2-F Ph : 6S-FNL-29 R=Cyclohexyl : 6S-FNL-30
R=Cyclopentyl : 6S-FNL-31 R=4-F Ph : 6S-FNL-25
R=4-OMe Ph : 6S-FNL-26 R=4-Me Ph : 6S-FNL-27

Synthesis of (2R, 3S)-4-amino-3-(2-(5-(1-benzyl-5-methyl-1H-1, 2, 3-triazole-4-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-4-oxobutan-2-yl acetate (6S-FNL-24):

[00366] To a stirring solution of **6S-AU** (4.0 g, 18.43 mmol) in CH_2Cl_2 (20 mL), DMF (0.1 mL) were added oxalyl chloride (3.34 mL, 36.86 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride. To a stirred solution of acid chloride in DCM (40 mL) was added **(6S-FNL-3)** (3.8 g, 11.65 mmol), *N, N*-diisopropylethylamine (6.44 mL, 37.04 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 2 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (2x 30 mL). Combined organic extracts were washed by $NaHCO_3$ (2x25 mL). The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-24)** (2.6 g, 42.5%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.87, 7.89 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H), 7.47 (d, J = 11.0 Hz, 2H), 7.38-7.31 (m, 2H), 7.17 (t, 3H), 5.63 (s, 2H), 5.20-5.16 (m, 1H), 4.43-4.41 (m, 1H), 4.24-4.14 (m, 1H), 4.02 (t, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.38-3.33 (m, 1H), 2.20-2.14 (m, 2H), 1.97 (s, 3H), 1.92-1.80 (m, 5H), 1.16 (t, J = 7.5 Hz, 3H)

LCMS m/z: 526.6 [M^++1];

HPLC: 51.34%&46.08% (enantiomers)

Synthesis of (2*R*, 3*S*)-4-amino-3-(2-(5-(1-(4-fluorobenzyl)-5-methyl-1H-1, 2, 3-triazole-4-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-4-oxobutan-2-yl acetate (6S-FNL-25):

[00367] To a stirring solution of **6S-BL** (100 mg, 0.42 mmol) in CH_2Cl_2 (5 mL), DMF (0.1 mL) were added oxalyl chloride (108 mg, 0.85 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in

presence of N_2 atmosphere to afford acid chloride (150 mg, crude). To a stirred solution of acid chloride (150 mg, 0.59 mmol, crude) in DCM (10mL) were added **(6S-FNL-3)** (193 mg, 0.59 mmol), *N, N*-diisopropylethylamine (229 mg, 1.77 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 8 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2x 20 mL). Combined organic extracts were washed by saturated NaHCO3 solution (2x30 mL) followed by citric acid solution (1 x 20 mL). The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-25)** (100 mg, 31.2%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ7.99 (dd, J = 8.4 Hz, 8.8 Hz, 1H), 7.48 (d, J = 9.6 Hz, 1H), 7.28-7.16 (m, 5H), 5.63 (s, 2H), 5.20-5.16 (m, 1H), 4.44-4.40 (m, 1H), 4.20 (d, J = 7.6 Hz, 1H), 3.92-3.81 (m, 3H), 3.39-3.29 (m, 2H), 2.50 (s, 3H), 2.22-2.15 (m, 2H), 1.92-1.86 (m, 2H), 1.81 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H);

LCMS *m/z*: 544.6 [M^++1];

HPLC: 97.6% (both enantiomers)

Synthesis of (2*R*,3*S*)-4-amino-3-(2-(5-(1-(4-methoxybenzyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-4-oxobutan-2-yl acetate (6S-FNL-26):

[00368] To a stirring solution of **6S-BO** (140 mg, 0.57 mmol) in CH_2Cl_2 (5 mL), DMF (0.2 mL) were added oxalyl chloride (0.1 mL, 1.14 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride (160 mg, crude). To a stirred solution of acid chloride (160 mg, crude) in DCM (10 mL) was added **(6S-FNL-3)** (186 mg, 0.57 mmol), *N, N*-diisopropylethylamine (220 mg, 1.71 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 1.5 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2x 30 mL). Combined organic extracts were washed by brine solution (2x 50 mL). The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 5% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-26)** (79 mg, 24%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ8.17 (t, J = 9.5 Hz, 1H), 7.42 (d, J = 18.8 Hz, 1H), 7.15 (d,J 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.55 (s, 2H), 5.17-5.16 (m, 1H), 4.46-4.45 (m, 1H), 3.99-

3.91 (m, 2H), 3.73 (s, 3H), 3.40-3.36 (m, 1H), 2.63(s, 3H), 2.40-2.36 (m, 2H), 2.21-2.14 (m, 2H), 1.98 (s, 3H), 1.96-1.92 (m, 2H), 1.40 (s, 2H), 1.12 (d, J = 6.0 Hz, 3H)

LCMS *m/z*: 556.6 [M^++1];

HPLC: 92.2% (both enantiomers)

Synthesis of (2*R*, 3*S*)-4-amino-3-(2-(5-(5-methyl-1-(4-methylbenzyl)-1H-1,2,3-triazole-4-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-4-oxobutan-2-yl acetate (6S-FNL-27):

