COMPOUNDS, COMPOSITIONS, AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) to U.S. Provisional Application Number 63/274,916, filed November 2, 2021, the entirety of which is hereby incorporated by reference.

FIELD

[0001] The present disclosure relates generally to small molecule modulators of chemotactic cytokines (chemokine) receptor CCR2 and their use as therapeutic agents.

BACKGROUND

[0002] Autoimmune diseases, allergy, inflammatory disorders, and cancer have a negative effect on the lives of millions of people. As chemokine receptors (a family of G-protein-coupled seven-transmembrane-domain proteins) play key roles in the pathogenesis of such diseases, they have been targets for ongoing drug development efforts.

[0003] Chemotactic cytokines, also known as chemokines, intercrines, and SIS cytokines, are a group of inflammatory/immunomodulatory polypeptide factors released at disease sites (e.g., inflammatory sites) by cells including, for example, macrophages, monocytes, fibroblasts, vascular endothelial cells, eosinophils, neutrophiles, smooth muscle cells, and mast cells. They bind to chemokine receptors, causing the transduction of an intracellular signal through the associated trimeric G proteins. As a result, a rapid increase in intracellular calcium concentration occurs, along with changes in cell shape, increased expression of cellular adhesion molecules, degranulation, and promotion of cell migration. Such directed cell migration is known as chemotaxis, which, for example, attract monocytes and lymphocytes to disease sites and mediate their activation.

[0004] Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a specific ligand for CCR2. Binding of MCP-1 to CCR2 induces chemotaxis, which regulates migration and infiltration of monocytes/macrophages. High expression of MCP-1 has been reported in diseases where accumulation of monocyte/macrophage and/or T cells is thought to be important in the initiation or progression of diseases. These diseases include, but are not limited to, psoriasis, uveitis, rheumatoid arthritis, multiple sclerosis, restenosis, asthma, obesity, chronic obstructive pulmonary disease, pulmonary fibrosis, atherosclerosis, myocarditis, ulcerative colitis, nephritis (nephropathy), lupus, systemic lupus erythematosus, hepatitis, pancreatitis, sarcoidosis, organ transplantation, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, experimental autoimmune encephalomyelitis, and sepsis in which tissue infiltration of blood leukocytes, such as monocytes and lymphocytes, play a major role in the initiation, progression or maintenance of the disease. Accordingly, chemokine receptor antagonists or modulators may be useful as pharmaceutical agents to inhibit the action of chemokines on the target cells.

[0005] CCR2 is a chemokine receptor, a member of the super family of seven-transmembrane G-protein coupled receptor, and is predominantly expressed on monocytes. The CCR2 receptor, a type of receptor for the CC family chemokines, is the primary receptor to MCP-1. Therefore, by modulating (e.g., antagonizing, such as using antagonists or inhibitors) the activity of CCR2 receptors, certain medical benefit may be realized. The "CC" family of chemokine contains two amino terminal cysteine residues (C) that are immediately adjacent (as opposed to be separated by one amino acid, known as the "CXC" family), and shows sequence similarities between 25 to 60% within the family. Thus, there remains a strong need to develop CCR2 inhibitors for treatment of several diseases.

DESCRIPTION

[0006] Provided herein are compounds, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, that are useful in treating and/or preventing diseases mediated, at least in part by, CCR2.

[0007] In some embodiments, provided are compounds that are modulators of chemokine receptor activity, in particular modulating activity of CCR2 receptor. In some embodiments, the compounds modulate the regulation of CCR2 receptor. In some aspects the compounds act via antagonism of the CCR2 receptor. In some embodiments, the compounds modulate the interaction between CCR2 receptor and ligands to the CCR2 receptor. In some embodiments, the compounds modulate the interaction between CCR2 receptor and chemokines. In some embodiments, the compounds modulate the interaction between CCR2 receptor and MCP-1. In some embodiments, provided are compounds that act as inhibitors to the CCR2 receptor by interfering with the binding of chemokines with the CCR2 receptor. In some embodiments, provided are compounds that act as CCR2 antagonists.

[0008] In another embodiment, provided is a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.

[0009] In another embodiment, provided is a method for treating a disease or condition mediated, at least in part, by CCR2 receptor, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

[0010] In another embodiment, provided is a method for treating a disease or condition, at least in part, by regulation of CCR2 receptor, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

[0011] In another embodiment, provided is a method for treating a disease or condition, at least in part, by a CCR2 antagonist, the method comprising administering an effective amount of the pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier, to a subject in need thereof.

[0012] The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using (or administering) and making the compounds. The disclosure further provides compounds or compositions thereof for use in a method of treating a disease, disorder, or condition that is mediated, at least in part, by CCR2 receptor. Moreover, the disclosure provides uses of the compounds or compositions thereof in the manufacture of a medicament for the treatment of a disease, disorder, or condition that is mediated, at least in part, by CCR2 receptor, such as lupus, atherosclerosis, fibrosis, cancer, metabolic, and autoimmune diseases.

DETAILED DESCRIPTION

[0013] The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

1. Definitions

[0014] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0015] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-C(O)NH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[0016] The prefix "C_{u-v}" indicates that the following group has from u to v carbon atoms. For example, "C_{1-6} alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms.

[0017] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term "about" includes the indicated amount ± 10%. In other embodiments, the term "about" includes the indicated amount ± 5%. In certain other embodiments, the term "about" includes the indicated amount ± 1%. Also, to the term "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0018] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C_{1-20} alkyl), 1 to 12 carbon atoms (i.e., C_{1-12} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$) and tert-butyl (i.e., $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$), and isopropyl (i.e., $-CH(CH_3)_2$).

[0019] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or an "arylenyl" group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0020] "Alkenyl" refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, e.g., ethenyl, propenyl, and butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0021] "Alkynyl" refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

[0022] "Alkoxy" refers to the group "alkyl-O-". Examples of alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0023] "Alkoxyalkyl" refers to the group "alkyl-O-alkyl".

[0024] "Alkylthio" refers to the group "alkyl-S-". "Alkylsulfinyl" refers to the group "alkyl-S(O)-". "Alkylsulfonyl" refers to the group "alkyl-$S(O)_2$-". "Alkylsulfonylalkyl" refers to -alkyl-$S(O)_2$-alkyl.

[0025] "Acyl" refers to a group -C(O)R^y, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0026] "Amido" refers to both a "C-amido" group which refers to the group -C(O)NR^yR^z and an "N-amido" group which refers to the group -NR^yC(O)R^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0027] "Amino" refers to the group -NR^yR^z wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0028] "Aminoalkyl" refers to the group "-alkyl-NR^yR^z," wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0029] "Amidino" refers to -C(NR^y)(NR^z_2), wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0030] "Aryl" refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Examples of aryl groups include, e.g., phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0031] "Arylalkyl" or "Aralkyl" refers to the group "aryl-alkyl-".

[0032] "Carbamoyl" refers to both an "O-carbamoyl" group which refers to the group -O-C(O)NR^yR^z and an "N-carbamoyl" group which refers to the group -NR^yC(O)OR^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0033] "Carboxyl ester" or "ester" refer to both -OC(O)R^x and -C(O)OR^x, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[0034] "Cyanoalkyl" refers to refers to an alkyl group as defined above, wherein one or more (e.g., one to three) hydrogen atoms are replaced by a cyano (-CN) group.

[0035] "Cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes "spirocycloalkyl" when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[0036] "Cycloalkoxy" refers to "-O-cycloalkyl."

[0037] "Cycloalkylalkyl" refers to the group "cycloalkyl-alkyl-".

[0038] "Cycloalkylalkoxy" refers to "-O-alkyl-cycloalkyl."

[0039] "Guanidino" refers to -NR^yC(=NR^z)(NR^yR^z), wherein each R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0040] "Hydrazino" refers to -NHNH_2.

[0041] "Imino" refers to a group -C(NR^y)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0042] "Imido" refers to a group -C(O)NR^yC(O)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0043] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo or iodo.

[0044] "Haloalkyl" refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two ("di") or three ("tri") halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0045] "Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a halogen.

[0046] "Hydroxyalkyl" refers to an alkyl group as defined above, wherein one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a hydroxy group.

[0047] "Heteroalkyl" refers to an alkyl group in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term "heteroalkyl" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, etc.), thioethers (e.g., $-CH_2SCH_3$, $-CH(CH_3)SCH_3$, $-CH_2CH_2SCH_3$, $-CH_2CH_2SCH_2CH_2SCH_3$, etc.), sulfones (e.g., $-CH_2S(O)_2CH_3$, $-CH(CH_3)S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_3$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_3$, etc.), and amines (e.g., $-CH_2NR^yCH_3$, $-CH(CH_3)NR^yCH_3$, $-CH_2CH_2NR^yCH_3$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_3$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0048] "Heteroalkylene" refers to a divalent alkyl group (i.e., alkylene) in which one or more (e.g., one to five or one to three) of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. "Heteroalkylene" groups must have at least one carbon and at least one heteroatomic group within the chain. The term "heteroalkylene" includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, $-NR^y-$, -O-, -S-, -S(O)-, $-S(O)_2-$, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkylene groups include, e.g., $-CH_2OCH_2-$, $-CH(CH_3)OCH_2-$, $-CH_2CH_2OCH_2-$, $-CH_2CH_2OCH_2CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH(CH_3)SCH_2-$, $-CH_2CH_2SCH_2-$, $-CH_2CH_2SCH_2CH_2SCH_2-$, $-CH_2S(O)_2CH_2-$, $-CH(CH_3)S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2-$, $-CH_2CH_2S(O)_2CH_2CH_2OCH_2-$, $-CH_2NR^yCH_2-$, $-CH(CH_3)NR^yCH_2-$, $-CH_2CH_2NR^yCH_2-$, $-CH_2CH_2NR^yCH_2CH_2NR^yCH_2-$, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkylene includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom. As used herein, the term "heteroalkylene" does not include groups such as amides or other functional groups having an oxo present on one or more carbon atoms.

[0049] "Heteroaryl" refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl); and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, thiophenyl (i.e., thienyl), triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound via either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0050] "Heteroarylalkyl" refers to the group "heteroaryl-alkyl-".

[0051] "Heterocyclyl" refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "heterocyclyl" includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro, and may comprise one or more (e.g., one to three or one or two) oxo (=O) or N-oxide ($-O^-$) moieties. Any non-aromatic ring or fused ring system containing at least one heteroatom and one non-aromatic ring is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C_{2-20} heterocyclyl), 2 to 12 ring carbon atoms (i.e., C_{2-12} heterocyclyl), 2 to 10 ring carbon atoms (i.e., C_{2-10} heterocyclyl), 2 to 8 ring carbon atoms (i.e., C_{2-8} heterocyclyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heterocyclyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidinyl, azepinyl, benzodioxolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. The term "heterocyclyl" also includes "spiroheterocyclyl" when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0052] "Heterocyclylalkyl" refers to the group "heterocyclyl-alkyl-".

[0053] "Oxime" refers to the group -CR^y(=NOH) wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0054] "Sulfonyl" refers to the group -S(O)$_2$R^y, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0055] "Sulfinyl" refers to the group -S(O)R^y, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0056] "Sulfonamido" refers to the groups -SO$_2$NR^{y}R^z and -NR^{y}SO$_2$R^z, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0057] The terms "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term "optionally substituted" refers to any one or more (e.g., one to five or one to three) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0058] In certain embodiments, R^y and R^z as used herein are optionally substituted. In certain embodiments, R^y and R^z as used herein are unsubstituted.

[0059] The term "substituted" used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, sulfinic acid, sulfonic acid, sulfonamido, thiol, thioxo, N-oxide, or -Si(R^y)$_3$ wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

[0060] In certain embodiments, "substituted" includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups in which one or more (e.g., one to five or one to three) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NR^gR^h$, $-NR^gC(=O)R^h$, $-NR^gC(=O)NR^gR^h$, $-NR^gC(=O)OR^h$, $-NR^gS(=O)_{1\text{-}2}R^h$, $-C(=O)R^g$, $-C(=O)OR^g$, $-OC(=O)OR^g$, $-OC(=O)R^g$, $-C(=O)NR^gR^h$, $-OC(=O)NR^gR^h$, $-OR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-OS(=O)_{1\text{-}2}R^g$, $-S(=O)_{1\text{-}2}OR^g$, $-NR^gS(=O)_{1\text{-}2}NR^gR^h$, $=NSO_2R^g$, $=NOR^g$, $-S(=O)_{1\text{-}2}NR^gR^h$, $-SF_5$, $-SCF_3$, or $-OCF_3$. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced with $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^gR^h$, $-CH_2SO_2R^g$, $-CH_2SO_2NR^gR^h$. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, "substituted" also means any of the above groups in which one or more (e.g., one to five or one to three) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and R^i are taken together with the atoms to which they are attached to form a heterocyclyl ring optionally substituted with oxo, halo or alkyl optionally substituted with oxo, halo, amino, hydroxyl, or alkoxy.

[0061] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl)substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term "substituted" may describe other chemical groups defined herein.

[0062] In certain embodiments, as used herein, the phrase "one or more" refers to one to five. In certain embodiments, as used herein, the phrase "one or more" refers to one to three.

[0063] Any compound or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. These forms of compounds may also be referred to as "isotopically enriched analogs." Isotopically labeled compounds have structures depicted herein, except that one or more (e.g., one to five or one to three) atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0064] The term "isotopically enriched analogs" includes "deuterated analogs" of compounds described herein in which one or more (e.g., one to five or one to three) hydrogens is/are replaced by deuterium, such as a hydrogen on a carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more (e.g., one to five or one to three) hydrogens have been replaced by deuterium.

[0065] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[0066] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0067] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0068] Provided are also or a pharmaceutically acceptable salt, isotopically enriched analog, deuterated analog, stereoisomer, mixture of stereoisomers, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0069] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines (i.e., NH_2(alkyl)), dialkyl amines (i.e., HN(alkyl)$_2$), trialkyl amines (i.e., N(alkyl)$_3$), substituted alkyl amines (i.e., NH_2(substituted alkyl)), di(substituted alkyl) amines (i.e., HN(substituted alkyl)$_2$), tri(substituted alkyl) amines (i.e., N(substituted alkyl)$_3$), alkenyl amines (i.e., NH_2(alkenyl)), dialkenyl amines (i.e., HN(alkenyl)$_2$), trialkenyl amines (i.e., N(alkenyl)$_3$), substituted alkenyl amines (i.e., NH_2(substituted alkenyl)), di(substituted alkenyl) amines (i.e., HN(substituted alkenyl)$_2$), tri(substituted alkenyl) amines (i.e., N(substituted alkenyl)$_3$, mono-, di- or tri-cycloalkyl amines (i.e., NH_2(cycloalkyl), HN(cycloalkyl)$_2$, N(cycloalkyl)$_3$), mono-, di- or tri- arylamines (i.e., NH_2(aryl), HN(aryl)$_2$, N(aryl)$_3$) or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0070] The term “hydrate” refers to the complex formed by the combining of a compound described herein and water.

[0071] A “solvate” refers to an association or complex of one or more solvent molecules and a compound of the disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethylacetate, acetic acid, and ethanolamine.

[0072] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0073] The compounds, or their pharmaceutically acceptable salts include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0074] A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes “enantiomers,” which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

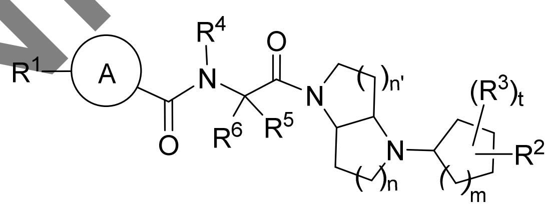
[0075] “Diastereomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[0076] Relative centers of the compounds as depicted herein are indicated graphically using the "thick bond" style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0077] "Prodrugs" means any compound which releases an active parent drug according to a structure described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein are prepared by modifying functional groups present in the compound described herein in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds described herein wherein a hydroxy, amino, carboxyl, or sulfhydryl group in a compound described herein is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate and benzoate derivatives), amides, guanidines, carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds described herein and the like. Preparation, selection and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

2. Compounds

[0078] Provided herein are compounds that are modulators of chemotactic cytokines (chemokine) receptor CCR2 (e.g., CCR2 antagonists). In certain embodiments, provided is a compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 1 or 2;

n′ is 1 or 2;

m is 0, 1, or 2;

t is 0, 1, 2, 3, 4, 5, or 6;

ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is independently optionally substituted with one to five Z^1;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-OC(O)N(R^{11})_2$, $-NR^{11}C(O)OR^{11}$, $-S(O)_{0-2}R^{11}$, $-NR^{11}S(O)_{1-2}R^{11}$, $-NR^{11}C(O)N(R^{11})_2$, or $-NR^{11}S(O)_{1-2}N(R^{11})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to six Z^1;

R^2 is C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L^1$-C_{3-10} cycloalkyl, $-L^1$-heterocyclyl, $-L^1$-aryl, or $-L^1$-heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1; or

R^2 and R^3 together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1;

L^1 is -O-, $-NR^7C(O)-$, $-C(O)NR^7-$, $-C(O)NR^7-C_{1-3}$ alkylene-, or $-NR^7(O)-C_{1-3}$ alkylene-;

each R^3 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{13}$, $-N(R^{13})_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{14}C(O)R^{13}$, $-OC(O)N(R^{13})_2$, $-NR^{13}C(O)OR^{13}$, $-S(O)_{0-2}R^{13}$, $-NR^{13}S(O)_{1-2}R^{13}$, $-NR^{13}C(O)N(R^{13})_2$, or $-NR^{13}S(O)_{1-2}N(R^{13})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^1; or

two R^3 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1;

R^4 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z^1;

R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{15})_2$, $-NR^{15}C(O)R^{15}$, $-OC(O)N(R^{15})_2$, $-NR^{15}C(O)OR^{15}$, $-S(O)_{0-2}R^{15}$, $-NR^{15}S(O)_{1-2}R^{15}$, $-NR^{15}C(O)N(R^{15})_2$, or $-NR^{15}S(O)_{1-2}N(R^{15})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl;

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$,

$-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{15} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

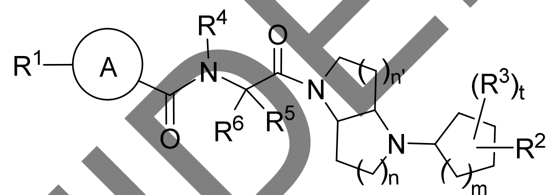
each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L-C_{1-6}$ alkyl, $-L-C_{2-6}$ alkenyl, $-L-C_{2-6}$ alkynyl, $-L-C_{1-6}$ haloalkyl, $-L-C_{3-10}$ cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, $-N(C_{1-6}$ alkyl)-, $-N(C_{2-6}$ alkenyl)-, $-N(C_{2-6}$ alkynyl)-, $-N(C_{1-6}$ haloalkyl)-, $-N(C_{3-10}$ cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-,

-C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, -NHS(O)$_2$NH, -S(O)NH-, -S(O)$_2$NH, -NHS(O)NH-, or -NHS(O)$_2$NH-;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, -OH, -SH, -NH$_2$, -NO$_2$, -SF$_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0079] In certain embodiments, provided is a compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 1 or 2;

n′ is 1 or 2;

m is 0, 1, or 2;

t is 0, 1, 2, 3, 4, 5, or 6;

ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is independently optionally substituted with one to five Z^1;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, -NO$_2$, -SF$_5$, -OR^{11}, -N(R^{11})$_2$, -C(O)R^{11}, -C(O)OR^{11}, -OC(O)R^{11}, -C(O)N(R^{11})$_2$, -NR^{11}C(O)R^{11}, -OC(O)N(R^{11})$_2$, -NR^{11}C(O)OR^{11}, -S(O)$_{0-2}$R^{11}, -NR^{11}S(O)$_{1-2}$R^{11}, -NR^{11}C(O)N(R^{11})$_2$, or -NR^{11}S(O)$_{1-2}$N(R^{11})$_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to six Z^1;

R^2 is C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -O-C_{3-10} cycloalkyl, -O-heterocyclyl,

-O-aryl, or -O-heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1;

each R^3 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{13}$, $-N(R^{13})_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{14}C(O)R^{13}$, $-OC(O)N(R^{13})_2$, $-NR^{13}C(O)OR^{13}$, $-S(O)_{0-2}R^{13}$, $-NR^{13}S(O)_{1-2}R^{13}$, $-NR^{13}C(O)N(R^{13})_2$, or $-NR^{13}S(O)_{1-2}N(R^{13})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^1; or

two R^3 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1;

R^4 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z^1;

R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{15})_2$, $-NR^{15}C(O)R^{15}$, $-OC(O)N(R^{15})_2$, $-NR^{15}C(O)OR^{15}$, $-S(O)_{0-2}R^{15}$, $-NR^{15}S(O)_{1-2}R^{15}$, $-NR^{15}C(O)N(R^{15})_2$, or $-NR^{15}S(O)_{1-2}N(R^{15})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{15} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

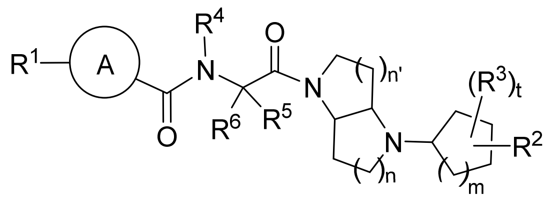
each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, $-NHS(O)_2NH$, -S(O)NH-, $-S(O)_2NH$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, -OH,

-SH, -NH$_2$, -NO$_2$, -SF$_5$, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{1-6}$ alkoxy, C$_{1-6}$ haloalkoxy, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0080] In certain embodiments, provided is a compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 1 or 2;

n′ is 1 or 2;

m is 0, 1, or 2;

t is 0, 1, 2, 3, 4, 5, or 6;

ring A is aryl or heteroaryl;

R^1 is hydrogen, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, -NO$_2$, -SF$_5$, -OR^{11}, -N(R^{11})$_2$, -C(O)R^{11}, -C(O)OR^{11}, -OC(O)R^{11}, -C(O)N(R^{11})$_2$, -NR^{11}C(O)R^{11}, -OC(O)N(R^{11})$_2$, -NR^{11}C(O)OR^{11}, -S(O)$_{0-2}$R^{11}, -NR^{11}S(O)$_{1-2}$R^{11}, -NR^{11}C(O)N(R^{11})$_2$, or -NR^{11}S(O)$_{1-2}$N(R^{11})$_2$;

R^2 is C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, -L^1-C$_{3-10}$ cycloalkyl, -L^1-heterocyclyl, -L^1-aryl, or -L^1-heteroaryl; wherein each C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1; or

R^2 and R^3 together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring;

L^1 is -O-, -NR^{7}C(O)-, -C(O)NR^7-, -C(O)NR^7-C$_{1-3}$ alkylene-, or -NR^7(O)-C$_{1-3}$ alkylene-;

each R^3 is independently C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, -NO$_2$, -SF$_5$, -OR^{13}, -N(R^{13})$_2$, -C(O)R^{13}, -C(O)OR^{13}, -OC(O)R^{13}, -C(O)N(R^{13})$_2$, -NR^{14}C(O)R^{13}, -OC(O)N(R^{13})$_2$, -NR^{13}C(O)OR^{13}, -S(O)$_{0-2}$R^{13}, -NR^{13}S(O)$_{1-2}$R^{13}, -NR^{13}C(O)N(R^{13})$_2$, or -NR^{13}S(O)$_{1-2}$N(R^{13})$_2$; or

two R^3 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring;

R^4 is hydrogen, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^5 and R^6 are each independently hydrogen, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{3-10}$ cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, -NO$_2$, -SF$_5$, -OR^{15}, -N(R^{15})$_2$, -C(O)R^{15},

$-C(O)OR^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{15})_2$, $-NR^{15}C(O)R^{15}$, $-OC(O)N(R^{15})_2$, $-NR^{15}C(O)OR^{15}$, $-S(O)_{0-2}R^{15}$, $-NR^{15}S(O)_{1-2}R^{15}$, $-NR^{15}C(O)N(R^{15})_2$, or $-NR^{15}S(O)_{1-2}N(R^{15})_2$;

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl;

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{15} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, $-NHS(O)_2NH$, -S(O)NH-, $-S(O)_2NH$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0081] In certain embodiments, R^5 and R^6 are both hydrogen or are both C_{1-3} alkyl. In certain embodiments, R^5 and R^6 are both C_{1-3} alkyl.

[0082] In certain embodiments, R^5 and R^6 are both hydrogen.

[0083] In certain embodiments, R^4 is hydrogen.

[0084] In certain embodiments, R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-OC(O)N(R^{11})_2$, $-NR^{11}C(O)OR^{11}$, $-S(O)_{0-2}R^{11}$, $-NR^{11}S(O)_{1-2}R^{11}$, $-NR^{11}C(O)N(R^{11})_2$, or $-NR^{11}S(O)_{1-2}N(R^{11})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to six Z^1.

[0085] In certain embodiments, each R^3 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{14}C(O)R^{13}$, $-OC(O)N(R^{13})_2$, $-NR^{13}C(O)OR^{13}$, $-S(O)_{0-2}R^{13}$, $-NR^{13}S(O)_{1-2}R^{13}$, $-NR^{13}C(O)N(R^{13})_2$, or $-NR^{13}S(O)_{1-2}N(R^{13})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl,

C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^1; or two R^3 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1.

[0086] In certain embodiments, n′ is 1.

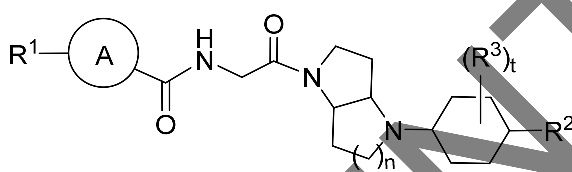
[0087] In certain embodiments, n′ is 2.

[0088] In certain embodiments, m is 0.

[0089] In certain embodiments, m is 1.

[0090] In certain embodiments, m is 2.

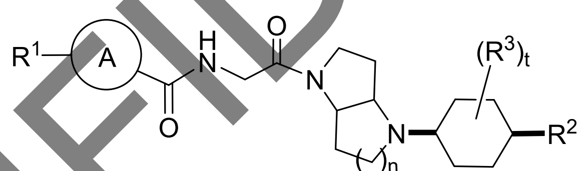
[0091] In certain embodiments, provided is a compound of Formula IA:



IA.

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein each ring A, R^1, R^2, R^3, n, and t are independently as defined herein.

[0092] In certain embodiments, provided is a compound of Formula IIA:



IIA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof wherein each ring A, R^1, R^2, R^3, n, and t are independently as defined herein.

[0093] In certain embodiments, t is 0, 1, or 2. In certain embodiments, t is 0 or 1.

[0094] In certain embodiments, t is 0, 1, or 2; and each R^3 is independently fluoro, $-NH_2$, -OH, $-C(O)NH_2$, -C(O)OH, or R^2 and R^3 together with the atom(s) to which they are attached form a heterocyclyl or heteroaryl ring. In certain embodiments, t is 1; and R^3 is fluoro, $-NH_2$, -OH, $-C(O)NH_2$, -C(O)OH, or R^2 and R^3 together with the atom(s) to which they are attached form a heterocyclyl or heteroaryl ring. In certain embodiments, t is 1; and R^3 is fluoro, -OH, or $-NH_2$. In certain embodiments, t is 0 or 1; and R^3 is fluoro, -OH, or $-NH_2$.

[0095] In certain embodiments, t is 2.

[0096] In certain embodiments, ring A is aryl.

[0097] In certain embodiments, ring A is phenyl.

[0098] In certain embodiments, ring A is heteroaryl. In certain embodiments, ring A is pyridyl.

[0099] In certain embodiments, ring A is benzo[d]isoxazole.

[0100] In certain embodiments R^1 is halo, -C(O)OR^{11}, or C_{1-6} haloalkyl. In certain embodiments, R^1 is fluoro, -C(O)OH, -C(O)OCH_3, or trifluoromethyl.

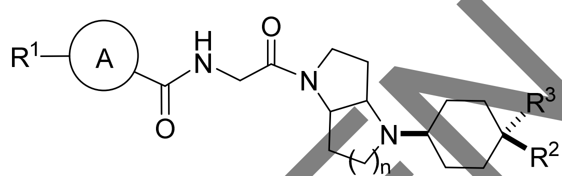
[0101] In certain embodiments, R^1 is C_{1-6} haloalkyl.

[0102] In certain embodiments, R^1 is trifluoromethyl.

[0103] In certain embodiments, each R^3 is independently halo, -NH_2, or -OH.

[0104] In certain embodiments, one R^3 is methyl or fluoro, and a second R^3 is hydroxy. In certain embodiments, one R^3 is methyl and a second R^3 is hydroxy.

[0105] In certain embodiments, provided is a compound of Formula IIIA:



IIIA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof wherein each ring A, R^1, R^2, R^3, and n are independently as defined herein.

[0106] In certain embodiments, n is 1.

[0107] In certain embodiments, n is 2.

[0108] In certain embodiments, R^2 is C_6 aryl, 5 or 6-membered heteroaryl, -O-aryl, or -O-heteroaryl; wherein each aryl or heteroaryl is optionally substituted with one to five Z^1.

[0109] In certain embodiments, R^2 is C_6 aryl or 5 or 10-membered heteroaryl; wherein the aryl or heteroaryl is optionally substituted with one to five Z^1, t is 0 or 1; and R^3 is hydrogen, -NH_2, -C(O)NH_2, or hydroxy.

[0110] In certain embodiments, R^2 is C_6 aryl or 5 or 6-membered heteroaryl; wherein the aryl or heteroaryl is optionally substituted with one to five Z^1.

[0111] In certain embodiments, R^2 is phenyl optionally substituted with one to five Z^1.

[0112] In certain embodiments, R^2 is pyridyl, pyrimidinyl, thiazolyl, naphthalenyl, oxadiazolyl, [1,2,4]triazolo[1,5-a]pyridinyl, or imidazo[1,5-a]pyridin-5-yl; wherein each is optionally substituted with one to five Z^1.

[0113] In certain embodiments, R^2 is pyridyl, pyrimidinyl, thiazolyl, or naphthalenyl, each of which is optionally substituted with one to five Z^1.

[0114] In certain embodiments, R^2 is 2-pyridyl, 2-thiazolyl, or 5-thiazolyl, each of which is optionally substituted with one to five Z^1. In certain embodiments, Z^1 is 2-pyrimidinyl, 2-thiazolyl, 1-triazolyl, -CN, or -C(O)NH_2.

[0115] In certain embodiments, R^2 is [1,2,4]triazolo[1,5-a]pyridinyl or oxazolyl, wherein each is optionally substituted with one to five Z^1.

[0116] In certain embodiments, R^2 is O-aryl or -O-heteroaryl; wherein each aryl or heteroaryl is optionally substituted with one to five Z^1. In certain embodiments, R^2 is -O-phenyl or -O-pyridyl; wherein each is optionally substituted with one to five Z^1.

[0117] In certain embodiments, R^2 and R^3 together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1. In certain embodiments, R^2 and R^3 together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring.

[0118] In certain embodiments, with respect to any of the formula described above, each Z^1 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)OR^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, pyrimidinyl, pyridazinyl, oxazolyl, imidazolyl, pyrrolidinyl, triazolyl, thiazolyl, tetrazolyl, pyridinyl, piperazinyl, pyrazinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, oxadiazolyl, 1,1-dioxothiomorpholinyl, 3-oxopiperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxopyrrolidinyl, piperidin-2-onyl, imidazolidin-2-onyl, 1,3,4-oxadiazol-2(3H)-onyl, 6-azaspiro[2.5]octanyl, 1,2,3,6-tetrahydropyridinyl, azetidinyl, 8-azabicyclo[3.2.1]octanyl, or morpholino, wherein each is independently substituted with one to five Z^{1a}.

[0119] In certain embodiments, R^2 is phenyl, pyridyl, -O-pyridyl, -NHC(O)-pyridyl, $-C(O)NHCH_2$-pyridyl, -O-phenyl, quinolinyl, pyrimidinyl, thiazolyl, oxazolyl, imizadolyl, imidazo[1,2-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, or imidazo[1,5-a]pyridinyl; wherein each is independently substituted with one to five Z^1.

[0120] In certain embodiments, R^2 is phenyl, pyridyl, -O-pyridyl, -O-phenyl, quinolinyl, pyrimidinyl, thiazolyl, oxazolyl, imizadolyl, imidazo[1,2-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, or imidazo[1,5-a]pyridinyl; wherein each is independently substituted with one to five Z^1;

each Z^1 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, heteroaryl, halo, cyano, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, or $-NR^{10}C(O)R^{10}$; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

each Z^{1a} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, halo, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, or $-C(O)N(R^{10a})_2$;

each R^{10a} is independently hydrogen or C_{1-6} alkyl.

t is 0, 1, or 2; and

each R^3 is independently halo, C_{1-6} alkyl, -OH, $-NH_2$, -C(O)OH, or $-C(O)NH_2$.

[0121] In certain embodiments, with respect to any of the formula described above, Z^1 is pyrimidinyl, oxazolyl, imidazolyl, or pyrrolidinyl.

[0122] In certain embodiments,

R^1 is C_{1-6} haloalkyl;

R^2 is aryl, heteroaryl, $-L^1$-aryl, or $-L^1$-heteroaryl; wherein each aryl, or heteroaryl is optionally substituted with one to five Z^1;

L^1 is -O-, $-NR^7C(O)-$, $-C(O)NR^7-$, $-C(O)NR^7-C_{1-3}$ alkylene-, or $-NR^7(O)-C_{1-3}$ alkylene-;

t is 0, 1, or 2;

each R^3 is independently halo, C_{1-6} alkyl, -OH, $-NH_2$, -C(O)OH, or $-C(O)NH_2$; or

R^2 and R^3 together with the atom(s) to which they are attached form a heterocyclyl;

R^4 is hydrogen;

R^5 and R^6 are each hydrogen;

R^7 is hydrogen or C_{1-6} alkyl;

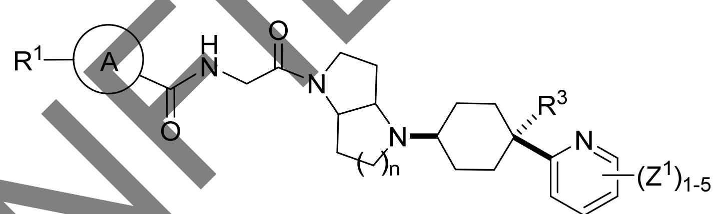
each Z^1 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, heteroaryl, halo, cyano, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, or $-NR^{10}C(O)R^{10}$; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

each Z^{1a} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, halo, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, or $-C(O)N(R^{10a})_2$; and

each R^{10a} is independently hydrogen or C_{1-6} alkyl.

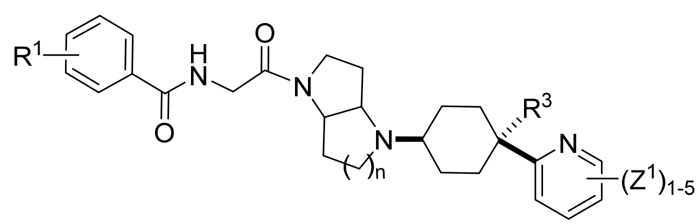
[0123] In certain embodiments, provided is a compound of Formula IVA:



IVA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof wherein each of ring A, R^1, Z^1, R^3, and n are independently as defined herein.

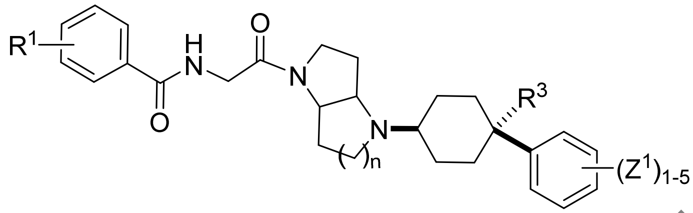
[0124] In certain embodiments, provided is a compound of Formula VA:



VA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof wherein each of ring A, R^1, Z^1, R^3, and n are independently as defined herein.

[0125] In certain embodiments, provided is a compound of Formula VIA:



VIA

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof wherein each of ring A, R^1, Z^1, R^3, and n are independently as defined herein.

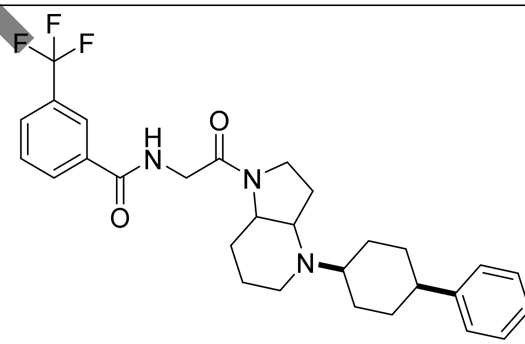
[0126] In certain embodiments, each Z^1 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, heteroaryl, halo, cyano, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)N(R^{10})_2$, or $-NR^{10}C(O)R^{10}$; wherein each C_{1-6} alkyl, C_{1-6} haloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to five Z^{1a}.

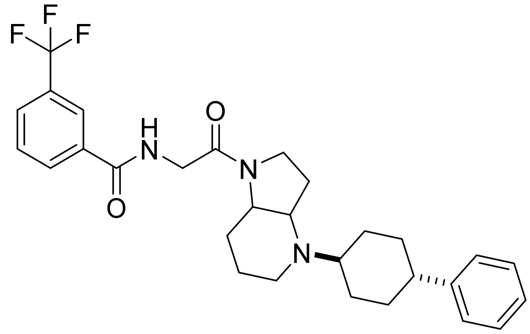
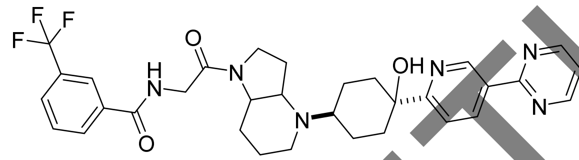
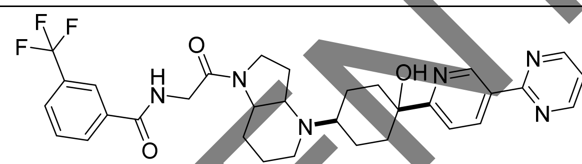
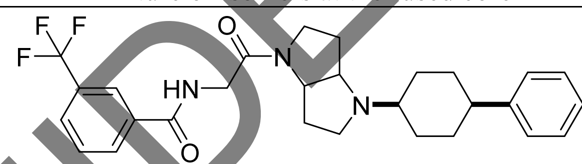
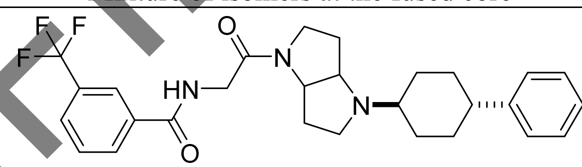
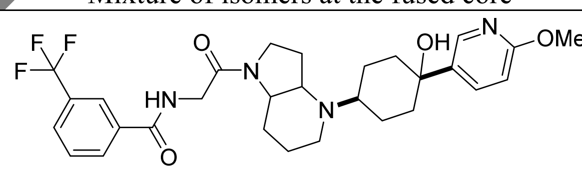
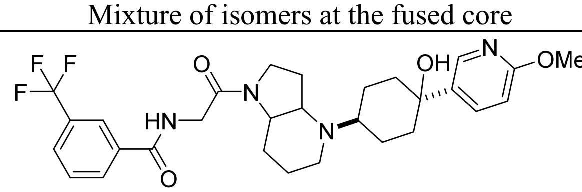
[0127] In certain embodiments, each Z^{1a} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, halo, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, or $-C(O)N(R^{10a})_2$.

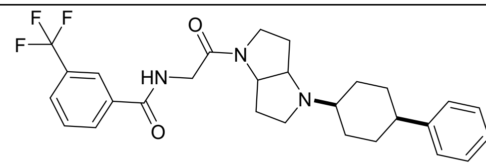
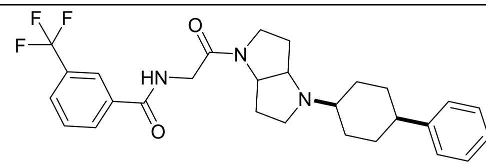
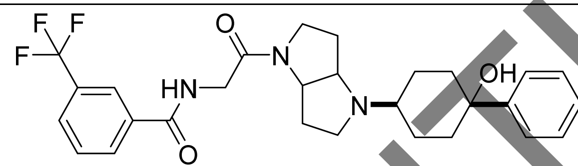
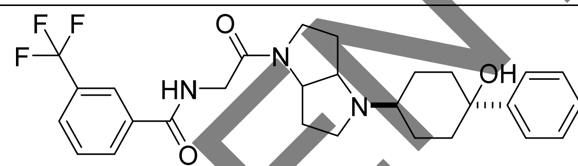
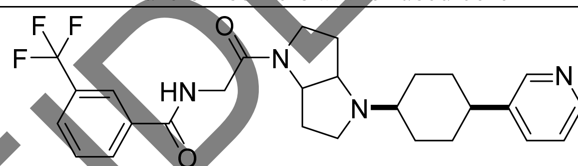
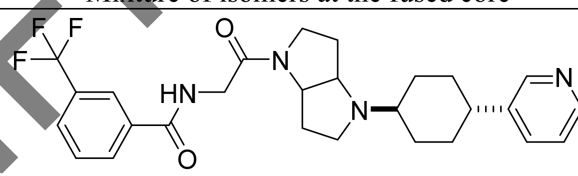
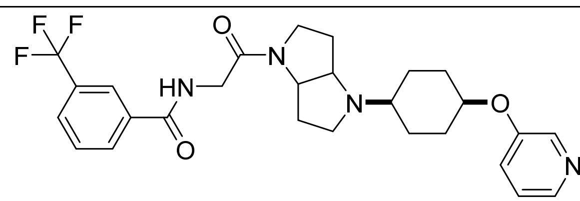
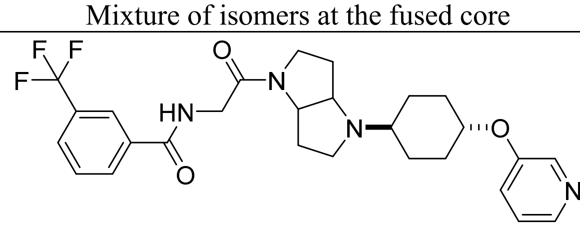
[0128] In certain embodiments, with respect to any of the formula described above, n is 2.

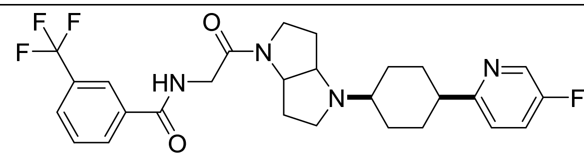
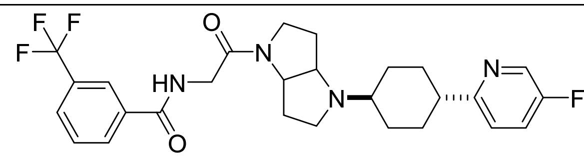
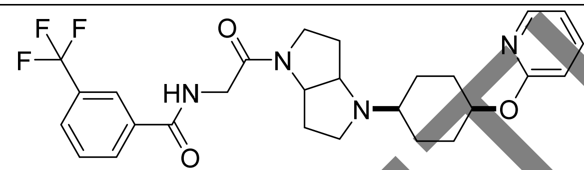
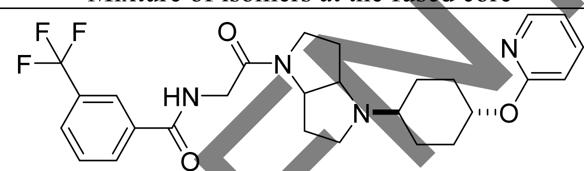
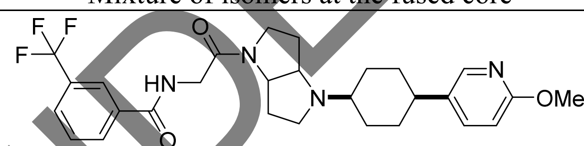
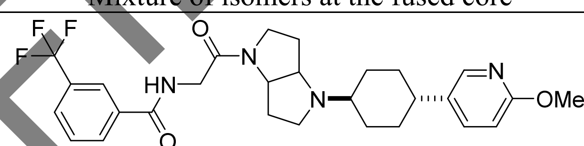
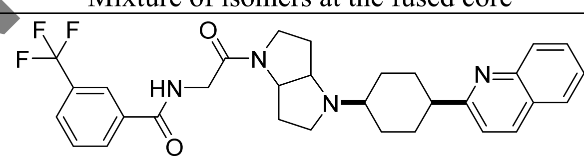
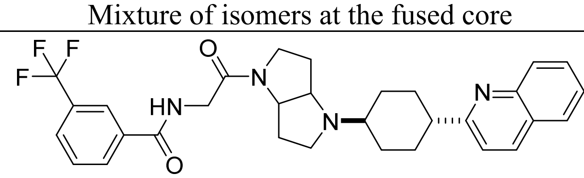
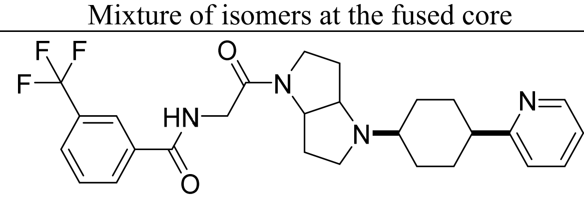
[0129] In certain embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof.