[00369] To a stirred solution of **6S-BS** (250 mg, crude, 1 mmol) in DCM (10 mL) was added **(6S-FNL-3)** (391 mg, 1.2 mmol), *N, N*-diisopropylethylamine (387 mg, 3 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 8 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2x 30 mL). Combined organic extracts were washed by $NaHCO_3$ solution (2x 20 mL) followed by citric acid solution (2 x 20 mL). The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-27)** (100 mg, 18.5%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ7.97 (dd, J = 9.2 Hz, 9.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.17 (d,J = 8.0 Hz, 3H), 7.07 (d, J = 8.0 Hz, 2H), 5.58 (s, 2H), 5.20-5.14 (m, 1H), 4.44-4.40 (m, 1H), 4.25 (s, 2H), 3.92-3.80 (m, 3H), 3.38 (dd, J = 15.2 Hz, 14.8 Hz, 1H), 2.37(s, 3H), 2.27 (s, 3H), 2.20-2.15 (m, 2H), 1.92-1.86 (m, 2H), 1.81 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H)

LCMS *m/z*: 540.6 [M^++1];

HPLC: 98.3% (both enantiomers)

Synthesis of (2*R*,3*S*)-4-amino-3-(2-(5-(1-(3-fluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-4-oxobutan-2-yl acetate (6S-FNL-28):

[00370] To a stirred solution of **6S-AX** (170 mg, 0.72 mmol) in DCM (10 mL) were added **(6S-FNL-3)** (235 mg, 0.72 mmol), *N, N*-diisopropylethylamine (280 mg, 2.17mmol), HATU (547 mg, 1.44 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 18 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 30 mL). Combined organic extracts were washed by $NaHCO_3$ solution (1 x 20 mL), citric acid solution (1 x 20 mL) followed by brine solution (2 x 30 mL). The separated organic layers were dried over anhydrous Na_2SO_4 and

concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-28)** (185 mg, 47.3%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ7.95 (dd, J = 8.8 Hz, 8.4 Hz, 1H), 7.50-7.39 (m, 2H), 7.17 (t, J = 11.2 Hz, 2H), 7.01 (dd, J = 9.6 Hz, 7.6 Hz, 2H), 5.75 (s, 2H), 5.21-5.16 (m, 1H), 4.44-4.40 (m, 1H), 4.26-4.15 (m, 1H), 4.06-4.03 (m, 1H), 3.95-3.81 (m, 3H), 3.39-3.34 (m, 1H), 2.39 (s, 3H), 2.23-2.12 (m, 2H), 1.98 (s, 3H), 1.93-1.81 (m, 2H), 1.17 (d, J = 6.4 Hz, 3H);

LCMS *m/z*: 544.3 [M^++1];

HPLC: 97.4% (both enantiomers)

Synthesis of (2*R*,3*S*)-4-amino-3-(2-(5-(1-(2-fluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-4-oxobutan-2-yl acetate (6S-FNL-29):

[00371] To a stirring solution of **6S-BA** (100 mg, 0.42 mmol) in CH_2Cl_2 (5 mL), DMF (0.1 mL) were added oxalyl chloride (108 mg, 0.85 mmol) at 0° C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride (100 mg, crude). To a stirred solution of acid chloride (100 mg, 0.39 mmol, crude) in DCM (5 mL) were added **(6S-FNL-3)** (144 mg, 0.47 mmol), *N, N*-diisopropylethylamine (142 mg, 1.17 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 8 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2x 20 mL). Combined organic extracts were washed by saturated NaHCO3 solution (2x30 mL) followed by citric acid solution (1 x 20 mL. The separated organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-29)** (120 mg, 56.8%) as an off-white solid.

^{1}H-NMR: (400 MHz, DMSO-d_6): δ8.00-7.91 (m, 1H), 7.50-7.39 (m, 2H), 7.28-7.13 (m, 4H), 5.67 (s, 2H), 5.21-5.16 (m, 1H), 4.44-4.40 (m, 1H), 4.20 (d, J = 7.6 Hz, 2H), 3.90-3.81 (m, 3H), 3.39-3.34 (m, 1H), 2.50 (s, 3H), 2.22-2.15 (m, 2H), 1.92-1.86 (m, 2H), 1.82 (s, 3H), 1.20 (d, J = 6.4 Hz, 3H);

LCMS *m/z*: 544.6 [M^++1]; HPLC: 98.6% (both enantiomers)

Synthesis of (2*R*, 3*S*)-4-amino-3-(2-(5-(1-(cyclohexylmethyl)-5-methyl-1H-1, 2, 3-triazole-4-carbonyl)-1-oxo-2, 5-diazaspiro [3.4] octan-2-yl) acetamido)-4-oxobutan-2-yl acetate (6S-FNL-30):

[00372] To a stirred solution of **6S-BE** (200 mg (crude), 0.82 mmol) in DCM (10 mL) was added **(6S-FNL-3)** (270 mg, 0.82 mmol), *N, N*-diisopropylethylamine (320 mg, 2.48 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 8 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2x 30 mL). Combined organic extracts were washed by $NaHCO_3$ solution (1 x 20 mL), citric acid solution (1 x 20 mL) followed by brine solution (2x30 mL). The separated organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-30)** (86 mg, 19.7%) as an off-white solid.

^{1}H-NMR: (500 MHz, DMSO-d_6): δ 7.98 (dd, J = 8.8 Hz, 9.2 Hz, 1H), 7.47 (dd, J = 7.6 Hz, 1H), 7.16 (dd, J = 7.6 Hz, 10.0 Hz, 1H), 5.22-5.13 (m, 1H), 4.43-4.39 (m, 1H), 4.20-4.14 (m, 3H), 4.02-3.99 (m, 1H), 3.87 (t, J = 6.0 Hz, 4H), 2.48 (s, 3H), 2.20-2.11 (m, 2H), 2.42-2.30 (s, 1H), 1.88-1.85 (m, 2H), 1.82 (s, 3H), 1.64-1.59 (m, 4H), 1.48-1.45 (m, 2H), 1.27-1.11 (m, 4H), 0.84 (d, J = 6.8 Hz, 3H);

LCMS *m/z*: 532.6 [M^++1]; HPLC: 91.2% .