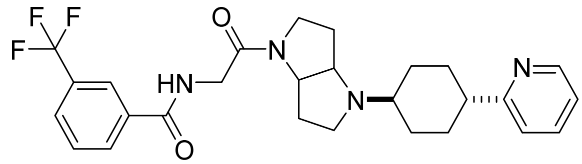
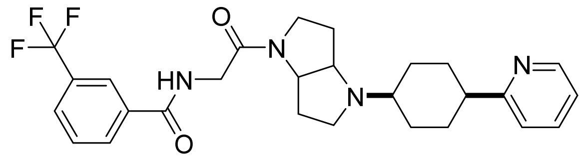
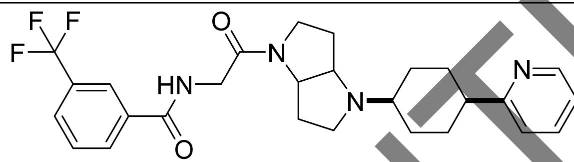
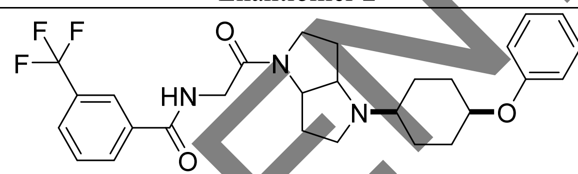
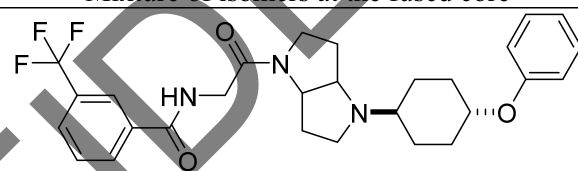
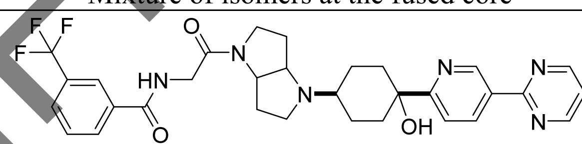
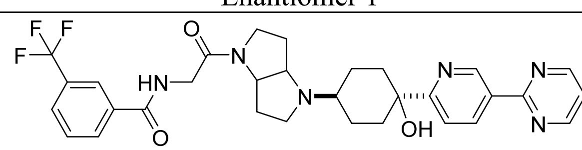
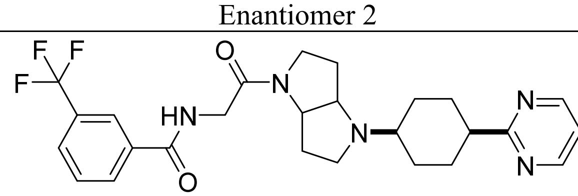
Table 1

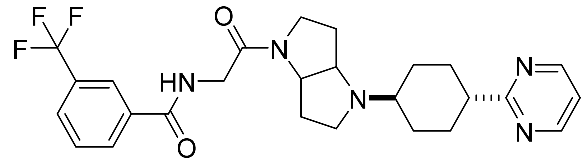
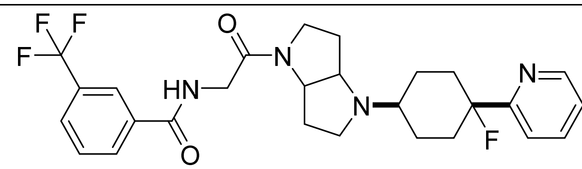
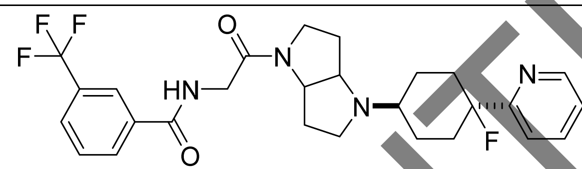
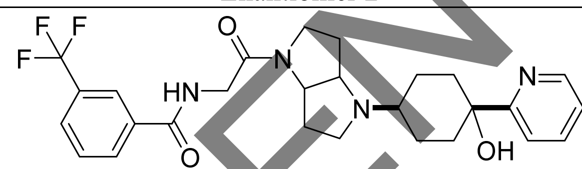
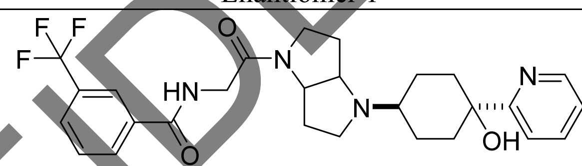
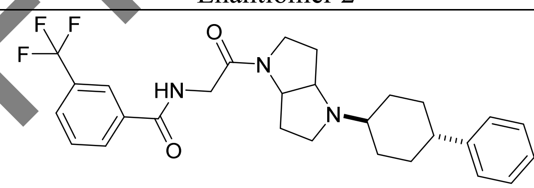
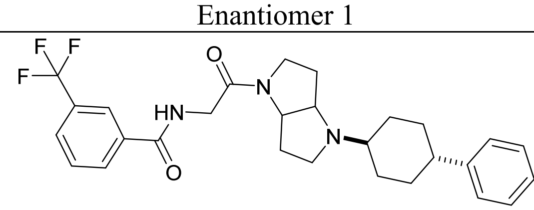
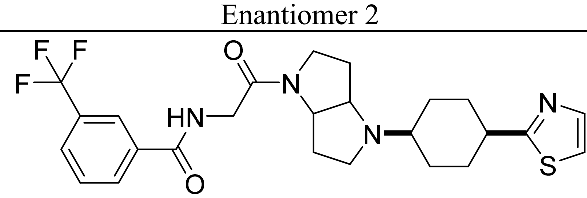
Ex. No.	Structure
1	 Mixture of isomers at the fused core

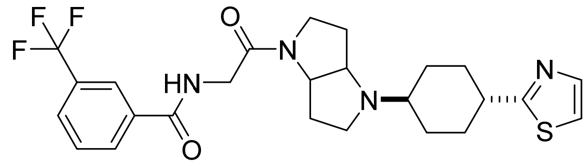
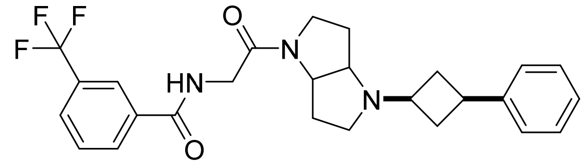
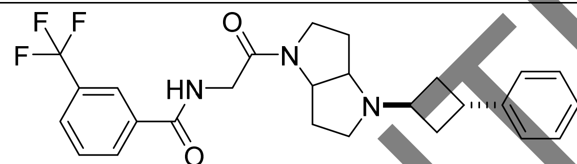
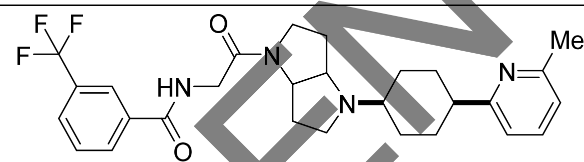
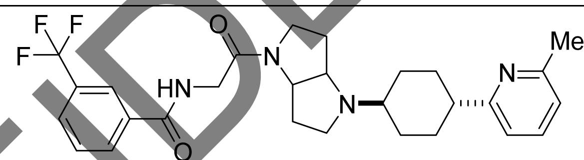
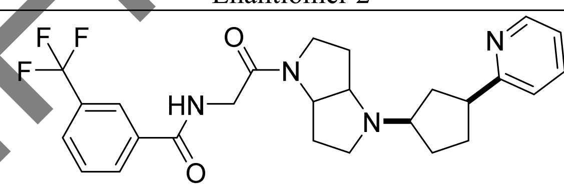
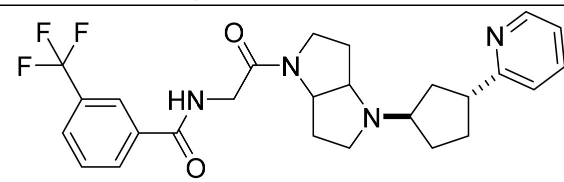
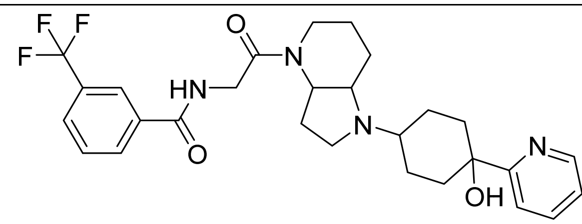
Ex. No.	Structure
2	 Mixture of isomers at the fused core
3	 Mixture of isomers at the fused core
4	 Mixture of isomers at the fused core
5	 Mixture of isomers at the fused core
6	 Mixture of isomers at the fused core
7	 Mixture of isomers at the fused core
8	 Mixture of isomers at the fused core

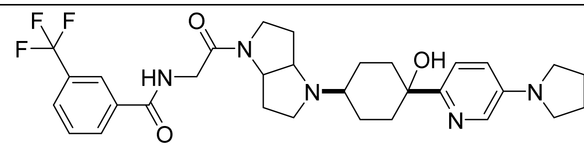
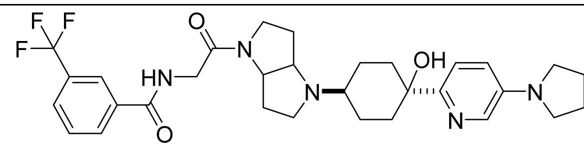
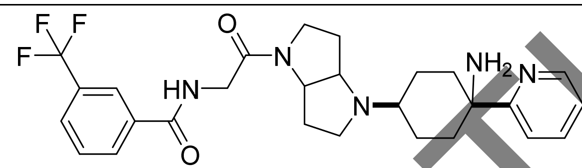
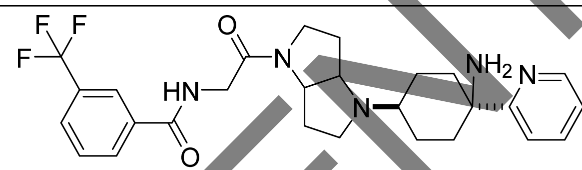
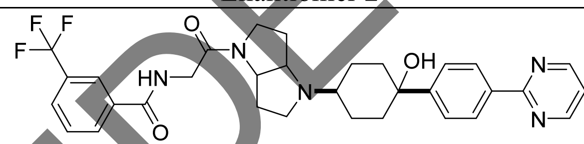
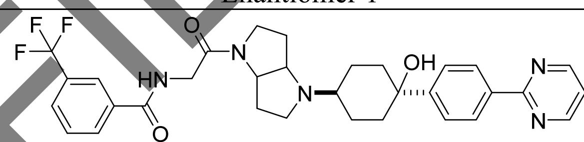
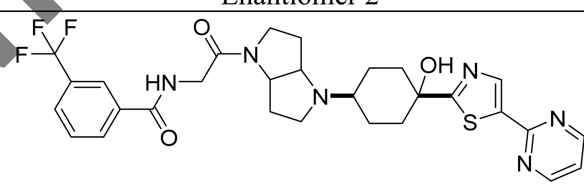
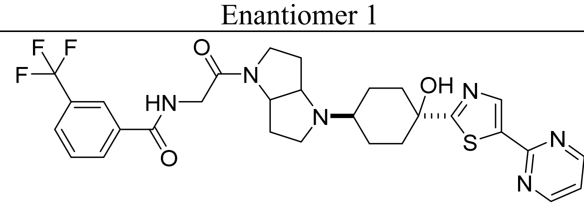
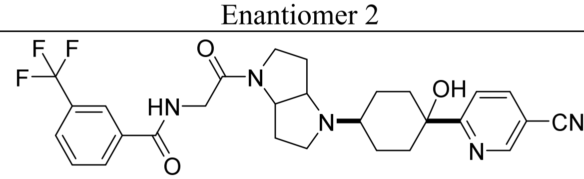
Ex. No.	Structure
9	 Enantiomer 1
10	 Enantiomer 2
13	 Mixture of isomers at the fused core
14	 Mixture of isomers at the fused core
15	 Mixture of isomers at the fused core
16	 Mixture of isomers at the fused core
17	 Mixture of isomers at the fused core
18	 Mixture of isomers at the fused core

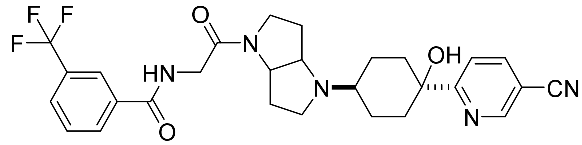
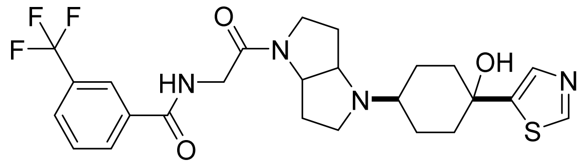
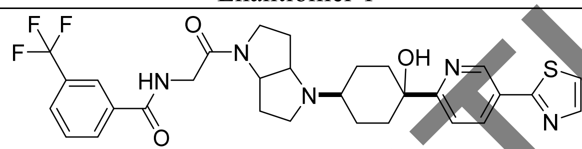
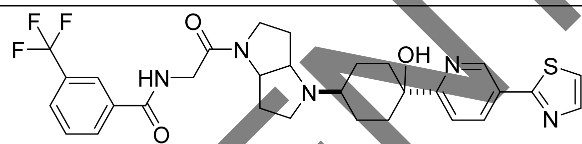
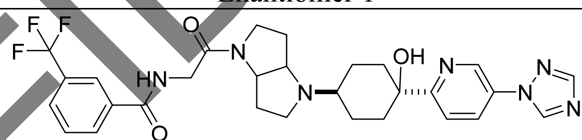
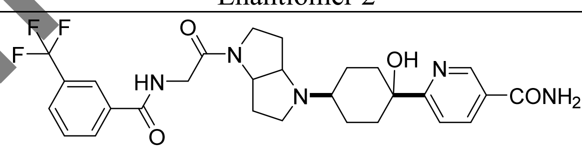
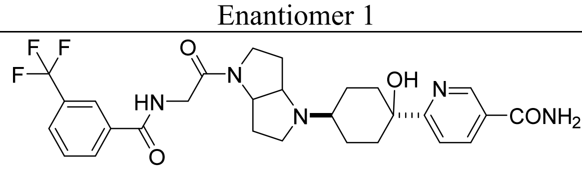
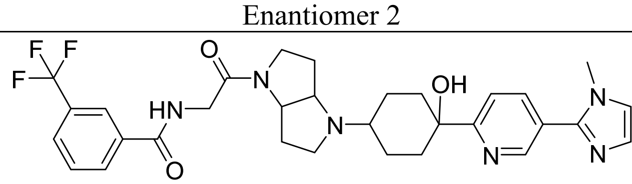
Ex. No.	Structure
19	 Mixture of isomers at the fused core
20	 Mixture of isomers at the fused core
21	 Mixture of isomers at the fused core
22	 Mixture of isomers at the fused core
23	 Mixture of isomers at the fused core
24	 Mixture of isomers at the fused core
25	 Mixture of isomers at the fused core
26	 Mixture of isomers at the fused core
27	 Mixture of isomers at the fused core

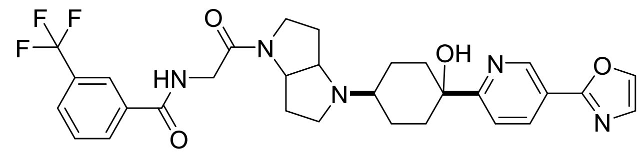
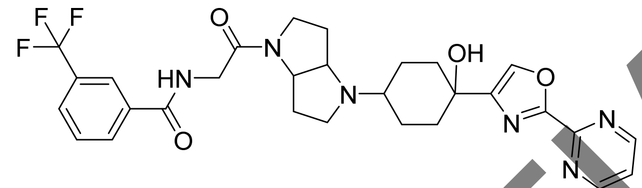
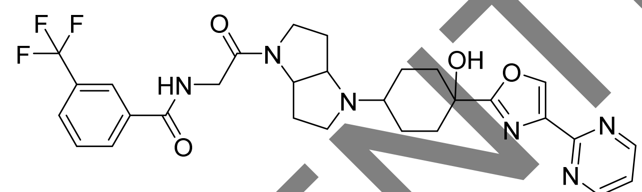
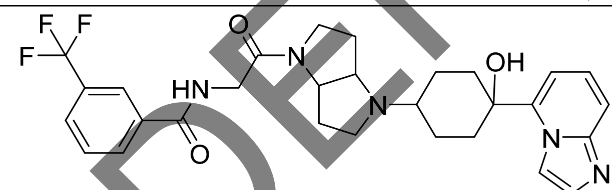
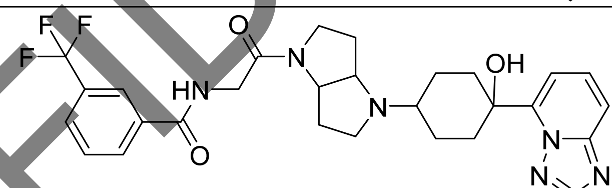
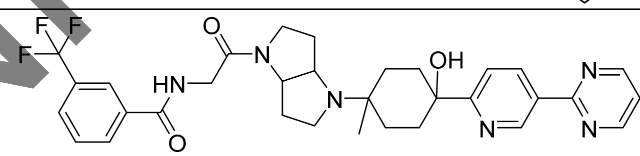
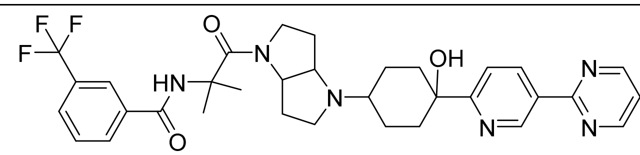
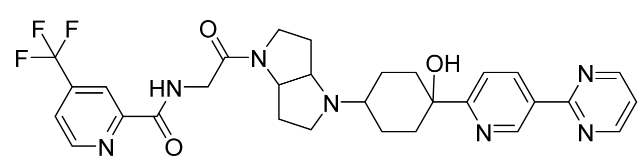
Ex. No.	Structure
28	 Mixture of isomers at the fused core
29	 Enantiomer 1
30	 Enantiomer 2
31	 Mixture of isomers at the fused core
32	 Mixture of isomers at the fused core
33	 Enantiomer 1
34	 Enantiomer 2
35	 Enantiomer 1

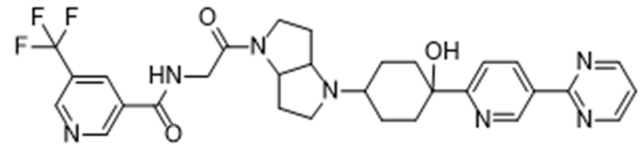
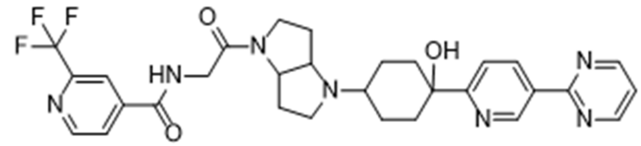
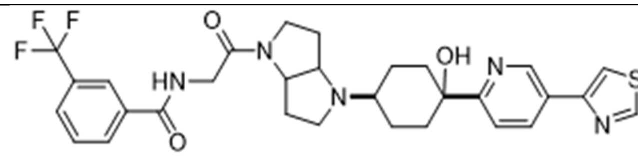
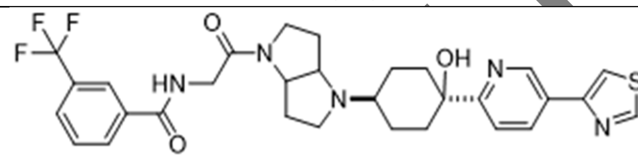
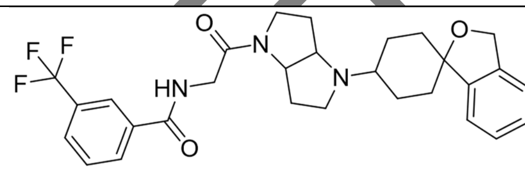
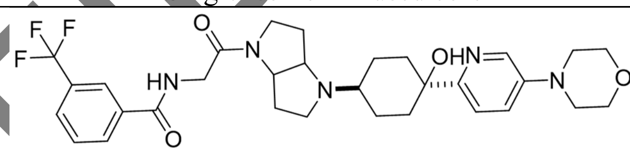
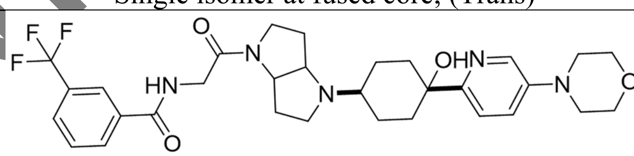
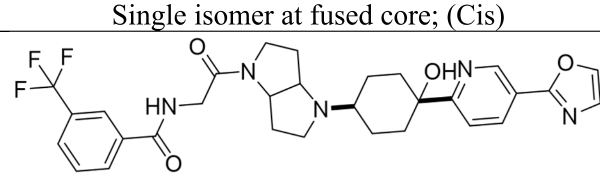
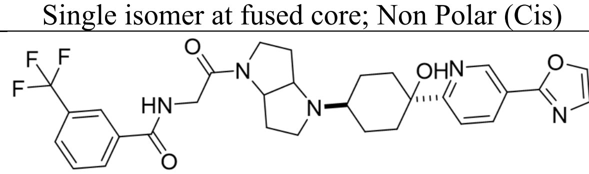
Ex. No.	Structure
36	 Enantiomer 2
37	 Enantiomer 1
38	 Enantiomer 2
39	 Enantiomer 1
40	 Enantiomer 2
41	 Enantiomer 1
42	 Enantiomer 2
43	 Enantiomer 1

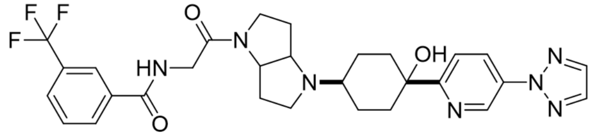
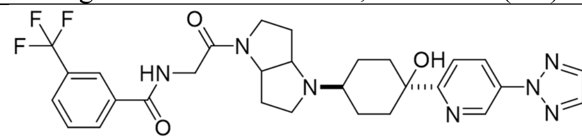
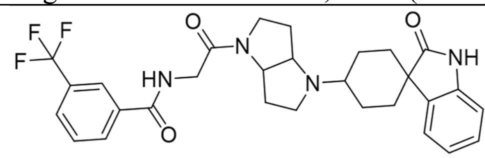
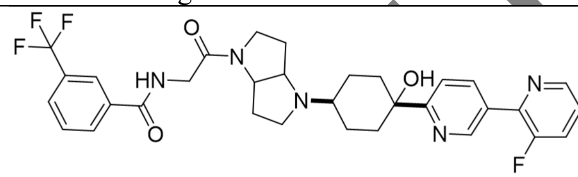
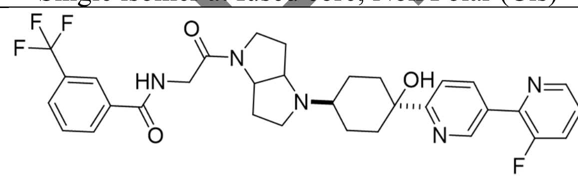
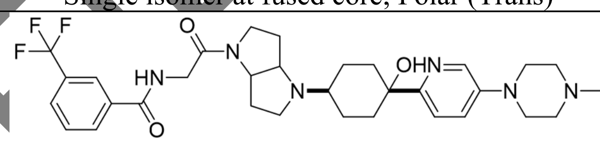
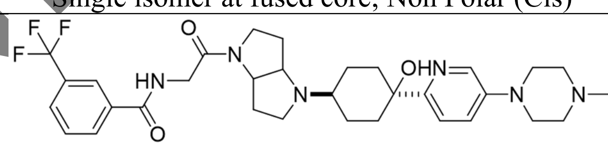
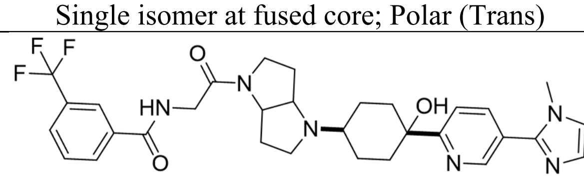
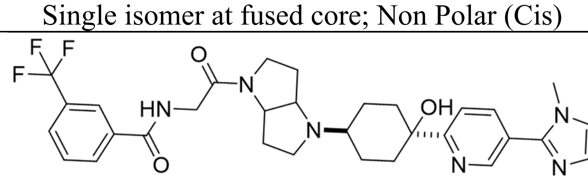
Ex. No.	Structure
44	 Enantiomer 2
45	 Mixture of isomers at the fused core
46	 Mixture of isomers at the fused core
47	 Enantiomer 1
48	 Enantiomer 2
49	
50	 Mixture of isomers at the fused core
51	 Mixture of isomers at the fused core; Mixture of isomers at the cyclohexyl ring