Synthesis of (2*R*,3*S*)-4-amino-3-(2-(5-(1-(cyclopentylmethyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamido)-4-oxobutan-2-yl acetate (6S-FNL-31):

[00373] To a stirring solution of **6S-BI** (250 mg, 1.19 mmol) in CH_2Cl_2 (10 mL), DMF (0.1 mL) were added oxalyl chloride (0.2 mL, 2.38 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. The volatiles were evaporated under reduced pressure in presence of N_2 atmosphere to afford acid chloride (300 mg, crude). To a stirred solution of acid chloride (300 mg, crude) in DCM (5 mL) was added **(6S-FNL-3)** (358 mg, 1.19 mmol), *N,N*-diisopropylethylamine (0.57 mL, 3.57 mmol) at 0 °C. The resulting reaction mixture was stirred at RT for 1 h. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). Combined organic extracts were washed by brine solution (2 x 10 mL) and dried over anhydrous Na_2SO_4 concentrated under reduced pressure to obtain crude product, which was purified by silica gel column chromatography eluting with 2% MeOH/CH_2Cl_2 to afford compound **(6S-FNL-31)** (100 mg, 16.2%) as pale brown solid.

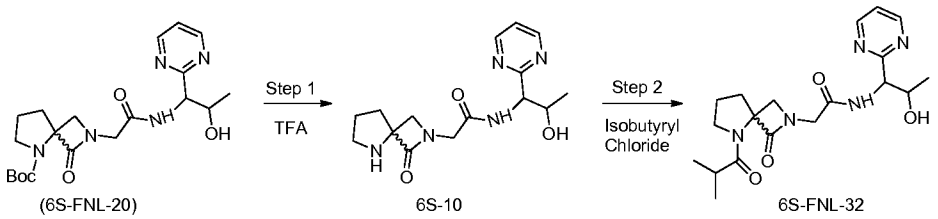
^{1}H-NMR: (500 MHz, DMSO-d_6, D_2O): δ5.22-5.19 (m, 1H), 4.39-4.37 (m, 1H), 4.22-4.14 (m, 2H), 3.98-3.96 (m, 2H), 3.91-3.85 (m, 2H), 3.38-3.34 (m, 1H), 2.50 (s, 3H), 2.41 (s, 2H), 2.36-

2.31 (m, 4H), 2.19 (s, 3H), 1.90 (d, J = 7.5 Hz, 3H), 1.58-1.47 (m, 4H), 1.22-1.16 (m, 4H)

LCMS *m/z*: 518.6 [M^++1];

HPLC: 90% (both enantiomers)

Scheme 6S-16:



Synthesis of *N*-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-2-(1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-10):

To a stirring solution of **(6S-FNL-20)** (1 g, 2.38 mmol) in DCM (20 mL) was added TFA (1.75 mL, 2.38 mmol) at 0 °C and stirred at RT for 2 h. After consumption of the starting material (by TLC), the reaction mixture was concentrated under reduced pressure to obtain crude residue which was triturated with *n*-pentane (10 mL) to afford **6S-10** (1 g, crude) as thick syrup was used directly for next step without any purification.

^{1}H-NMR: (400 MHz, D_2O): 9.10 (d, J = 5.2 Hz, 1H), 8.96-8.85 (m, 1H), 7.89-7.60 (m, 1H), 4.40-4.22 (m, 1H), 4.12-4.00 (m, 2H), 3.95-3.84 (m, 1H), 3.78-3.67 (m, 1H), 3.50-3.44 (m, 2H), 3.20-3.16 (m, 1H), 2.44-2.36 (m, 2H), 2.21-2.07 (m, 2H), 1.15-1.12 (m, 3H);

LCMS (ESI): *m/z* 320.3 [M^++1];

Synthesis of *N*-(2-hydroxy-1-(pyrimidin-2-yl)propyl)-2-(5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)acetamide (6S-FNL-32):

To a stirring solution of compound **6S-10** (1 g, 2.30 mmol) in DCM (25 mL) was added TEA (0.96 mL, 6.9 mmol) at 0 °C and stirred at RT for 5 min. After added isobutyryl chloride (292 mg, 2.76 mmol) slowly and stirred for 2 h at RT. After consumption of the starting material (by TLC), the reaction mixture was diluted with water (15 mL). The separated organic layer was washed with brine solution (1 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude compound which was purified by column chromatography by eluting 10% MeOH/EtOAc to obtained **(6S-FNL-32)** (230 mg, 25.7%) as thick syrup.

^{1}H-NMR: (500 MHz, CD_3OD): 8.75 (d, J = 12.5 Hz, 2H), 7.37 (d, J = 10.5 Hz, 1H), 4.52-4.45 (m, 1H), 4.22-4.00 (m, 1H), 3.96-3.66 (m, 2H), 3.64-3.57 (m, 1H), 3.47-3.33 (m, 3H), 2.84-2.65 (m, 2H), 2.31-2.24 (m, 2H), 2.06-1.99 (m, 2H), 1.39-1.24 (m, 3H), 1.19-1.05 (m, 6H);

LCMS (ESI): *m/z* 390.4 [M^++1];

HPLC: 98.4%

Example 12 - [^{3}H] MK-801 binding assay

Methods

[00374] Assays were conducted as described in Moskal et al. (Moskal, J.R., Kuo, A.G., 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 [^{3}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 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 [^{3}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_{50}, expressed in pM) and maximal activity (% maximal stimulation) were calculated for the test compound.