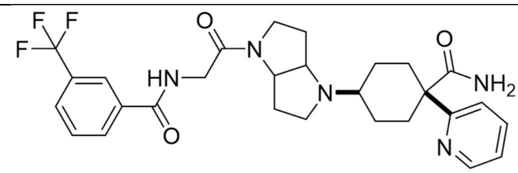
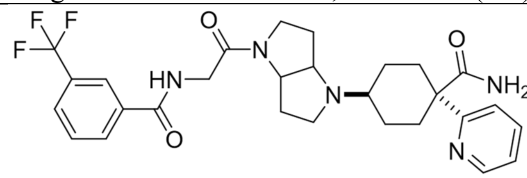
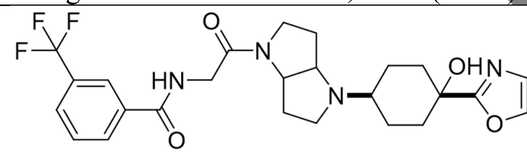
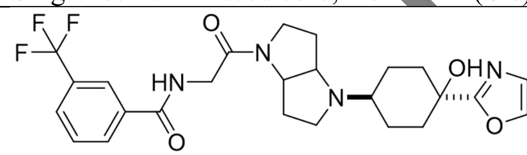
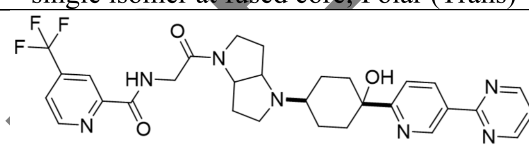
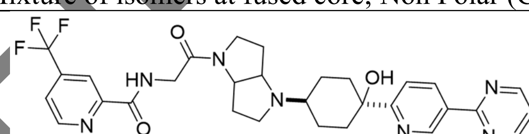
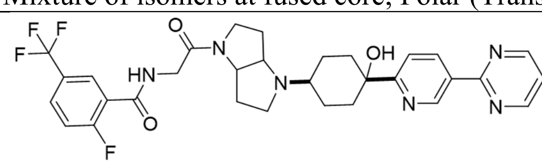
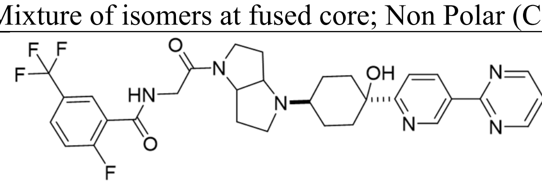
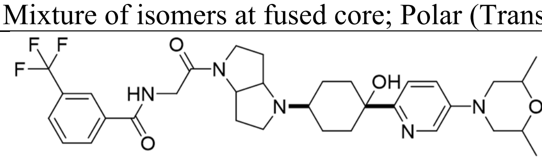
Ex. No.	Structure
52	 Enantiomer 1
53	 Enantiomer 2
54	 Enantiomer 1
55	 Enantiomer 2
56	 Enantiomer 1
57	 Enantiomer 2
58	 Enantiomer 1
59	 Enantiomer 2
60	 Enantiomer 1

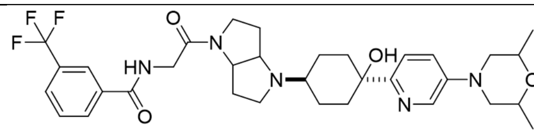
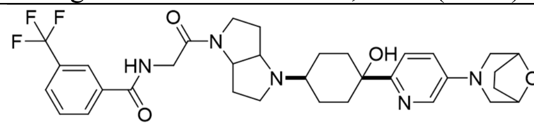
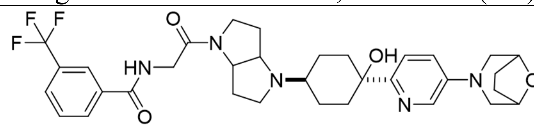
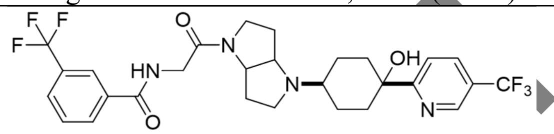
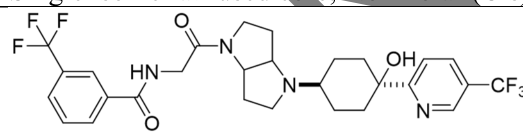
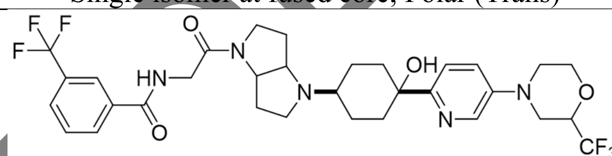
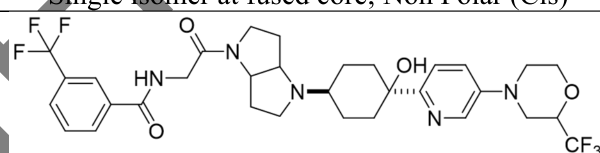
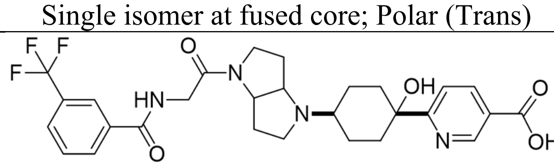
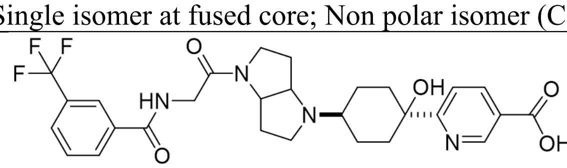
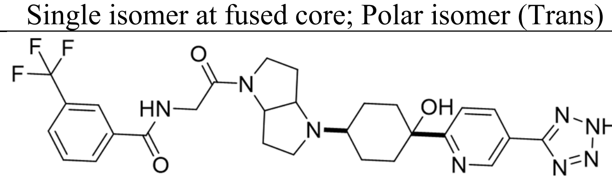
Ex. No.	Structure
61	 Enantiomer 2
62	 Enantiomer 1
63	 Enantiomer 1
64	 Enantiomer 2
65	 Enantiomer 1
66	 Enantiomer 2
67	 Enantiomer 1
68	 Enantiomer 2
69	

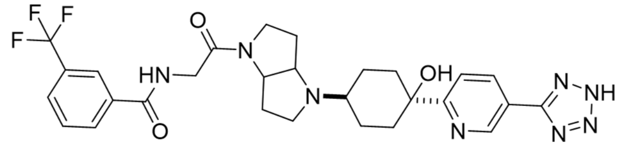
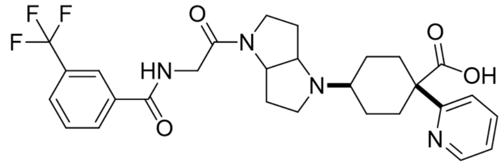
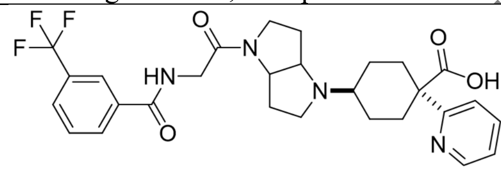
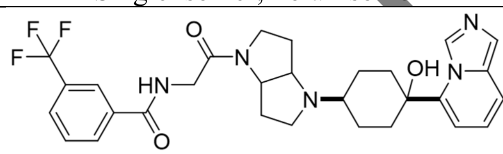
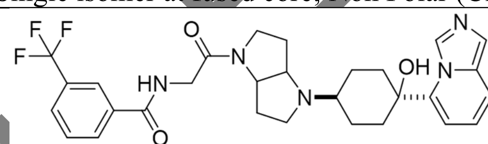
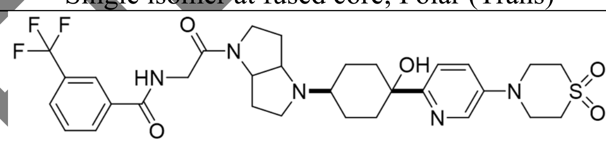
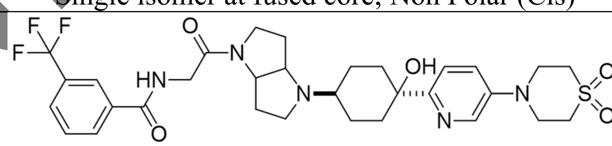
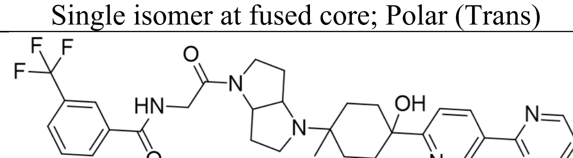
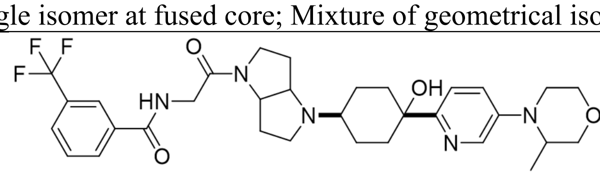
Ex. No.	Structure
70	 Enantiomer 1
71	
72	
73	
74	
75	
76	
77	

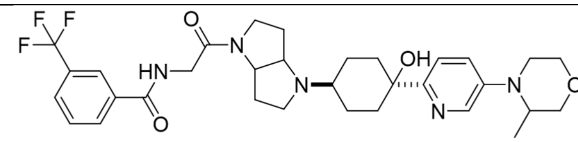
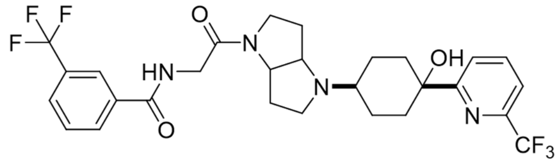
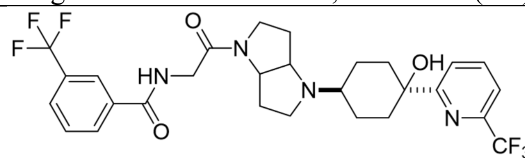
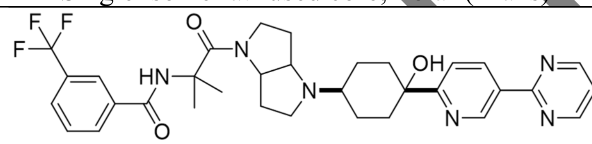
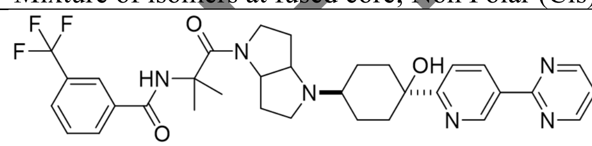
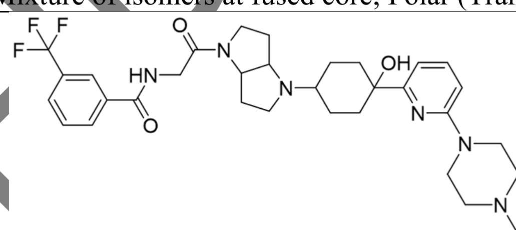
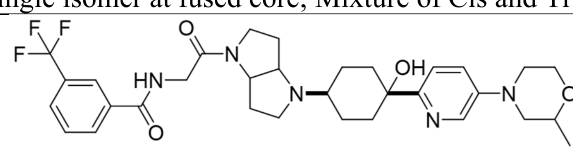
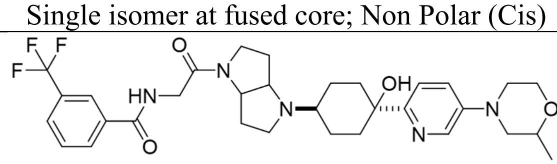
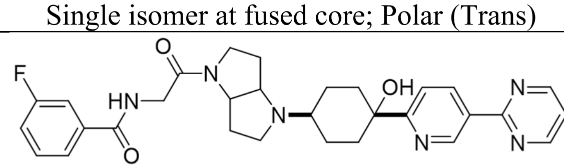
Ex. No.	Structure
78	
79	
80	 Enantiomer 1
81	 Enantiomer 2
82	 Single isomer at fused core
83	 Single isomer at fused core; (Trans)
84	 Single isomer at fused core; (Cis)
85	 Single isomer at fused core; Non Polar (Cis)
86	 single isomer at fused core; Polar (Trans)

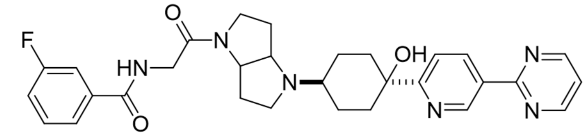
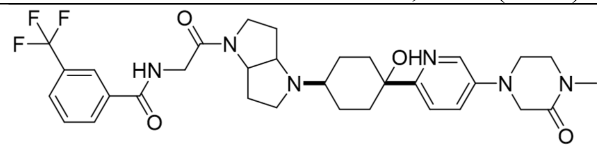
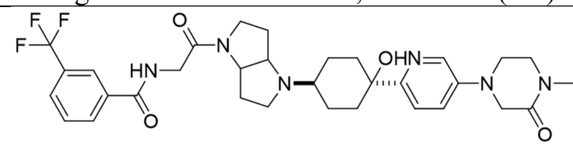
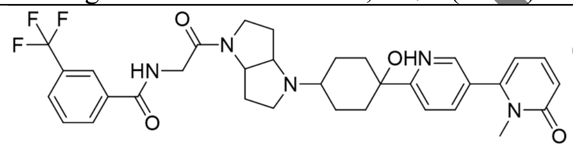
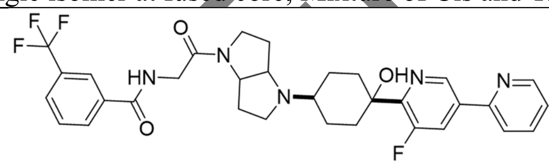
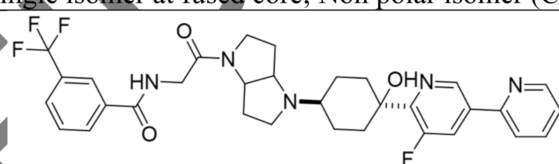
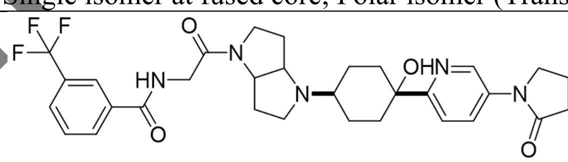
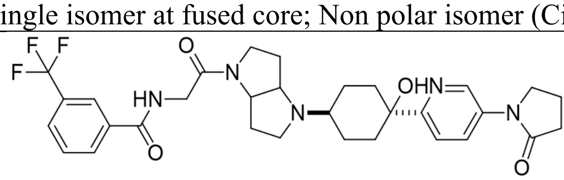
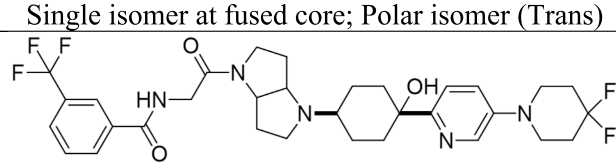
Ex. No.	Structure
87	 Single isomer at fused core; Non Polar (Cis)
88	 Single isomer at fused core; Polar (Trans)
89	 Single isomer at fused core
90	 Single isomer at fused core; Non Polar (Cis)
91	 Single isomer at fused core; Polar (Trans)
92	 Single isomer at fused core; Non Polar (Cis)
93	 Single isomer at fused core; Polar (Trans)
94	 Single isomer at fused core; Non Polar (Cis)
95	 Single isomer at fused core; Polar (Trans)

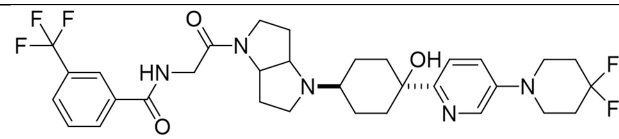
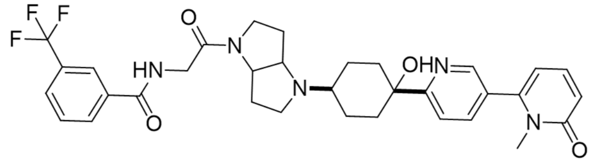
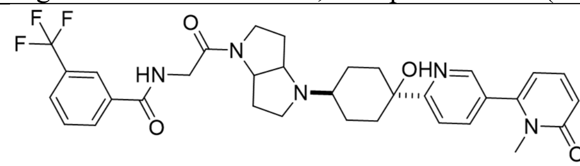
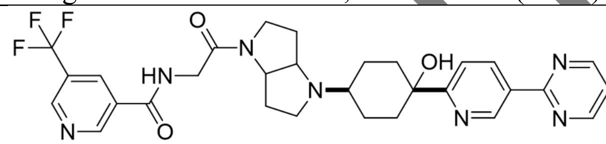
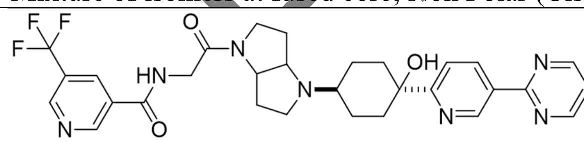
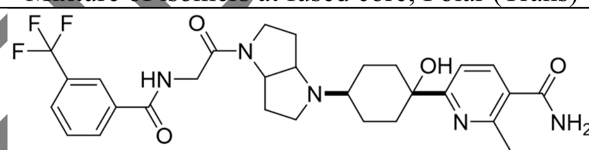
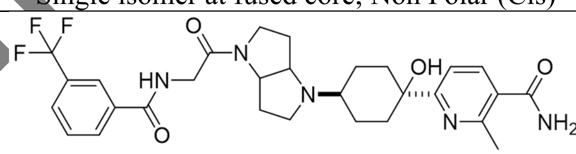
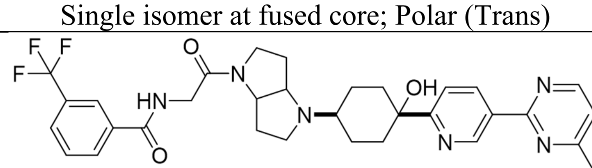
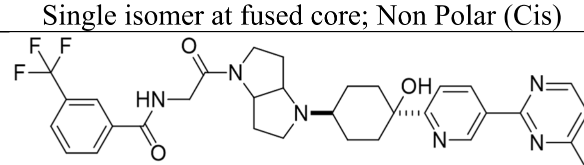
Ex. No.	Structure
96	 Single isomer at fused core; Non Polar (Cis)
97	 Single isomer at fused core; Polar (Trans)
98	 Single isomer at fused core; Non Polar (Cis)
99	 single isomer at fused core; Polar (Trans)
100	 Mixture of isomers at fused core; Non Polar (Cis)
101	 Mixture of isomers at fused core; Polar (Trans)
102	 Mixture of isomers at fused core; Non Polar (Cis)
103	 Mixture of isomers at fused core; Polar (Trans)
104	 Single isomer at fused core; Non Polar (Cis)

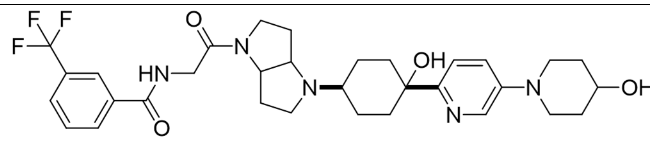
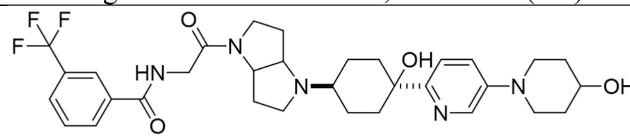
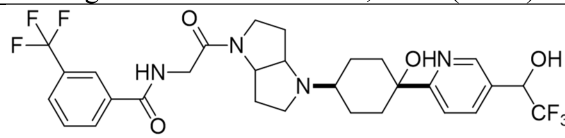
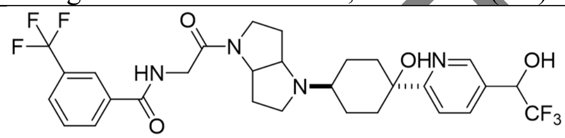
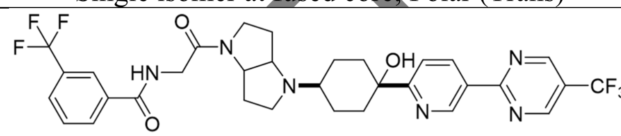
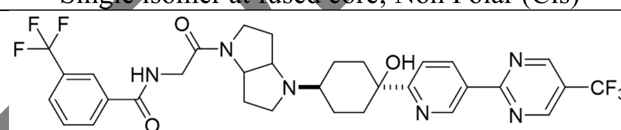
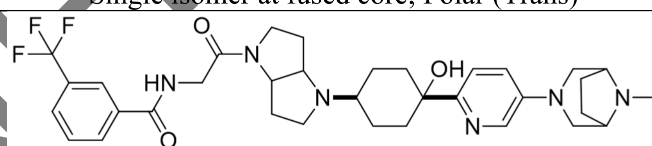
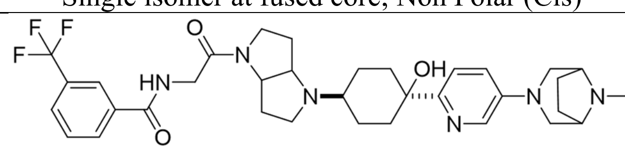
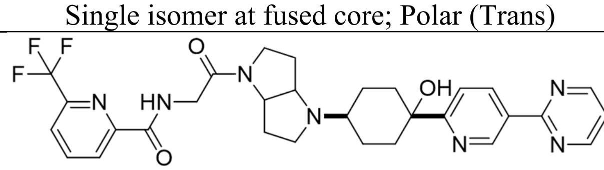
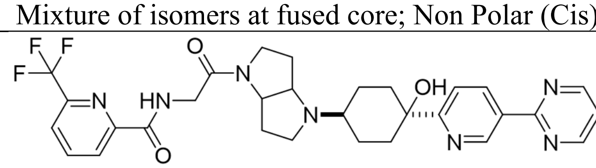
Ex. No.	Structure
105	 Single isomer at fused core; Polar (Trans)
106	 Single isomer at fused core; Non Polar (Cis)
107	 Single isomer at fused core; Polar (Trans)
108	 Single isomer at fused core; Non Polar (Cis)
109	 Single isomer at fused core; Polar (Trans)
110	 Single isomer at fused core; Non Polar (Cis)
111	 Single isomer at fused core; Polar (Trans)
112	 Single isomer at fused core; Non polar isomer (Cis)
113	 Single isomer at fused core; Polar isomer (Trans)
114	 Single isomer at fused core; Non polar isomer (Cis)

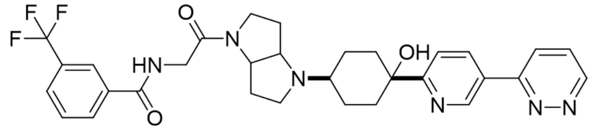
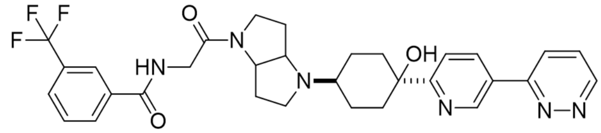
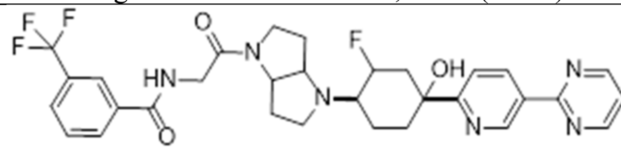
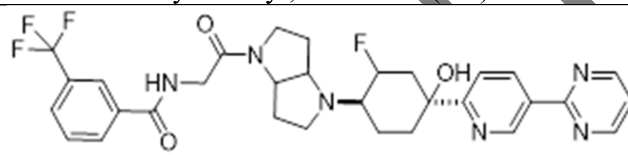
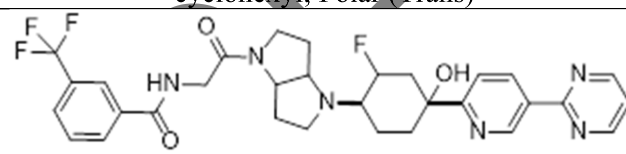
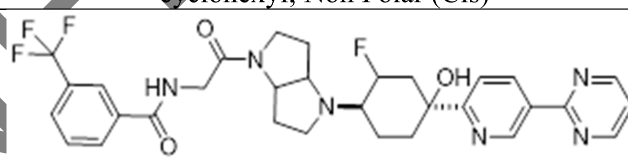
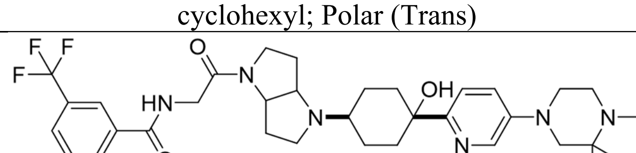
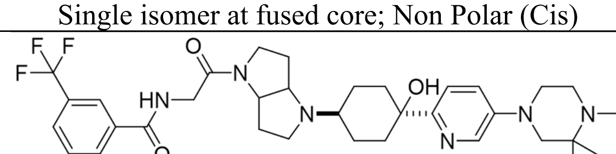
Ex. No.	Structure
115	 Single isomer at fused core; Polar isomer (Trans)
116	 Single isomer; Non polar isomer
117	 Single isomer; Polar isomer
118	 Single isomer at fused core; Non Polar (Cis)
119	 Single isomer at fused core; Polar (Trans)
120	 Single isomer at fused core; Non Polar (Cis)
121	 Single isomer at fused core; Polar (Trans)
122	 Single isomer at fused core; Mixture of geometrical isomers
123	 Single isomer at fused core; Non Polar (Cis)

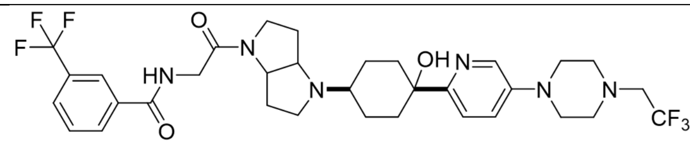
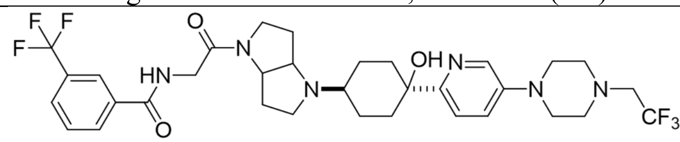
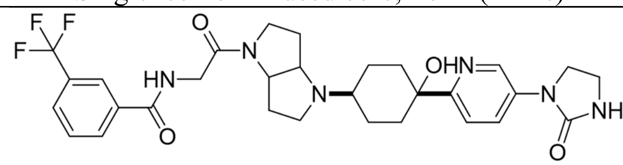
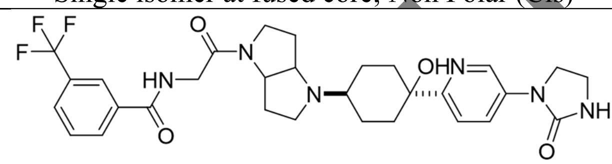
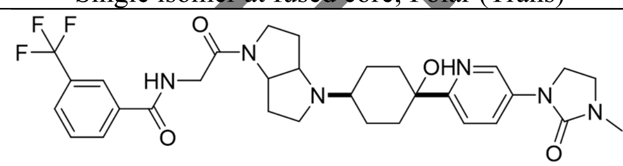
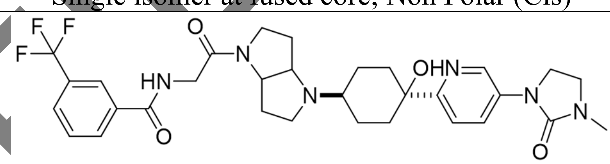
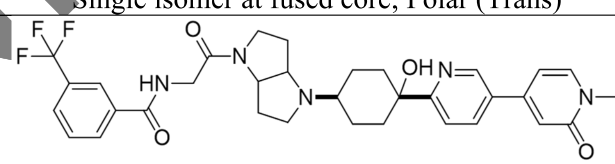
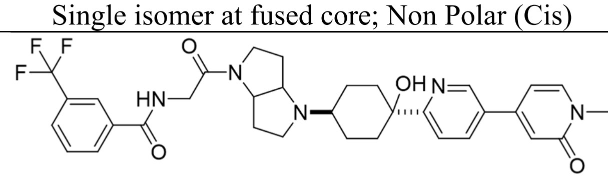
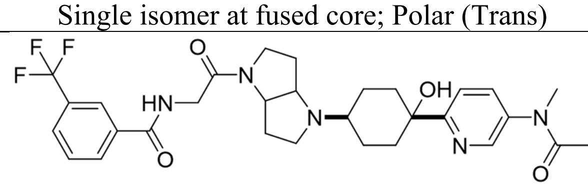
Ex. No.	Structure
124	 Single isomer at fused core; Polar (Trans)
125	 Single isomer at fused core; Non Polar (Cis)
126	 Single isomer at fused core; Polar (Trans)
127	 Mixture of isomers at fused core; Non Polar (Cis)
128	 Mixture of isomers at fused core; Polar (Trans)
129	 Single isomer at fused core; Mixture of Cis and Trans
130	 Single isomer at fused core; Non Polar (Cis)
131	 Single isomer at fused core; Polar (Trans)
132	 Mixture of isomers at fused core; Non Polar (Cis)

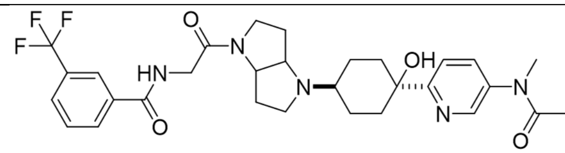
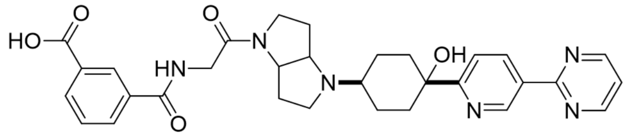
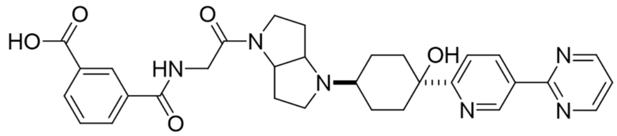
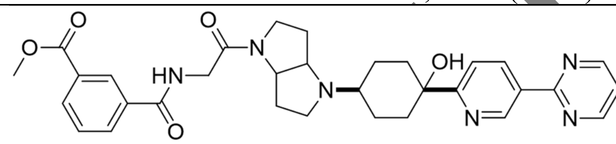
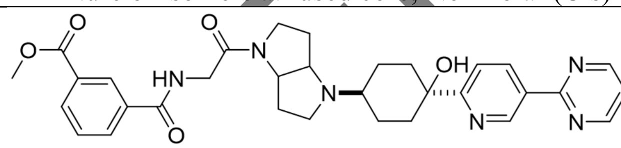
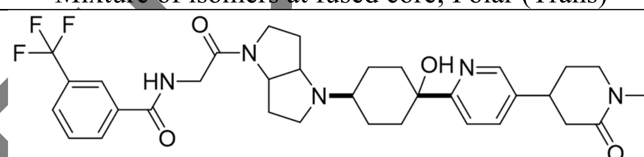
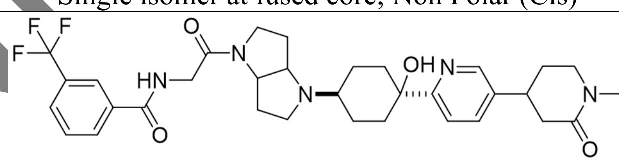
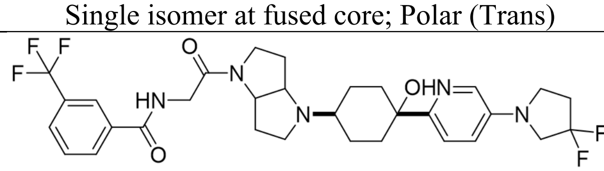
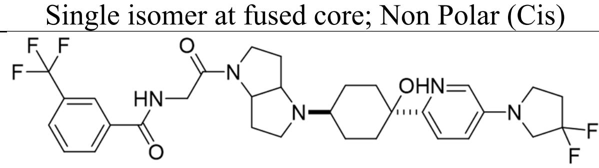
Ex. No.	Structure
133	 Mixture of isomers at fused core; Polar (Trans)
134	 Single isomer at fused core; Non Polar (Cis)
135	 Single isomer at fused core; Polar (Trans)
136	 Single isomer at fused core; Mixture of Cis and Trans
137	 Single isomer at fused core; Non polar isomer (Cis)
138	 Single isomer at fused core; Polar isomer (Trans)
139	 Single isomer at fused core; Non polar isomer (Cis)
140	 Single isomer at fused core; Polar isomer (Trans)
141	 Single isomer at fused core; Non Polar (Cis)

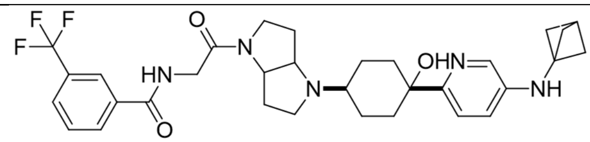
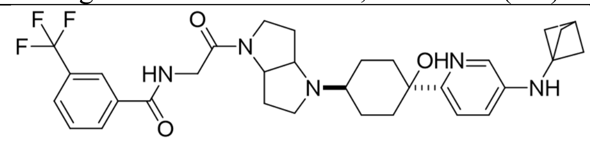
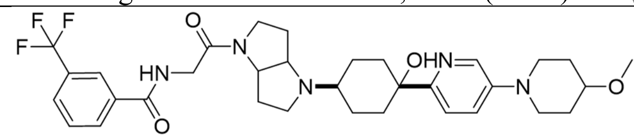
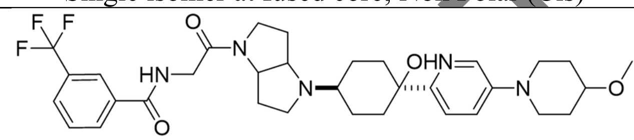
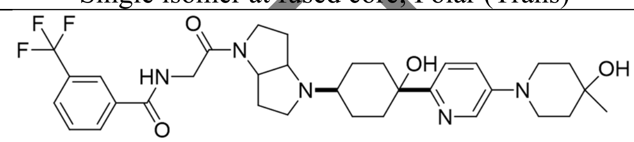
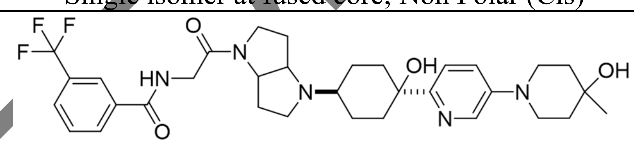
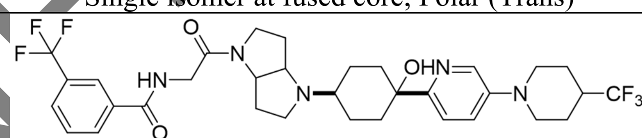
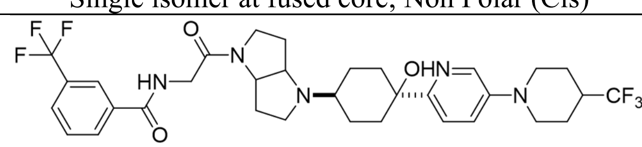
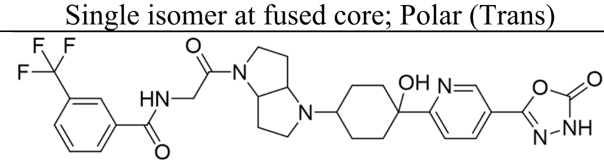
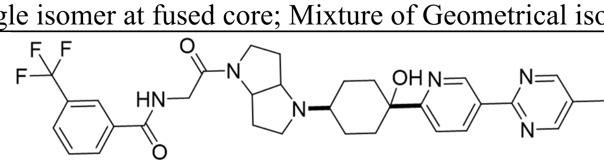
Ex. No.	Structure
142	 Single isomer at fused core; Polar (Trans)
143	 Single isomer at fused core; Non polar isomer (Cis)
144	 Single isomer at fused core; Polar isomer (Trans)
145	 Mixture of isomers at fused core; Non Polar (Cis)
146	 Mixture of isomers at fused core; Polar (Trans)
147	 Single isomer at fused core; Non Polar (Cis)
148	 Single isomer at fused core; Polar (Trans)
149	 Single isomer at fused core; Non Polar (Cis)
150	 Single isomer at fused core; Polar (Trans)

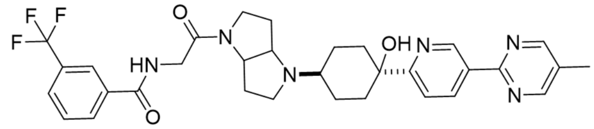
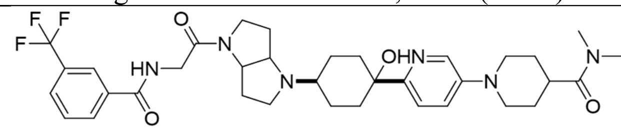
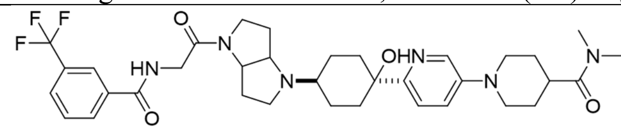
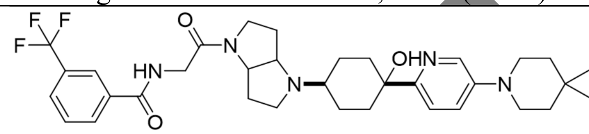
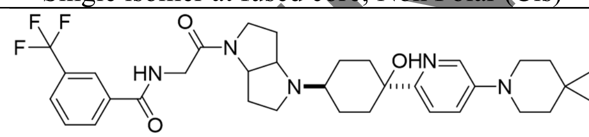
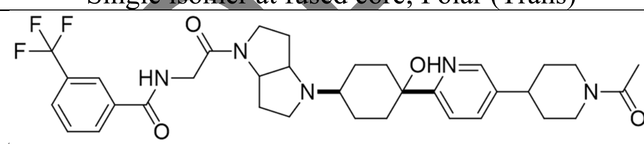
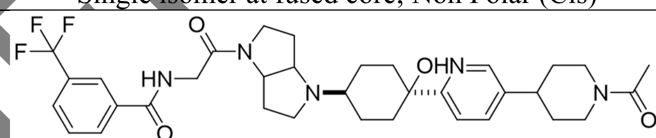
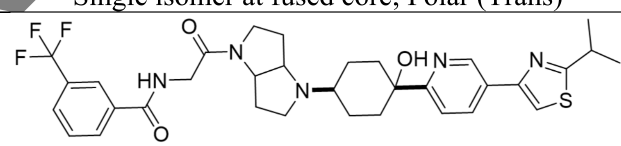
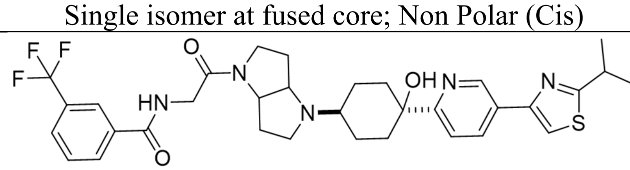
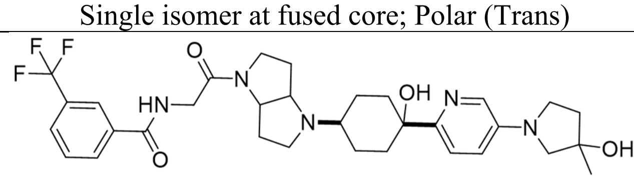
Ex. No.	Structure
151	 Single isomer at fused core; Non Polar (Cis)
152	 Single isomer at fused core; Polar (Trans)
153	 Single isomer at fused core; Non Polar (Cis)
154	 Single isomer at fused core; Polar (Trans)
155	 Single isomer at fused core; Non Polar (Cis)
156	 Single isomer at fused core; Polar (Trans)
157	 Single isomer at fused core; Non Polar (Cis)
158	 Single isomer at fused core; Polar (Trans)
159	 Mixture of isomers at fused core; Non Polar (Cis)
160	 Mixture of isomers at fused core; Polar (Trans)

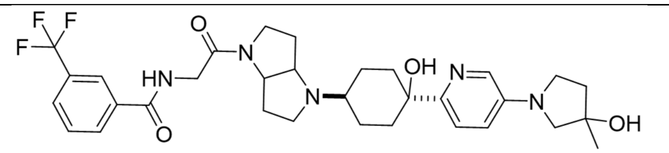
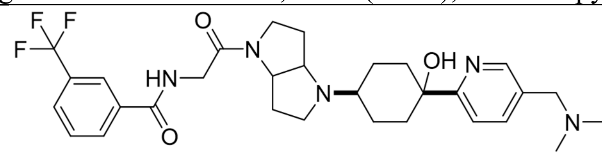
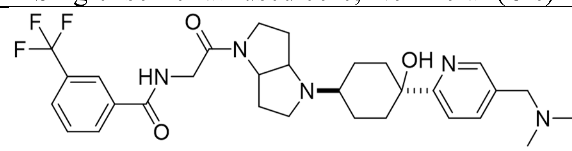
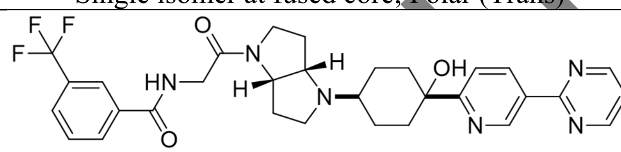
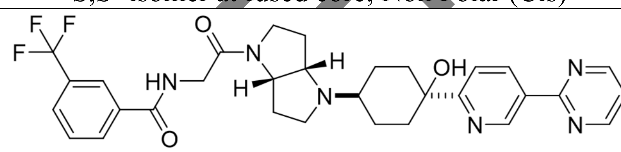
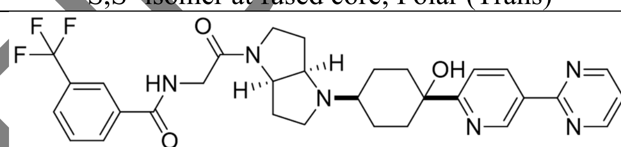
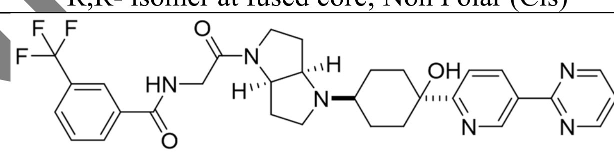
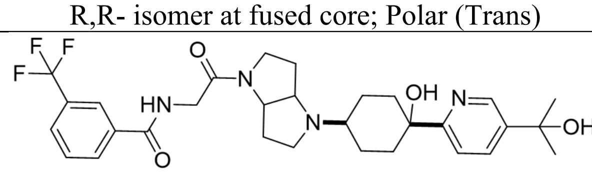
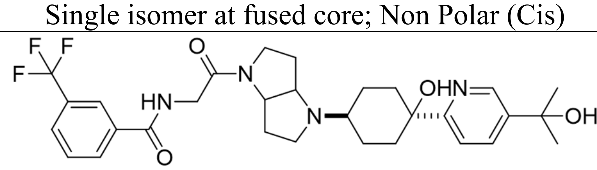
Ex. No.	Structure
161	 Single isomer at fused core; Non Polar (Cis)
162	 Single isomer at fused core; Polar (Trans)
163	 Single isomer at fused core; Diastereoisomer 1 at cyclohexyl; Non Polar (Cis)
164	 Single isomer at fused core; Diastereoisomer 1 at cyclohexyl; Polar (Trans)
165	 Single isomer at fused core; Diastereoisomer 2 at cyclohexyl; Non Polar (Cis)
166	 Single isomer at fused core; Diastereoisomer 2 at cyclohexyl; Polar (Trans)
167	 Single isomer at fused core; Non Polar (Cis)
168	 Single isomer at fused core; Polar (Trans)