Results

[00375] The potency and maximal activity for Compounds B-D and H are as shown in Tables 2 and 3 and Figures 1-4.

Table 2.

Compounds	pEC50 (pM)	Activity (%)
B	6	47
C	7	10
D	159	5
H	195	20

Table 3. Additional Biological Data

Cmpd.	[3H] MK-801 binding assay: EC50 (M)	Unified Activity Data: MK-801 Binding	Unified Activity Data: LTP Augmentation (Percent)	Unified Activity Data: LTP Concentration (uM)	Unified Activity Data: LTP, Significant	Unified Activity Data: Porsolt Floating	Unified Activity Data: Porsolt Dose	Unified Activity Data: Porsolt Dose,	Unified Activity Data: Porsolt Time

		EC50 (pM)			(S) or Non-significant (NS)	Time Inhibition (Percent)	(mg/kg)	route	Post Dose (Hours)
6S-FNL-2	1.8E-13								
6S-FNL-4	> 1e-05								
6S-FNL-3	0.00000169								
6S-FNL-24	7.27E-12		110	0.1	S	86	3	IV	1
6S-FNL-7-F2			150	1	S	80	3	IV	1

Example 13 - Long Term Potentiation in Hippocampal Slices

Methods

[00376] Assays were conducted as described in Zhang et al. (Zhang, X.L., Sullivan, J.A., Moskal, J.R., Stanton, P.K., 2008. A NMDA receptor glycine site partial agonist, GLYX-13, simultaneously enhances LTP and reduces LTD at Schaffer collateral-CA1 synapses in hippocampus. Neuropharmacology. 55, 1238-50) Sprague-Dawley rats (12–18 days old; Taconic Farms) were deeply anesthetized with isoflurane and decapitated. Rat brains were removed rapidly, submerged in ice-cold artificial cerebrospinal fluid (ACSF, 2–4 °C), which contained (in mM): 124 NaCl, 4 KCl, 2 $MgSO_4$, 2 $CaCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 10 glucose; at pH 7.4, gassed continuously with 95% O_2/5% CO_2). The rat brains were hemisected, the frontal lobes cut off, and individual hemispheres glued using cyanoacrylate adhesive onto a stage immersed in ice-cold ACSF gassed continuously with 95% O_2/5% CO_2 during slicing. Coronal slices (400 μm thick) were cut using a Vibratome (Leica VT1200S), and transferred to an interface holding chamber for incubation at room temperature for a minimum of one hour before transferring to a Haas-style interface recording chamber continuously perfused at 3 ml/min with oxygenated ACSF at 32 ± 0.5 °C. Low resistance recording electrodes were made from thin-walled borosilicate glass (1–2 MΩ after filling with ACSF) and inserted into the apical dendritic region of the Schaffer collateral termination field in stratum radiatum of field CA1 region to record field excitatory postsynaptic potentials (fEPSPs). A bipolar stainless steel stimulating electrode (FHC Co.) was placed on Schaffer

collateral-commissural fibers in CA3 stratum radiatum, and constant current stimulus intensity adjusted to evoke approximately half-maximal fEPSPs once each 30 s (50–100 pA; 100 μs duration). fEPSP slope was measured before and after induction of LTP by linear interpolation from 20 to 80% of maximum negative deflection, and slopes confirmed to be stable to within ± 10% for at least 15 min before commencing an experiment. Bath application of the test compound (1 μM) was applied 30 min prior to application of Schaffer collateral stimulus trains to elicit LTP. LTP was induced by stimulation of Schaffer collateral axons with four high frequency theta burst stimulus trains of 10 × 100 Hz/5 pulse bursts each, applied at an inter-burst interval of 200 ms. Each train was 2 seconds in duration, and trains were applied 15 seconds apart. The signals were recorded using a Multiclamp 700B amplifier and digitized with a Digidata 1322 (Axon Instruments, USA). Data were analyzed using pClamp software (version 9, Axon Instruments) on an IBM-compatible personal computer.

Results

[00377] As shown in Figure 5, Compound B tested at 0.11 μM increased long-term potentiation after high frequency stimulation of rat Schaffer collateral-evoked NMDA e.p.s.c.s recorded in CA1 pyramidal neurons.

EQUIVALENTS

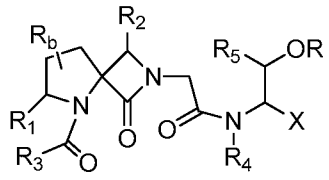
[00378] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

INCORPORATION BY REFERENCE

[00379] The entire contents of all patents, published patent applications, websites, and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

What is claimed is:

1. A compound represented by formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is C_1-C_6 alkyl; C_1-C_6 alkoxy; -O-C_1-C_6 alkylene-phenyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl; phenyl; or 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;, wherein R_3 is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one, two, or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), and C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents

independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

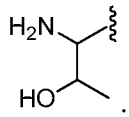
2. The compound of claim 1, wherein R_1 is H.