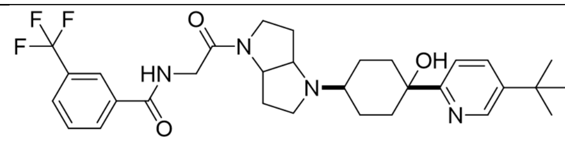
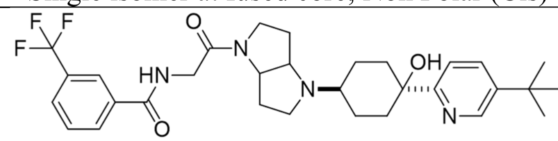
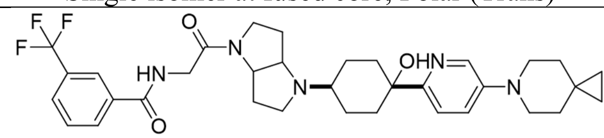
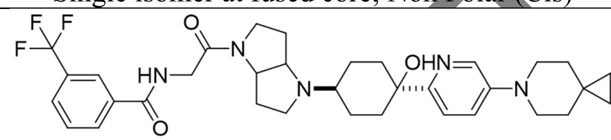
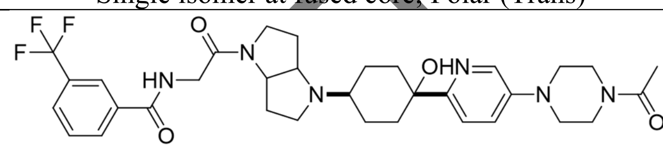
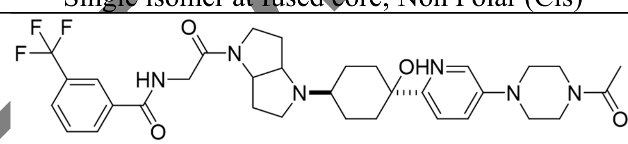
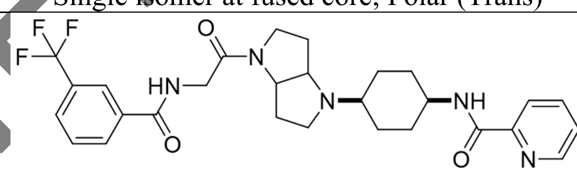
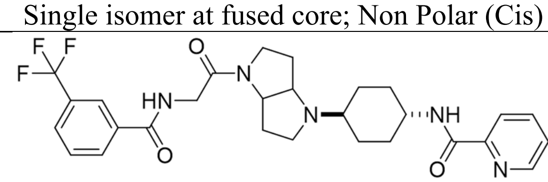
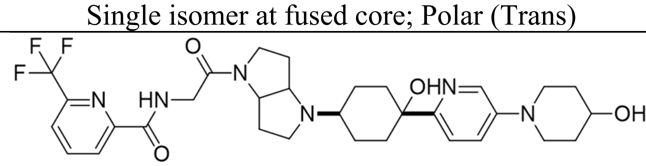
Ex. No.	Structure
169	 Single isomer at fused core; Non Polar (Cis)
170	 Single isomer at fused core; Polar (Trans)
171	 Single isomer at fused core; Non Polar (Cis)
172	 Single isomer at fused core; Polar (Trans)
173	 Single isomer at fused core; Non Polar (Cis)
174	 Single isomer at fused core; Polar (Trans)
175	 Single isomer at fused core; Non Polar (Cis)
176	 Single isomer at fused core; Polar (Trans)
177	 Single isomer at fused core; Non Polar (Cis)

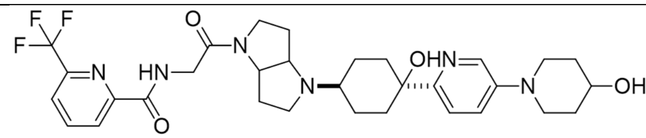
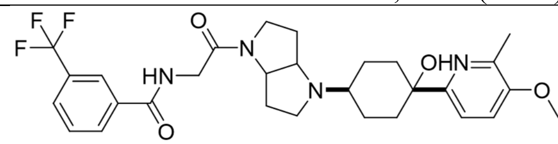
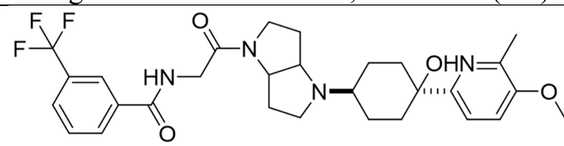
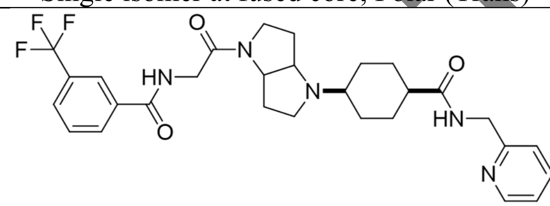
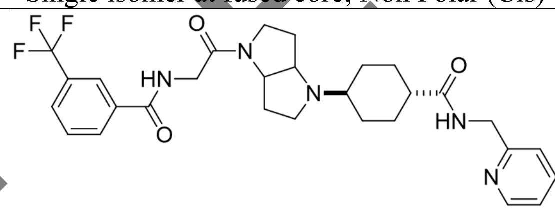
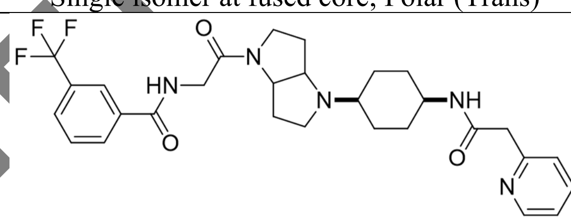
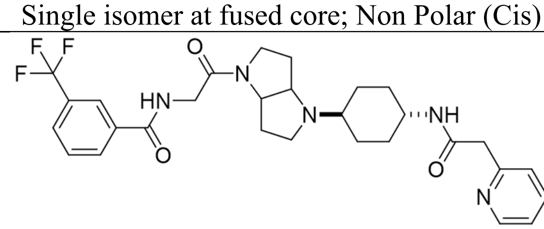
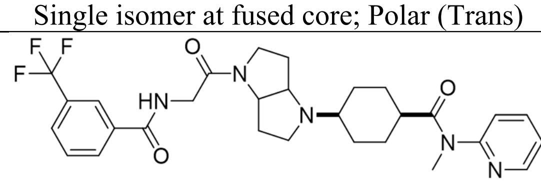
Ex. No.	Structure
178	 Single isomer at fused core; Polar (Trans)
179	 Mixture of isomers at fused core; Non Polar (Cis)
180	 Mixture of isomers at fused core; Polar (Trans)
181	 Mixture of isomers at fused core; Non Polar (Cis)
182	 Mixture of isomers at fused core; Polar (Trans)
183	 Single isomer at fused core; Non Polar (Cis)
184	 Single isomer at fused core; Polar (Trans)
185	 Single isomer at fused core; Non Polar (Cis)
186	 Single isomer at fused core; Polar (Trans)

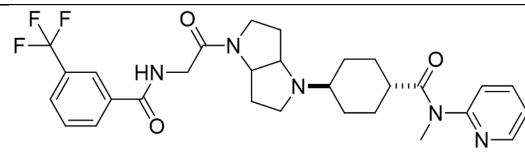
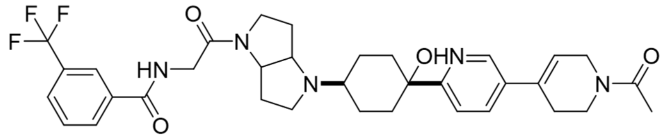
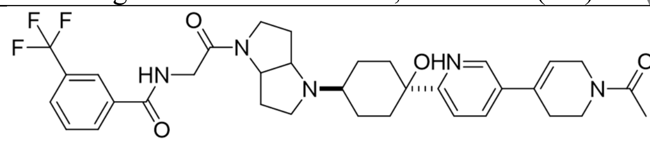
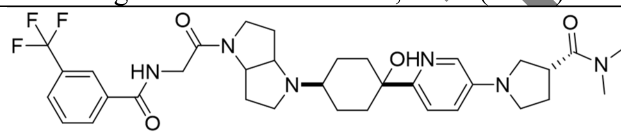
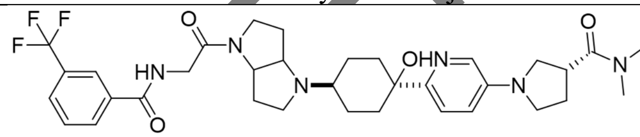
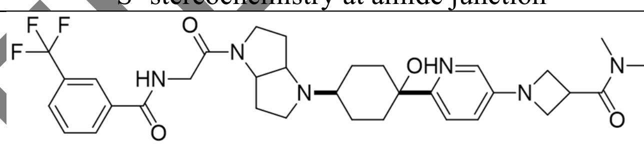
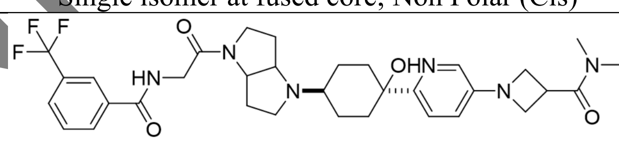
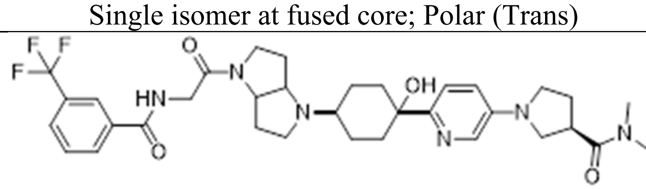
Ex. No.	Structure
187	 Single isomer at fused core; Non Polar (Cis)
188	 Single isomer at fused core; Polar (Trans)
189	 Single isomer at fused core; Non Polar (Cis)
190	 Single isomer at fused core; Polar (Trans)
191	 Single isomer at fused core; Non Polar (Cis)
192	 Single isomer at fused core; Polar (Trans)
193	 Single isomer at fused core; Non Polar (Cis)
194	 Single isomer at fused core; Polar (Trans)
195	 Single isomer at fused core; Mixture of Geometrical isomers
196	 Single isomer at fused core; Non Polar (Cis)

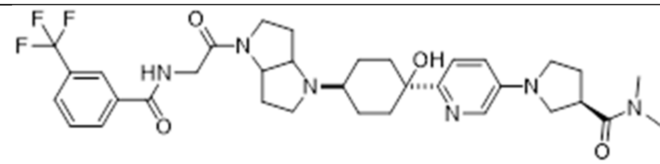
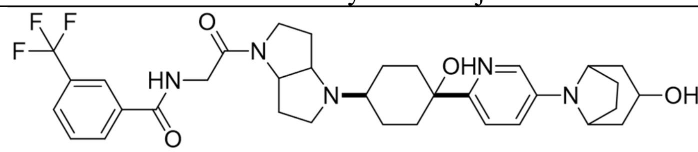
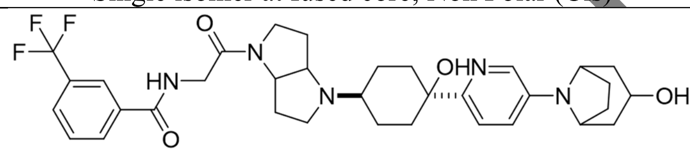
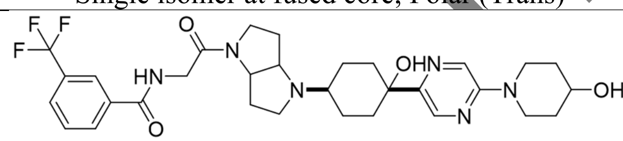
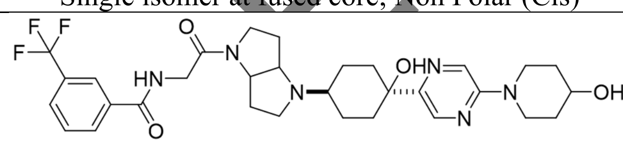
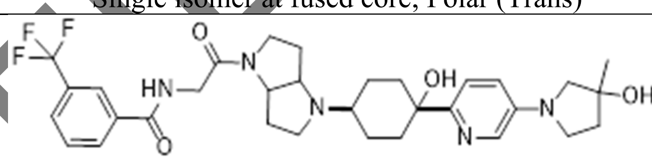
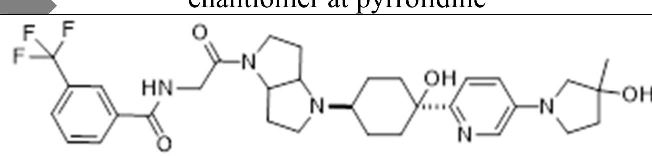
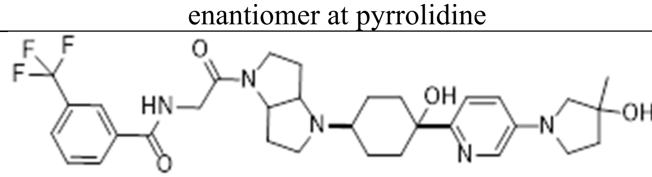
Ex. No.	Structure
197	 Single isomer at fused core; Polar (Trans)
198	 Single isomer at fused core; Non Polar (Cis)
199	 Single isomer at fused core; Polar (Trans)
200	 Single isomer at fused core; Non Polar (Cis)
201	 Single isomer at fused core; Polar (Trans)
202	 Single isomer at fused core; Non Polar (Cis)
203	 Single isomer at fused core; Polar (Trans)
204	 Single isomer at fused core; Non Polar (Cis)
205	 Single isomer at fused core; Polar (Trans)
206	 Single isomer at fused core; Non Polar (Cis); Racemic pyrrole

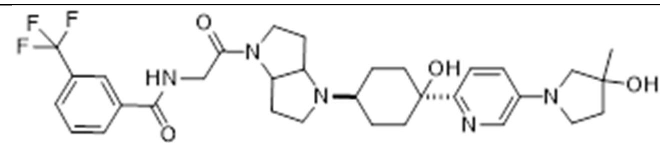
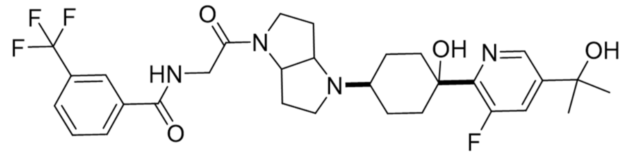
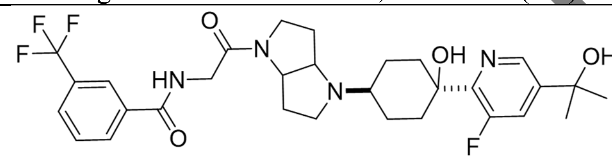
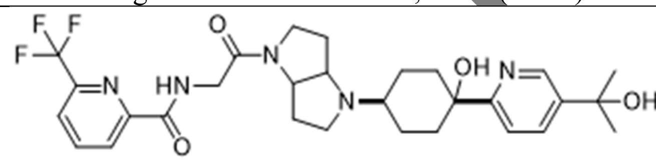
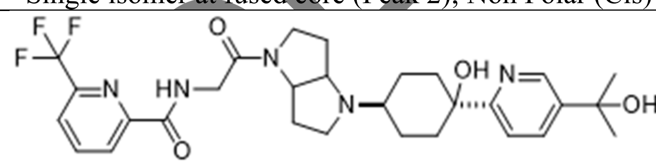
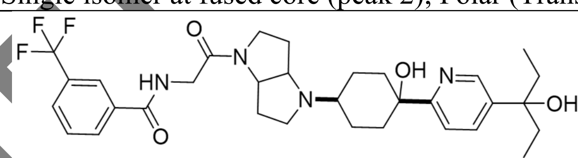
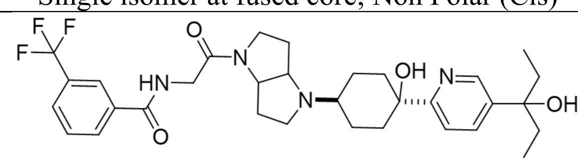
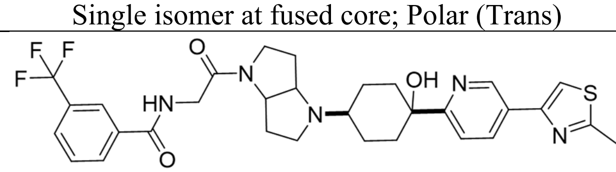
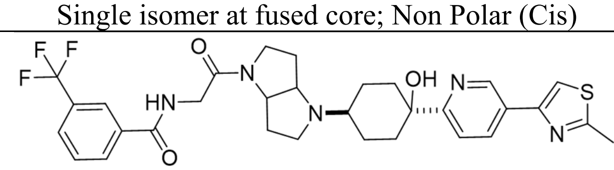
Ex. No.	Structure
207	 Single isomer at fused core; Polar (Trans); Racemic pyrrole
208	 Single isomer at fused core; Non Polar (Cis)
209	 Single isomer at fused core; Polar (Trans)
210	 S,S- isomer at fused core; Non Polar (Cis)
211	 S,S- isomer at fused core; Polar (Trans)
212	 R,R- isomer at fused core; Non Polar (Cis)
213	 R,R- isomer at fused core; Polar (Trans)
214	 Single isomer at fused core; Non Polar (Cis)
215	 Single isomer at fused core; Polar (Trans)

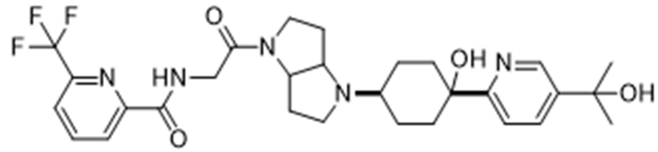
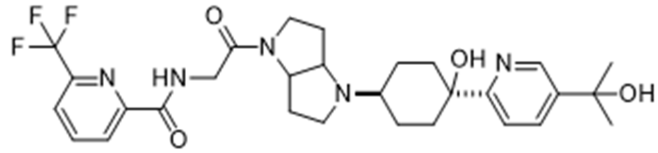
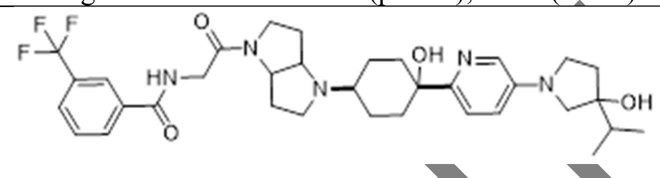
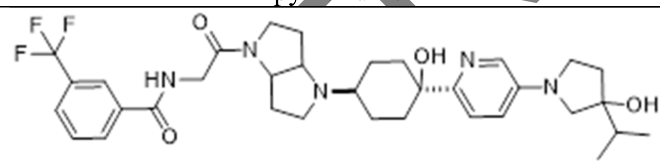
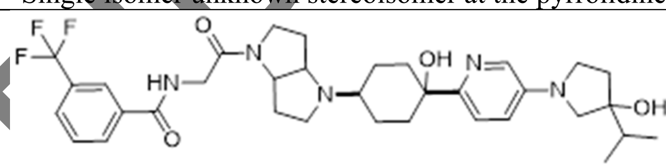
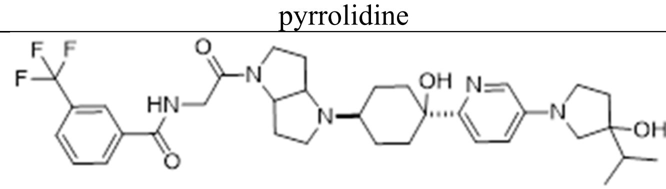
Ex. No.	Structure
216	 Single isomer at fused core; Non Polar (Cis)
217	 Single isomer at fused core; Polar (Trans)
218	 Single isomer at fused core; Non Polar (Cis)
219	 Single isomer at fused core; Polar (Trans)
220	 Single isomer at fused core; Non Polar (Cis)
221	 Single isomer at fused core; Polar (Trans)
222	 Single isomer at fused core; Non Polar (Cis)
223	 Single isomer at fused core; Polar (Trans)
224	 Mixture of isomers at fused core; Non Polar (Cis)

Ex. No.	Structure
225	 Mixture of isomers at fused core; Polar (Trans)
226	 Single isomer at fused core; Non Polar (Cis)
227	 Single isomer at fused core; Polar (Trans)
228	 Single isomer at fused core; Non Polar (Cis)
229	 Single isomer at fused core; Polar (Trans)
230	 Single isomer at fused core; Non Polar (Cis)
231	 Single isomer at fused core; Polar (Trans)
232	 Single isomer at fused core; Non Polar (Cis)

Ex. No.	Structure
233	 Single isomer at fused core; Polar (Trans)
234	 Single isomer at fused core; Non Polar (Cis)
235	 Single isomer at fused core; Polar (Trans)
236	 Single isomer at fused core; Non Polar (Cis); S- stereochemistry at amide junction
237	 Single isomer at fused core; Polar (Trans); S- stereochemistry at amide junction
238	 Single isomer at fused core; Non Polar (Cis)
239	 Single isomer at fused core; Polar (Trans)
240	 Single isomer at fused core; Non Polar (Cis); R- stereochemistry at amide junction

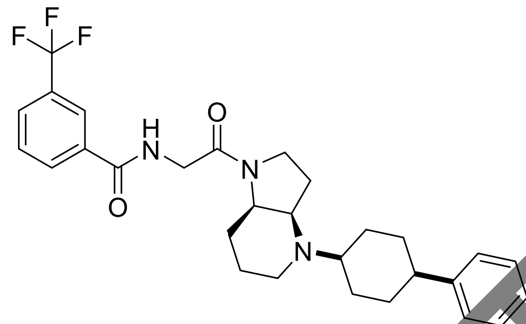
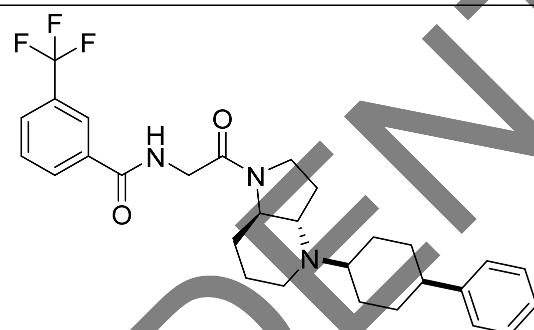
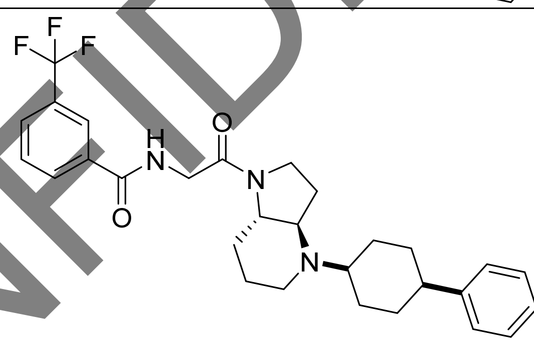
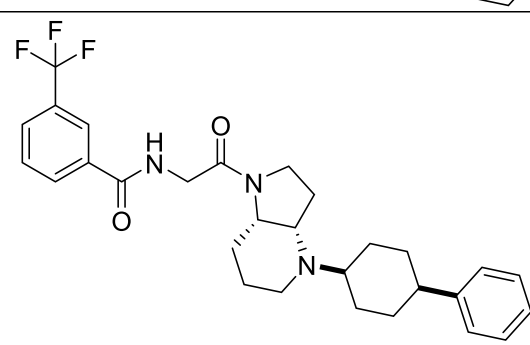
Ex. No.	Structure
241	 Single isomer at fused core; Polar (Trans); R- stereochemistry at amide junction
242	 Single isomer at fused core; Non Polar (Cis)
243	 Single isomer at fused core; Polar (Trans)
244	 Single isomer at fused core; Non Polar (Cis)
245	 Single isomer at fused core; Polar (Trans)
246	 Single isomer at fused core; Peak 1; Non Polar (Cis); single enantiomer at pyrrolidine
247	 Single isomer at fused core; Peak 1; Polar (Trans); single enantiomer at pyrrolidine
248	 Single isomer at fused core; Peak 2; Non Polar (Cis); single enantiomer at pyrrolidine