3. The compound of claim 1 or 2, wherein R_2 is H.

4. The compound of any one of claims 1-3, wherein R_3 is C_1-C_6 alkyl.

5. The compound of any one of claims 1-3, wherein R_3 is methyl.

6. The compound of any one of claims 1-3, wherein R_3 is C_1-C_6 alkyl substituted with one, two or three substituents each selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two, or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl).

7. The compound of any one of claims 1-3, wherein R_3 is 

.

8. The compound of any one of claims 1-3, wherein R_3 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(C1-C3 alkyl), O, and S; which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6

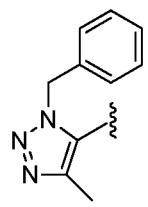
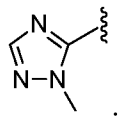
cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl).

9. The compound of any one of claims 1-3, wherein R_3 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(C1-C3 alkyl), O, and S; which is optionally substituted with one, two, or three substituents independently selected from the group consisting of C_1-C_6 alkyl and benzyl (optionally substituted by one two or three substituents each independently selected from R^a).

10. The compound of any one of claims 1-3, wherein R_3 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(C1-C3 alkyl), O, and S; which is optionally substituted with one, two, or three substituents independently selected from the group consisting of $-CH_3$ and benzyl.

11. The compound of any one of claims 1-3, wherein R_3 is -O-C_1-C_6 alkylene-phenyl, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and -C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl).

12. The compound of any one of claims 1-3, wherein R_3 is -O-CH_2-phenyl, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of amino, protected amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a), benzyl (optionally substituted by one two or three substituents each independently selected from R^a), and --C_1-C_6 alkylene-C_3-C_6 cycloalkyl (optionally substituted by one, two or three substituents independent selected from halogen and C_1-C_6 alkyl).

13. The compound of any one of claims 1-3, wherein R_3 is selected from the group consisting of benzyloxy, $-CH_3$,  and  .

14. The compound of any one of claims 1-13, wherein X is -C(O)NR^cR^d.

15. The compound of claim 14, wherein R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl.

16. The compound of claim 14, wherein R^c and R^d are both H.

17. The compound of any one of claims 1-13, 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(C1-C3 alkyl), O, and S, which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl.

18. The compound of claim 17, wherein X is selected from the group consisting of 1,2,4-oxadiazolyl, 1,3,4- oxadiazolyl, 1,2,4-triazolyl (optionally substituted with from 1-2 independently selected C_1-C_6 alkyl), pyridyl, and pyrimidinyl..

19. The compound of any one of claims 1-18, wherein R is H.

20. The compound of any one of claims 1-18, wherein R is –C(O)-C_1-C_6alkyl.

21. The compound of claim 20, wherein R is –C(O)-CH_3.

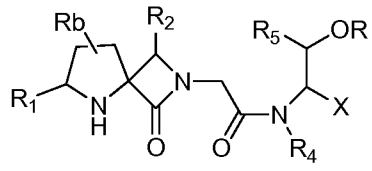
22. The compound of any one of claims 1-21, wherein R_5 is C_1-C_6 alkyl.

23. The compound of claim 22, wherein R_5 is –CH_3.

24. The compound of any one of claims 1-23, wherein R_4 is H.

25. The compound of any one of claims 1-24, wherein R_b is H.

26. A compound represented by formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H; C_1-C_6 alkyl; -OH; C_1-C_6 alkoxy; -CO_2H; -C(O)NR^cR^d; and 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, wherein the heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or R^c and R^d together with the nitrogen to which they are attached, form heterocyclyl including from 4 to 6 ring atoms; wherein the heterocyclyl includes not more than two ring heteroatoms (including the nitrogen atom attached to R^c and R^d), and the second ring heteroatom, when present, is independently selected from the group consisting of N, NH, N(C1-C3 alkyl), O, and S; and wherein wherein the heterocyclyl is optionally substituted with from 1-3 substituents independently selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

27. The compound of claim 26, wherein R_1 is H.

28. The compound of claim 26 or 27, wherein R_2 is H.

29. The compound of any one of claims 26-28, wherein X is -C(O)NR^cR^d.

30. The compound of claim 29, wherein R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, and phenyl.

31. The compound of claim 30, wherein R^c and R^d are both H.

32. The compound of any one of claims 26-31, wherein R is H.

33. The compound of any one of claims 26-31, wherein R is –C(O)-C_1-C_6alkyl.

34. The compound of claim 33, wherein R is –C(O)-CH_3.

35. The compound of any one of claims 26-34, wherein R_5 is C_1-C_6 alkyl.

36. The compound of claim 35, wherein R_5 is –CH_3.

37. The compound of any one of claims 26-36, wherein R_4 is H.

38. The compound of any one of claims 26-37, wherein R_b is H.

39. The compound of claim 1 or 26, wherein the compound is selected from the compounds delineated in Table 1.

40. A pharmaceutical composition comprising a compound of any one of claims 1-39, and a pharmaceutically acceptable excipient.

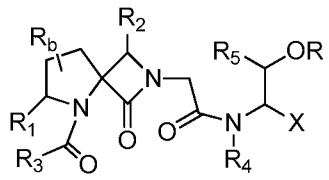
41. The pharmaceutical composition of claim 40, suitable for oral administration.

42. The pharmaceutical composition of claim 40, suitable or intravenous administration.

43. A method of treating of treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof, comprising administering to said patient:

a pharmaceutically effective amount of a compound of any one of claims 1-39.

44. A compound represented by formula I:



(I)

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

R_b is selected from the group consisting of H, halogen, hydroxyl, cyano and C_1-C_6alkyl;

R is H, C_1-C_6 alkyl or –C(O)-C_1-C_6alkyl;

R_1 is H or C_1-C_6 alkyl;

R_2 is H or C_1-C_6 alkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, or a 4-6 membered heteroaryl with one, two or three heteroatoms each selected from O, S or N, wherein R_3 may be optionally substituted with one two or three substituents each selected from the group consisting of amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one, two or three substituents each independently selected from R^a) or benzyl (optionally substituted by one two or three substituents each independently selected from R^a);

R^a is selected from the group consisting of halogen, C_1-C_6alkyl (optionally substituted by one, two or three halogens), C_3-C_6 cycloalkyl (optionally substituted by one, two or three halogens), or C_1-C_6 alkoxy (optionally substituted by one, two or three halogens);

R_4 is H or C_1-C_6 alkyl;

R_5 is H or C_1-C_6 alkyl;

X is selected from the group consisting of: H, C_1-C_6 alkyl, -OH, C_1-C_6 alkoxy, $-CO_2H$, $-C(O)NR^cR^d$, and a 4- to 6-membered heteroaryl ring with one, two or three heteroatoms each selected from O, S or N, wherein the heteroaryl ring may be optionally substituted with one two or three substituents each selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl and phenyl; and

R^c and R^d are each independently selected from the group consisting of H, C_1-C_6 alkyl, or phenyl, or together with the nitrogen to which they are attached, form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of halogen, cyano, oxo, and C_1-C_6 alkyl.

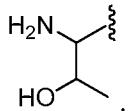
45. The compound of claim 44, wherein R_1 is H.

46. The compound of claim 44 or 45, wherein R_2 is H.

47. The compound of any one of claims 44-46, wherein R_3 is C_1-C_6 alkyl.

48. The compound of any one of claims 44-46, wherein R_3 is methyl.

49. The compound of any one of claims 44-46, wherein R_3 is C_1-C_6 alkyl optionally substituted with one, two or three substituents each selected from the group consisting of amino, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, phenyl (optionally substituted by one two or three substituents each independently selected from R^a) and benzyl (optionally substituted by one two or three substituents each independently selected from R^a).

50. The compound of any one of claims 44-46, wherein R_3 is 

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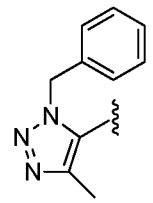
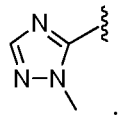
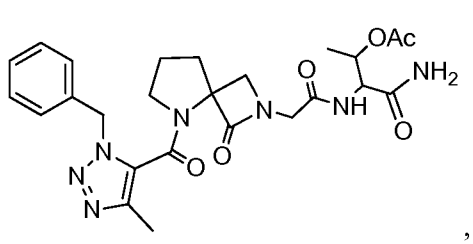
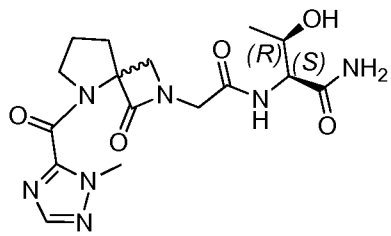
51. The compound of any one of claims 44-46, wherein R_3 is heteroaryl.

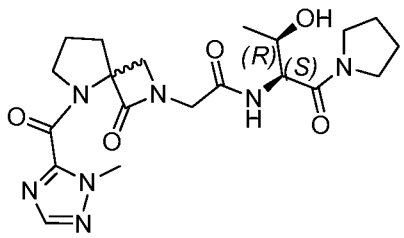
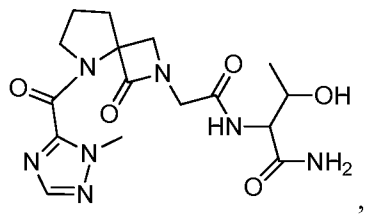
52. The compound of any one of claims 44-46, wherein R_3 is selected from the group consisting of $-CH_3$,  and  .

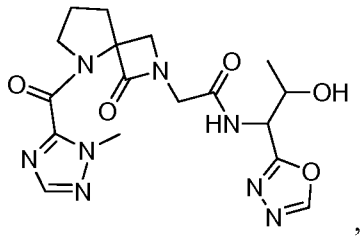
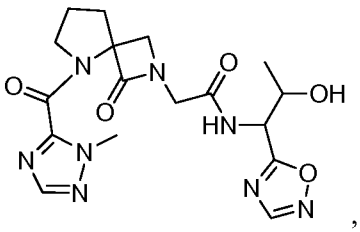
53. The compound of any one of claims 44-52, wherein X is $-C(O)NR^cR^d$.

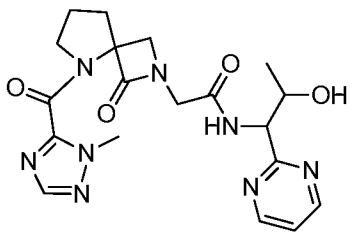
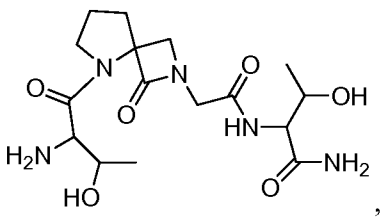
54. The compound of any one of claims 44-52, wherein X is a 4- to 6-membered heteroaryl ring.