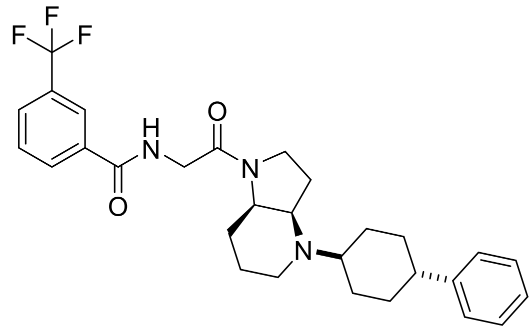
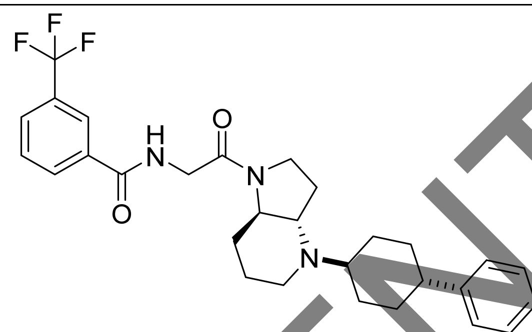
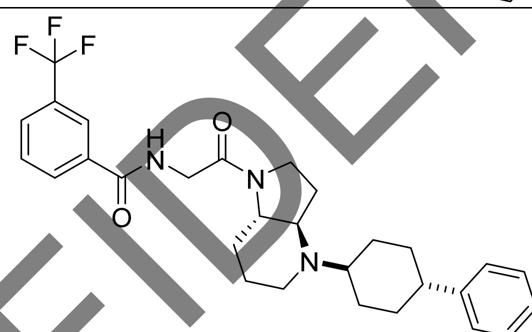
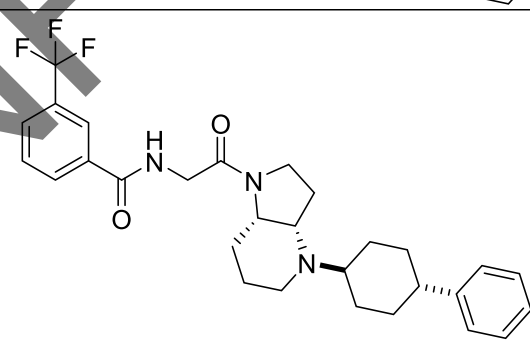
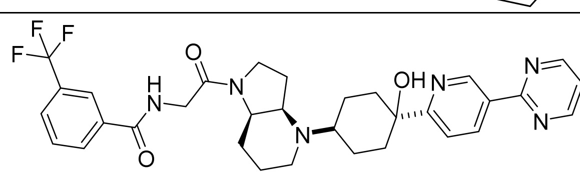
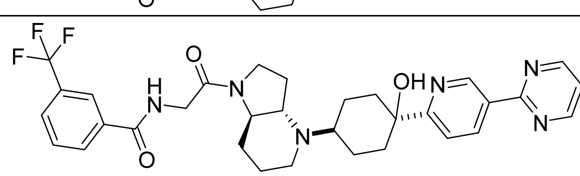
Ex. No.	Structure
249	 Single isomer at fused core; Peak 2; Polar (Trans); single enantiomer at pyrrolidine
250	 Single isomer at fused core; Non Polar (Cis)
251	 Single isomer at fused core; Polar (Trans)
252	 Single isomer at fused core (Peak 2); Non Polar (Cis)
253	 Single isomer at fused core (peak 2); Polar (Trans)
254	 Single isomer at fused core; Non Polar (Cis)
255	 Single isomer at fused core; Polar (Trans)
256	 Single isomer at fused core; Non Polar (Cis)
257	 Single isomer at fused core; Polar (Trans)

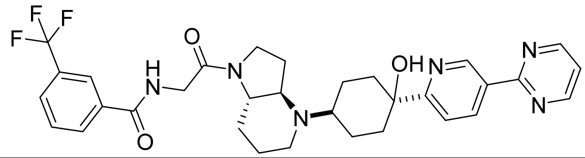
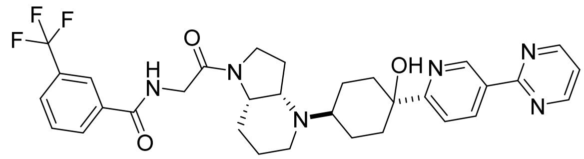
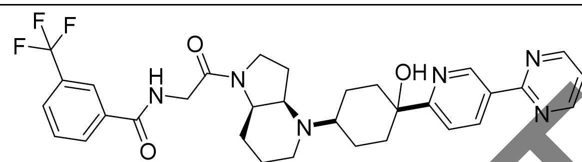
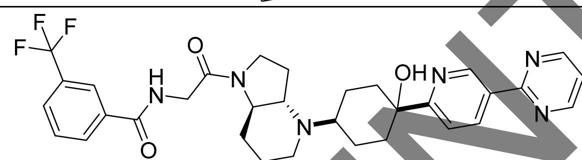
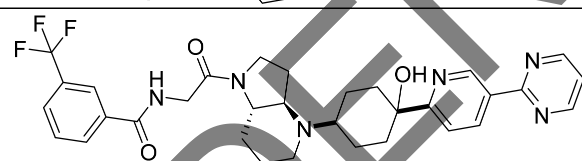
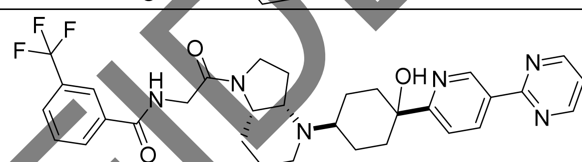
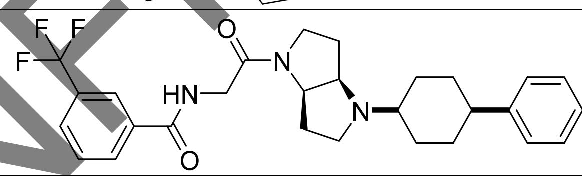
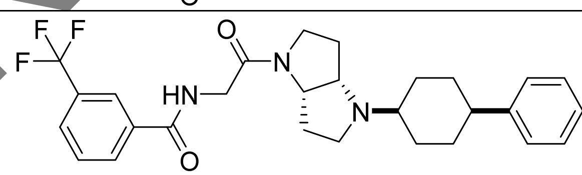
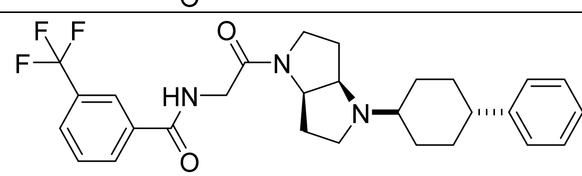
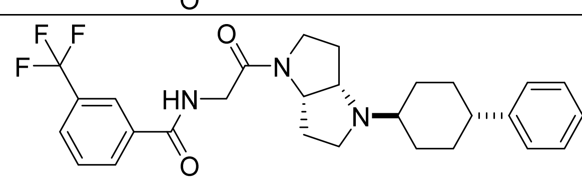
Ex. No.	Structure
258	 Single isomer at fused core (Peak 1); Non Polar (Cis)
259	 Single isomer at fused core (peak 1); Polar (Trans)
260	 Single isomer at fused core (peak 1); Non-polar isomer (Cis); Single isomer unknown stereoisomer at the pyrrolidine
261	 Single isomer at fused core (peak 1); Polar isomer (Trans); Single isomer unknown stereoisomer at the pyrrolidine
262	 Single isomer at fused core (peak 2); Non-polar isomer (Cis); Single isomer unknown stereoisomer at the pyrrolidine
263	 Single isomer at fused core (peak 2); polar isomer (Trans); Single isomer unknown stereoisomer at the pyrrolidine

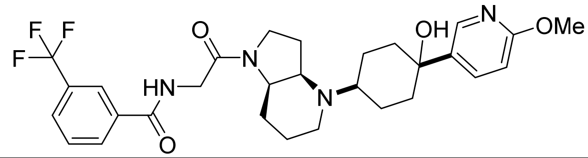
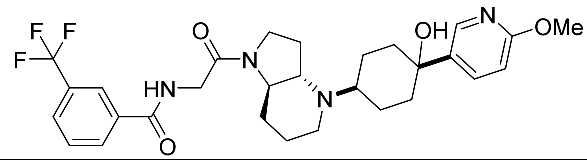
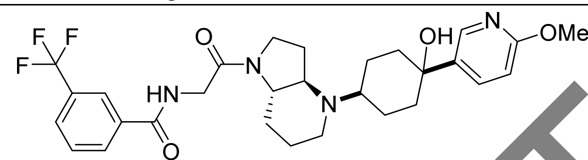
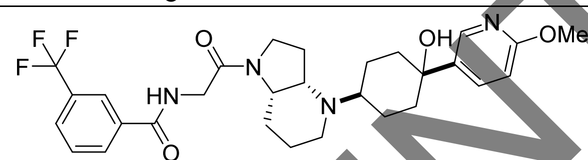
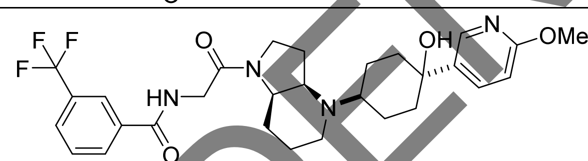
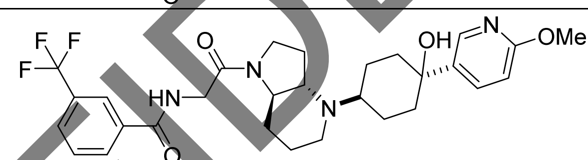
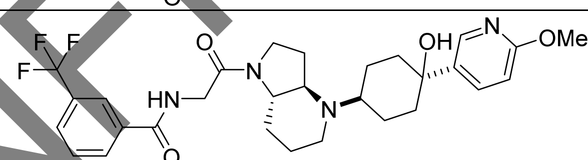
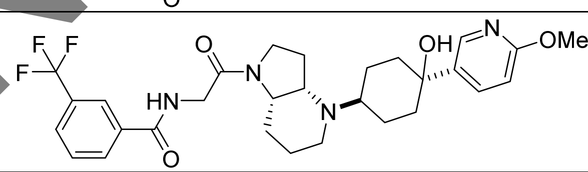
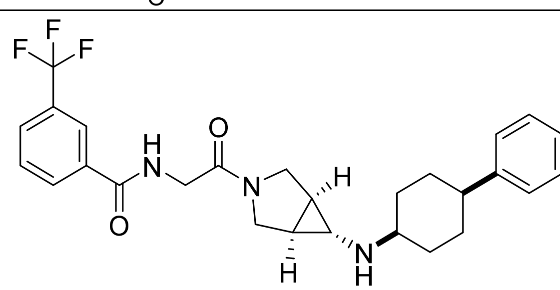
[0130] In certain embodiments, provided is a compound selected from Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, or prodrug thereof:

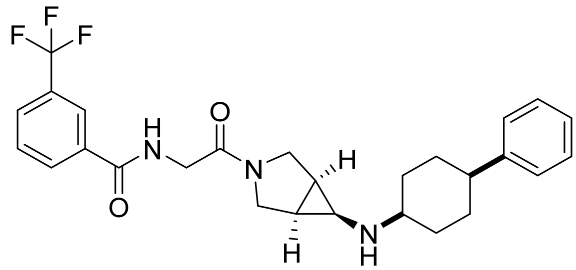
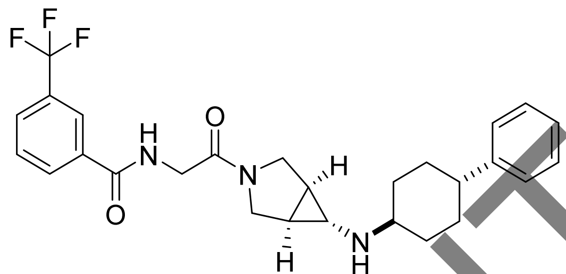
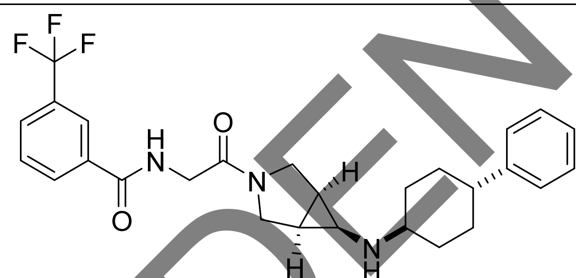
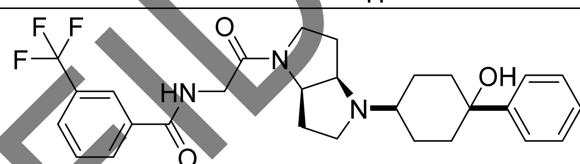
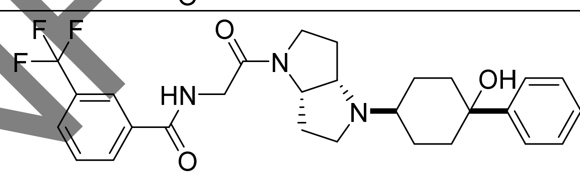
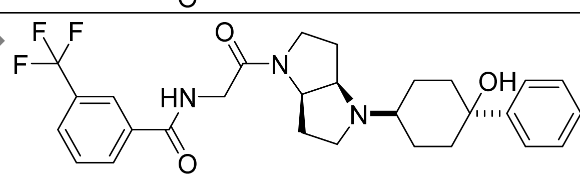
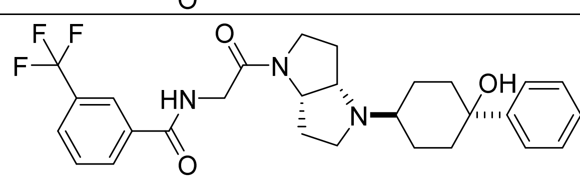
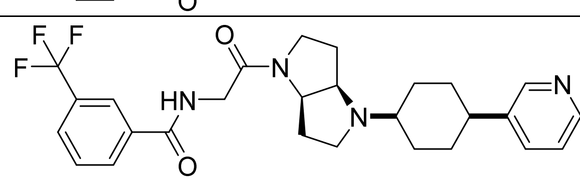
Table 2

Structure





Structure







Structure











Structure










Structure









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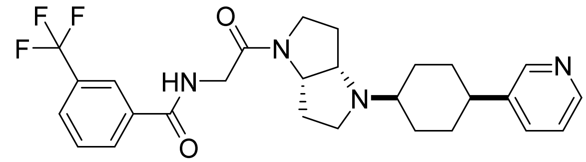
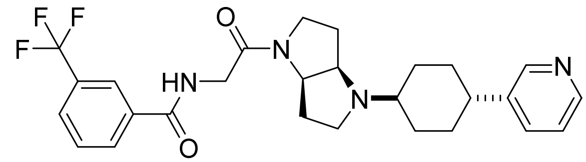
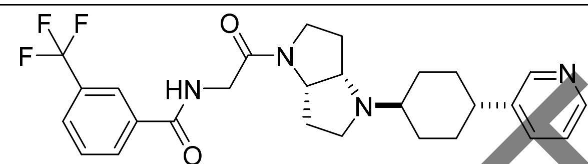
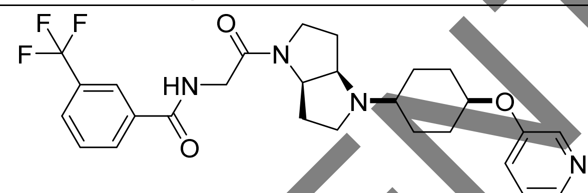
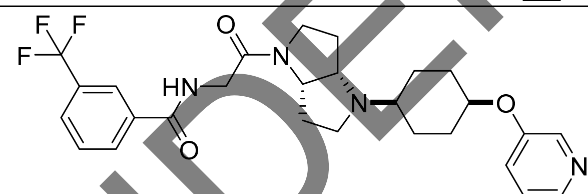
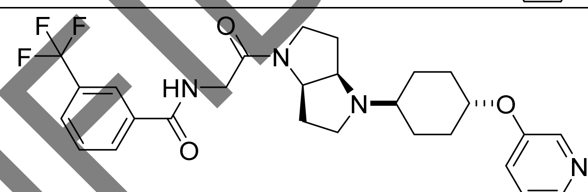
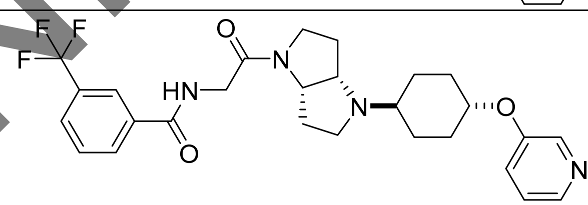
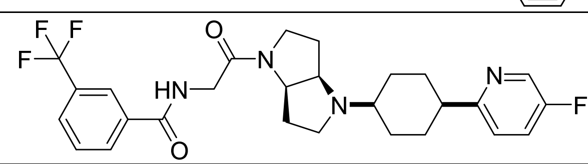
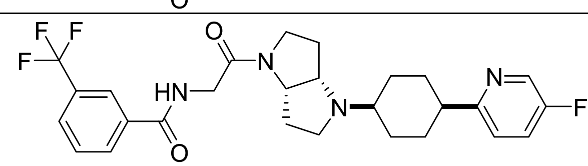

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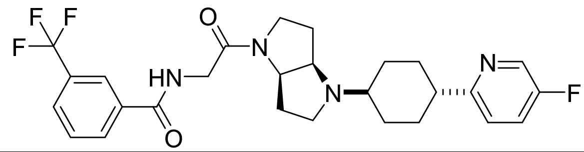
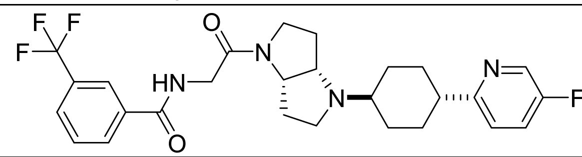
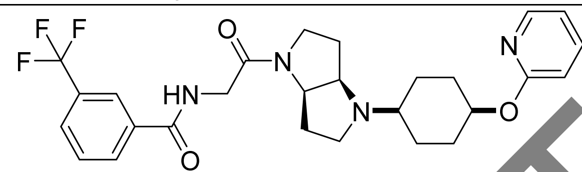
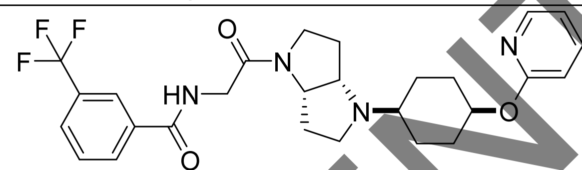
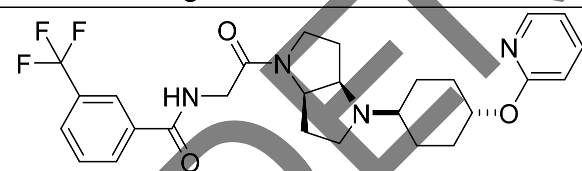
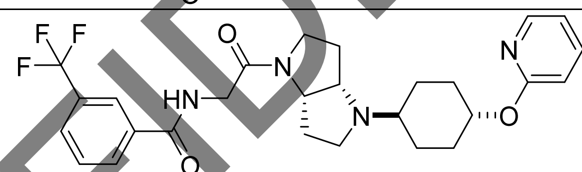
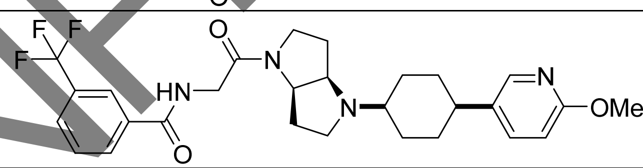
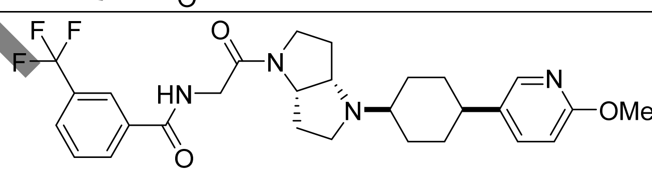
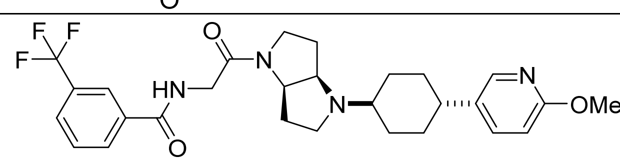
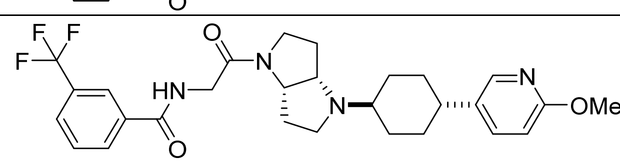

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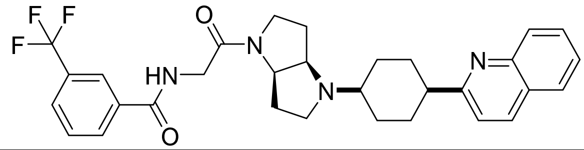
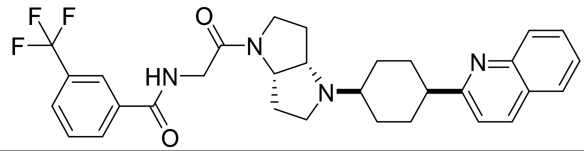
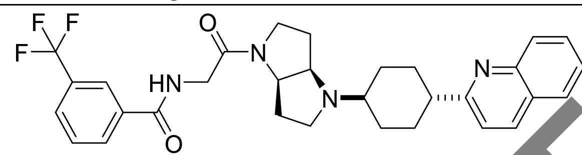
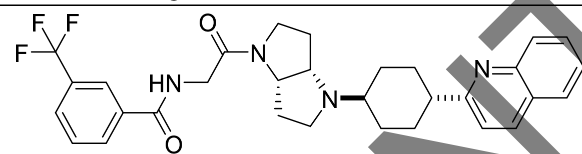
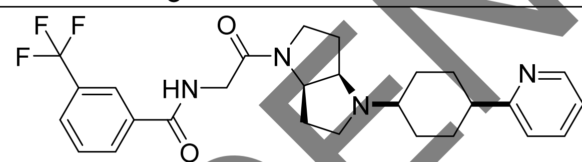
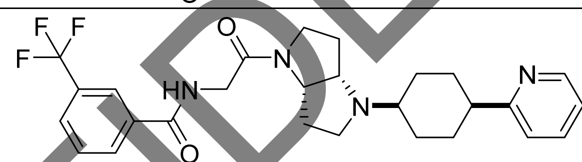
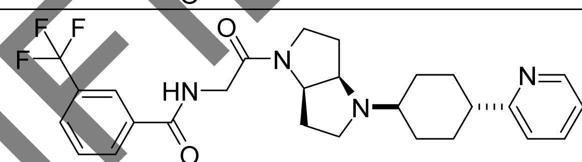
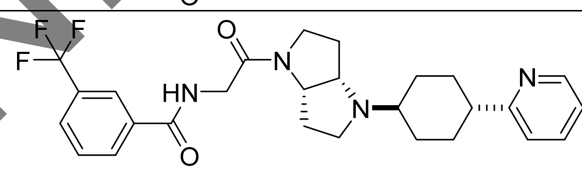
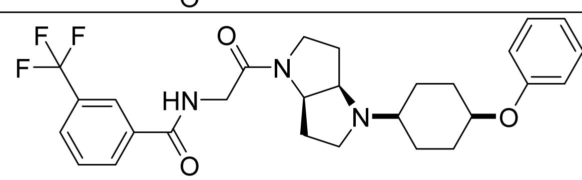
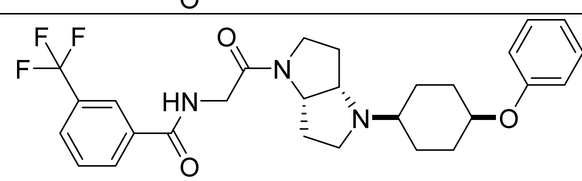