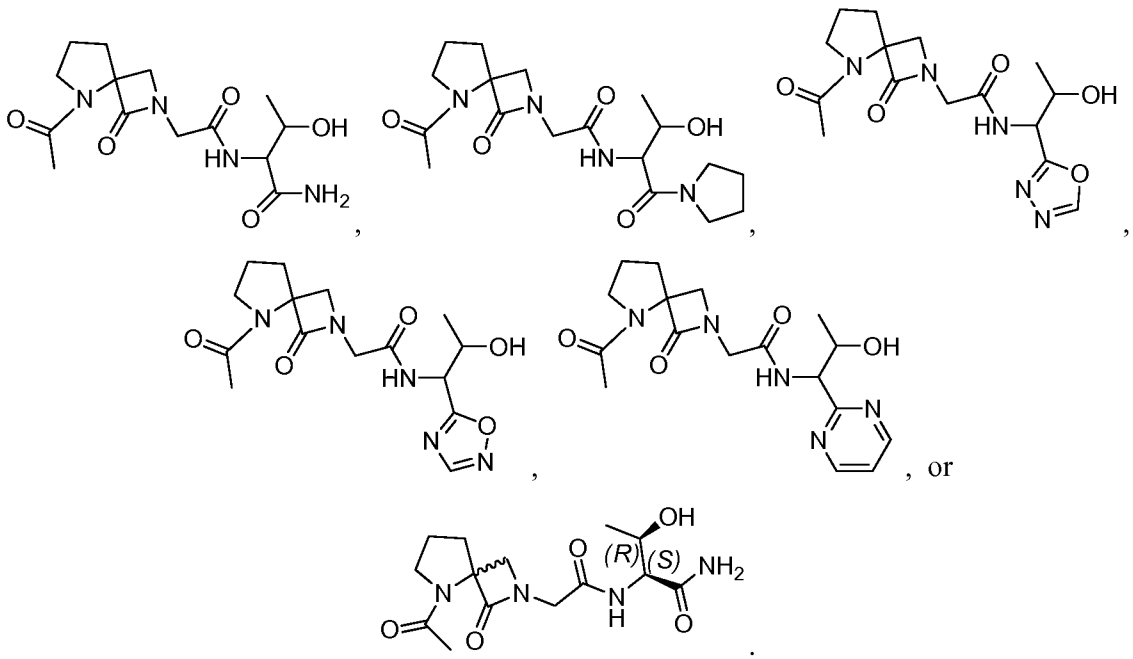
55. The compound of claim 44, wherein the compound is selected from

 ,  ,

 ,  ,

 ,  ,

 ,  ,



56. A pharmaceutical composition comprising a compound of any one of claims 44-55, and a pharmaceutically acceptable excipient.

57. The pharmaceutical composition of claim 56, suitable for oral administration.

58. The pharmaceutical composition of claim 56, suitable or intravenous administration.

59. A method of treating of treating depression, Alzheimer's disease, attention deficit disorder, schizophrenia, or anxiety, in a patient in need thereof, comprising administering to said patient:

a pharmaceutically effective amount of a compound of any one of claims 44-55.

Figure 1

Compound B

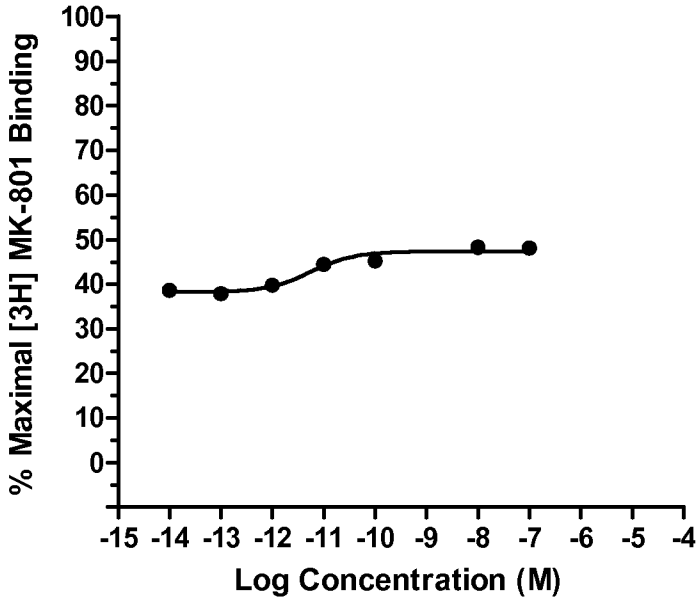


Figure 2

Compound C

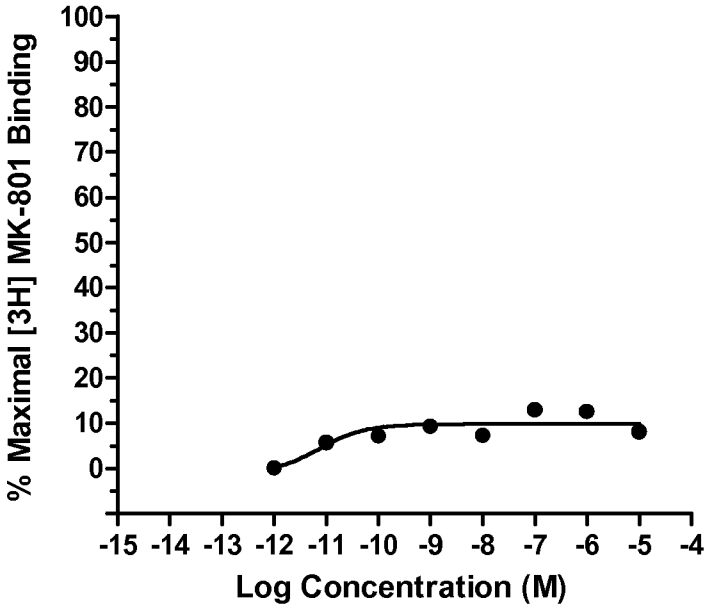


Figure 3

Compound D

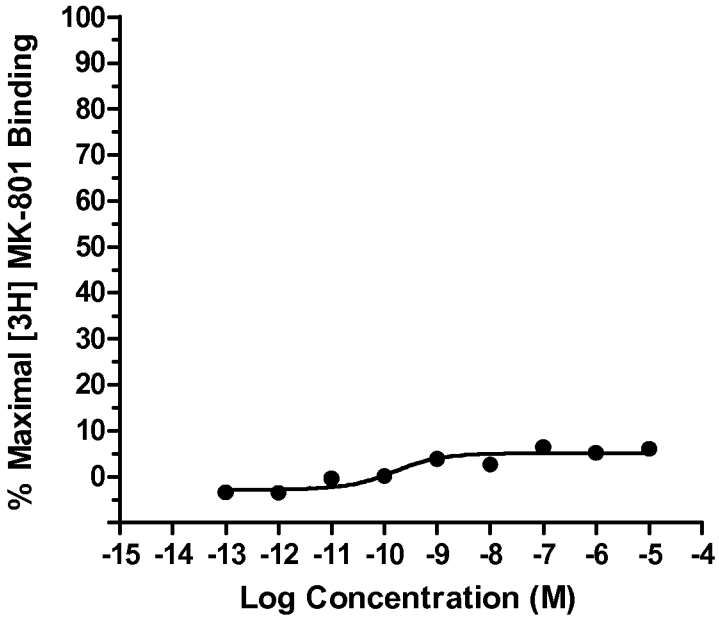


Figure 4

Compound H

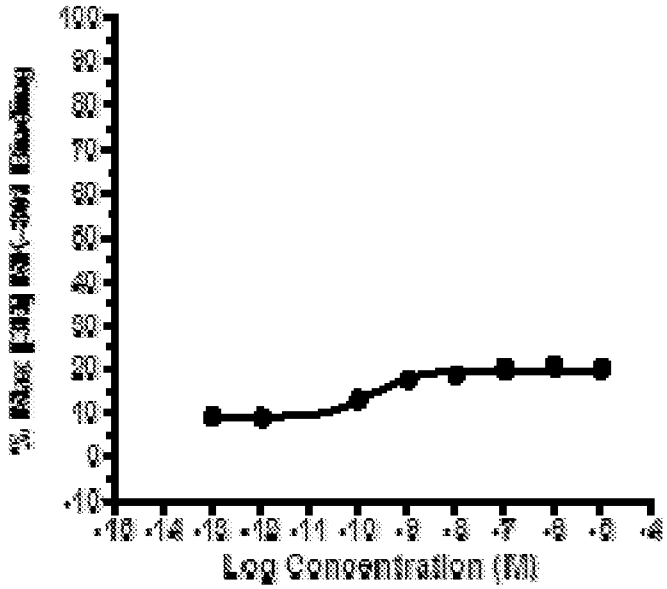
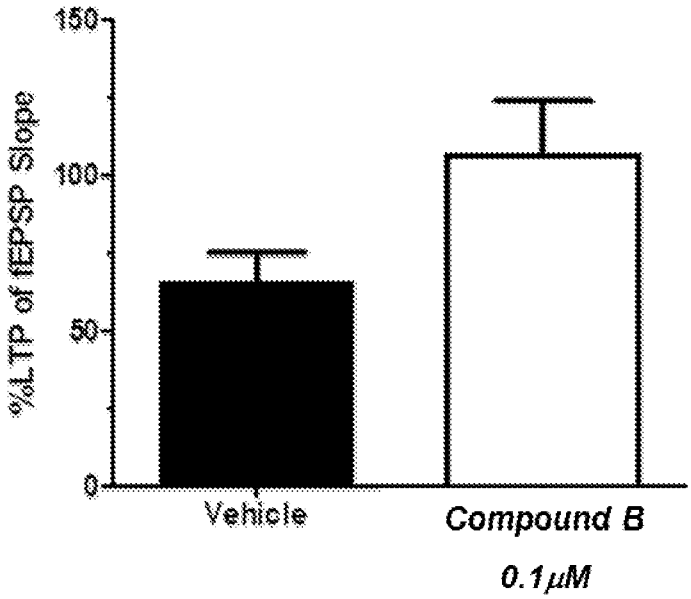


Figure 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/013639

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/10 A61K31/40 A61P25/00
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/033757 A1 (NAUREX INC [US]; KHAN AMIN [US]; MOSKAL JOSEPH [US]; WOOD PAUL [CA]) 25 March 2010 (2010-03-25) claim 1 -----	1-59

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2014	13/03/2014

Name and mailing address of the ISA/	Authorized officer
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/013639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010033757 A1	25-03-2010	AU 2009293164 A1	25-03-2010
		CA 2740628 A1	25-03-2010
		CN 102186883 A	14-09-2011
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		KR 20110076941 A	06-07-2011
		RU 2011114982 A	27-10-2012
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		WO 2010033757 A1	25-03-2010