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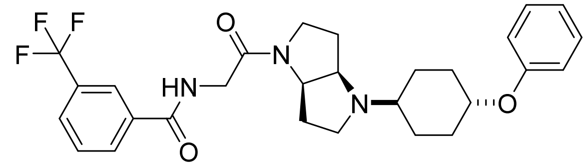
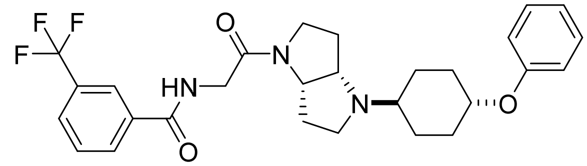
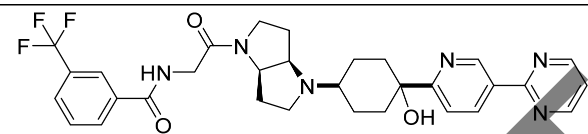
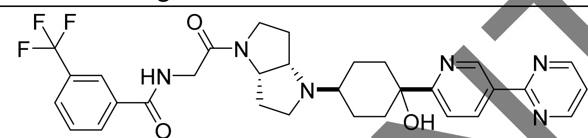
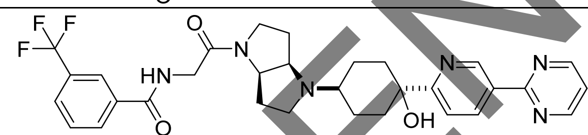
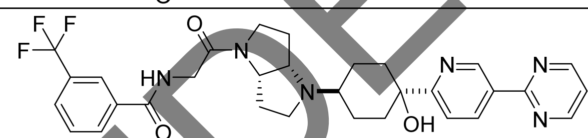
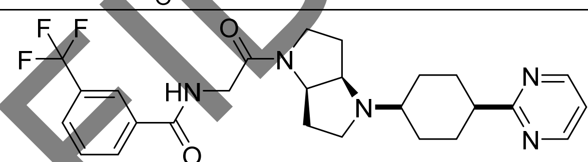
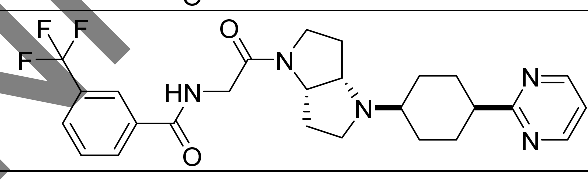
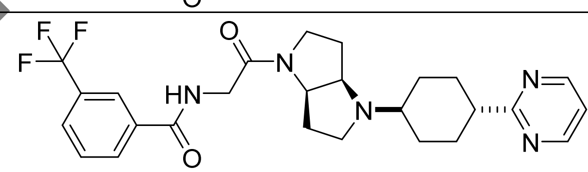
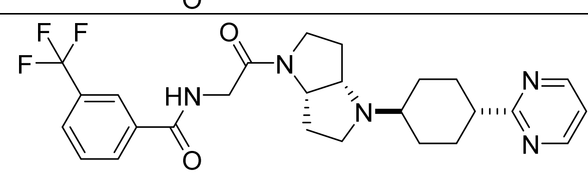
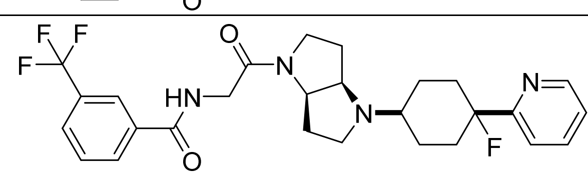

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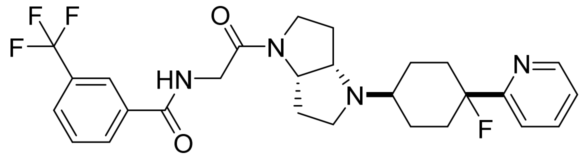
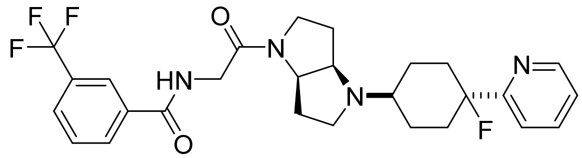
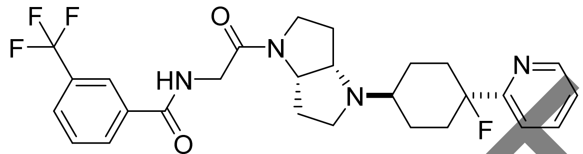
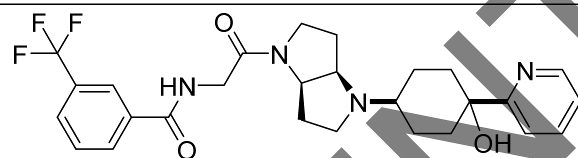
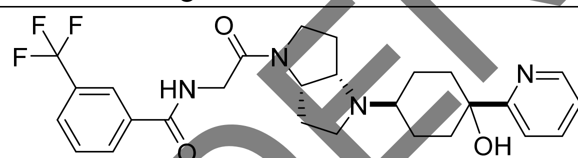
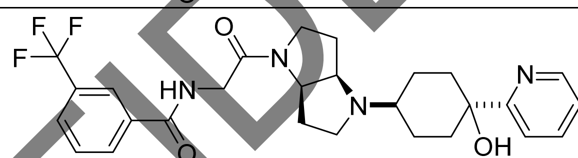
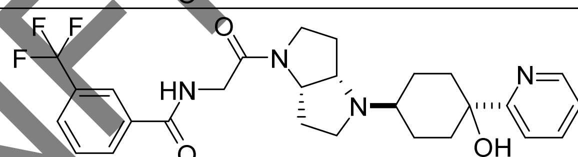
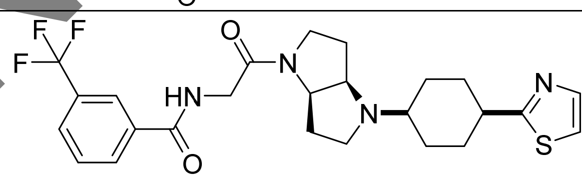
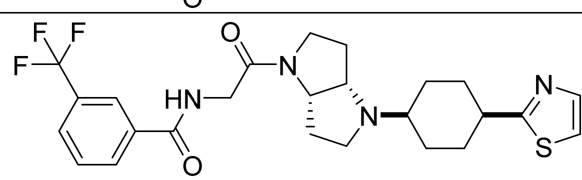
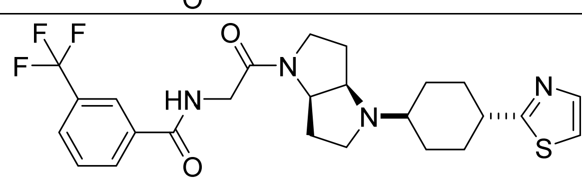

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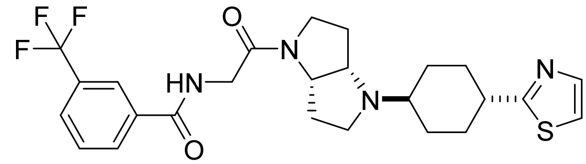
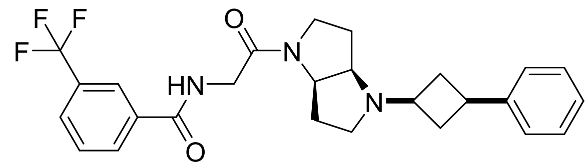
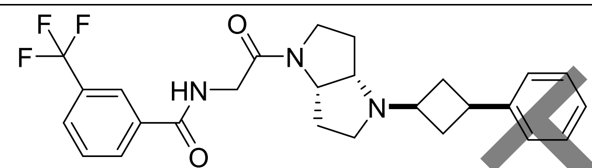
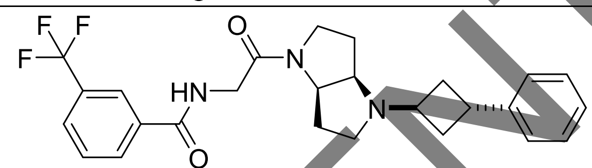
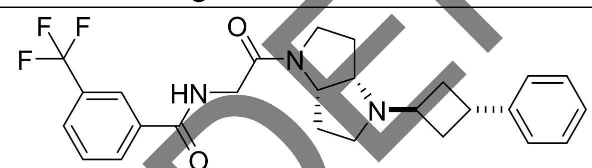
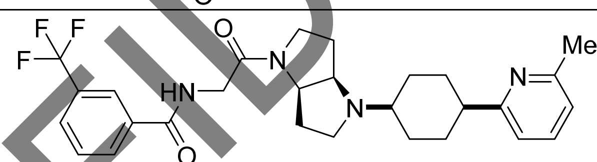
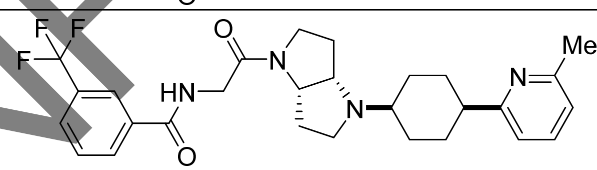
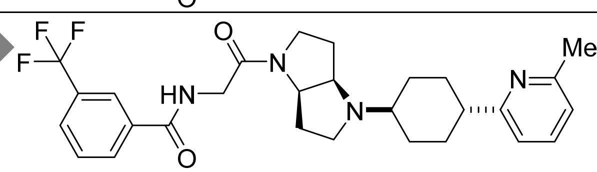
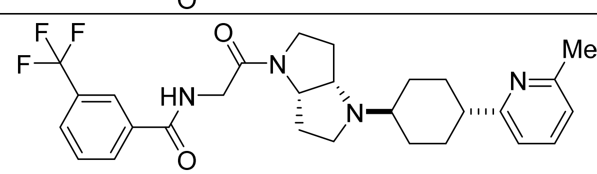
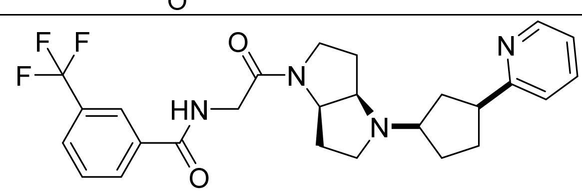

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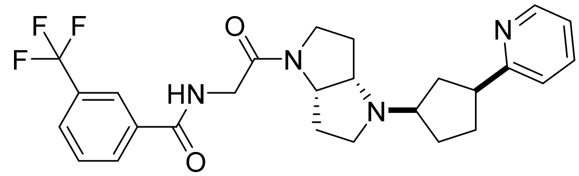
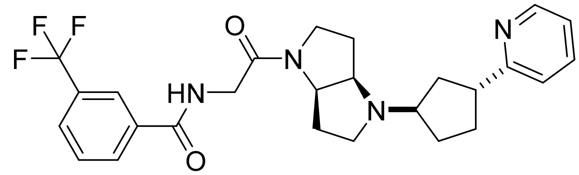
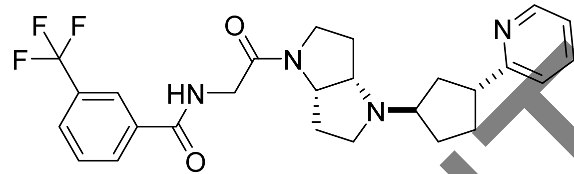
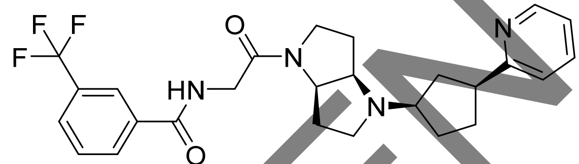
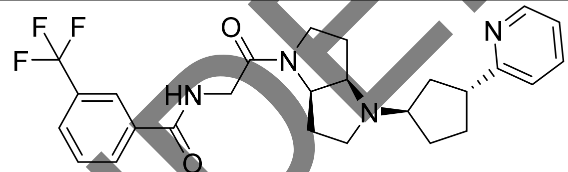
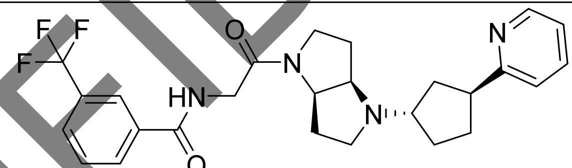
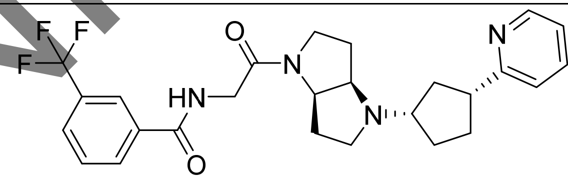
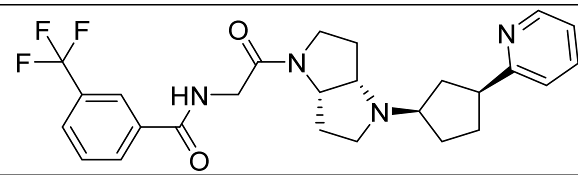
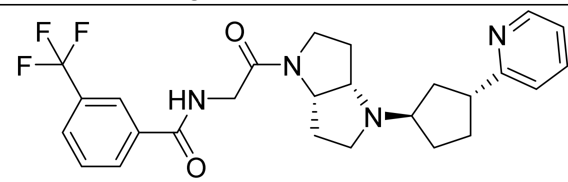

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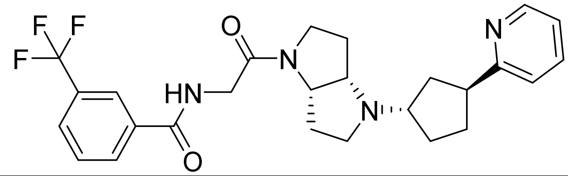
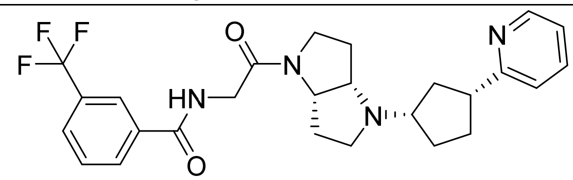
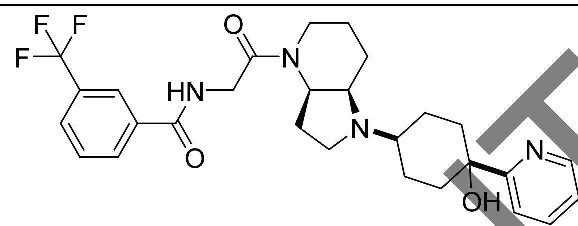
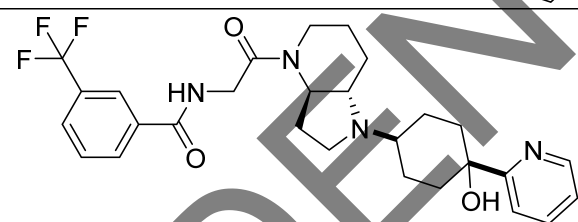
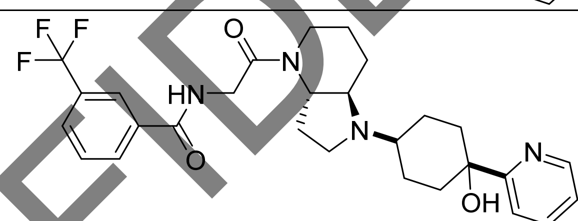
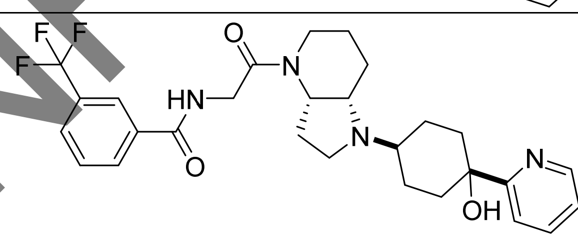
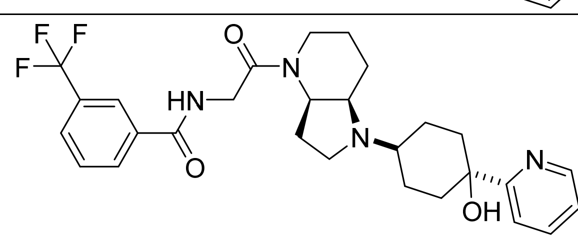
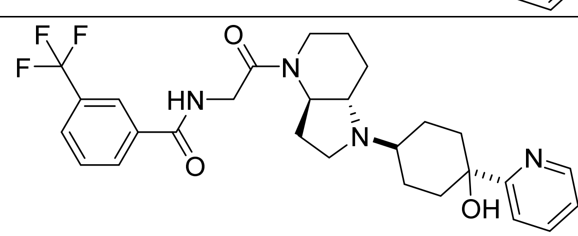

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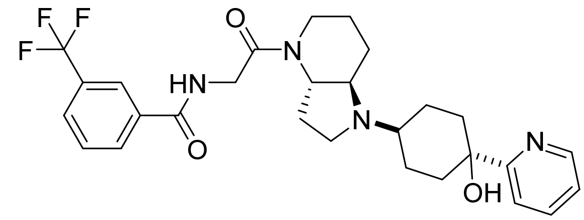
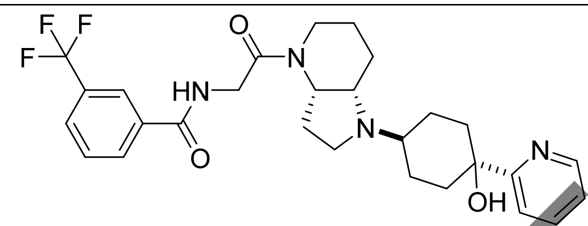
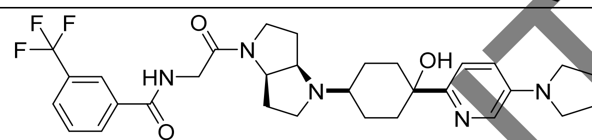
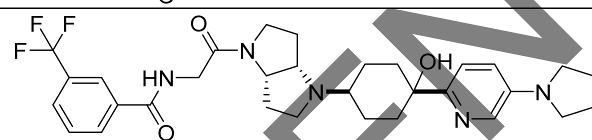
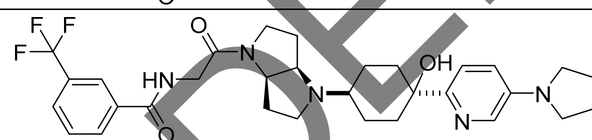
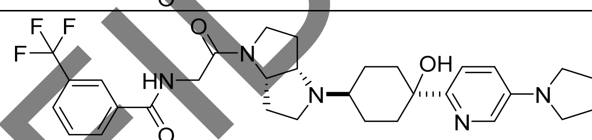
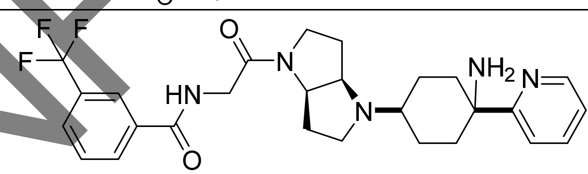
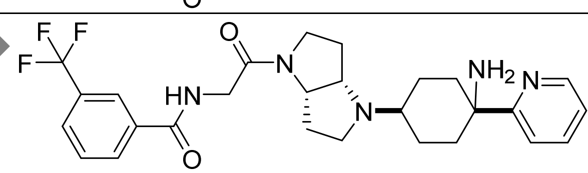
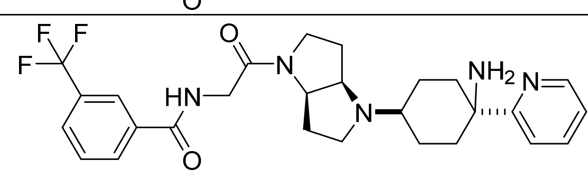
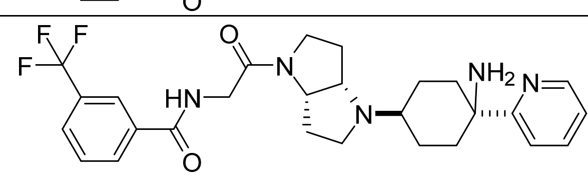

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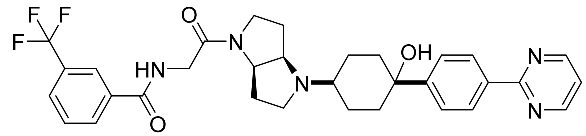
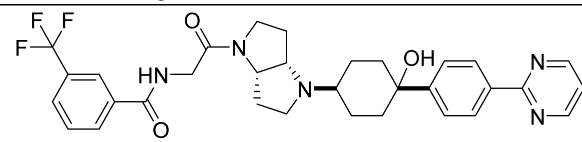
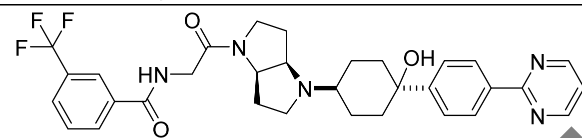
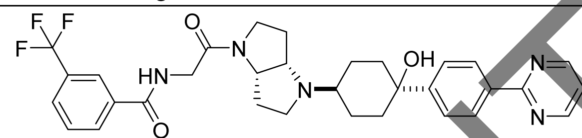
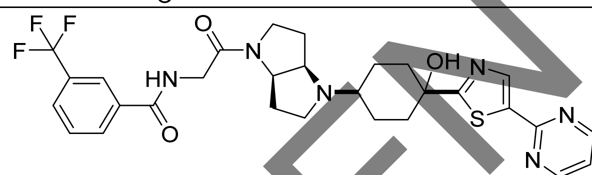
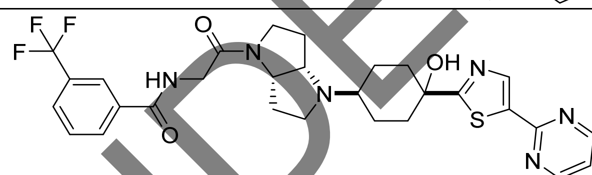
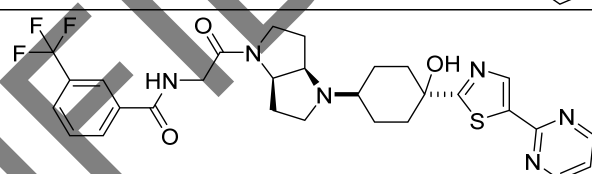
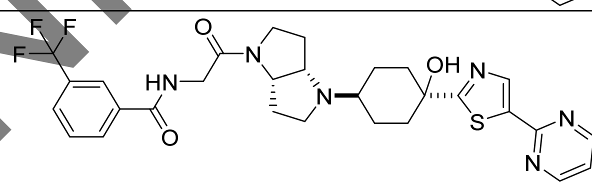
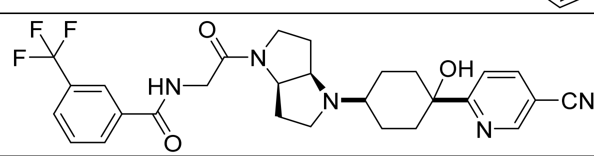
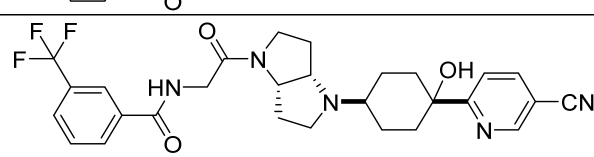
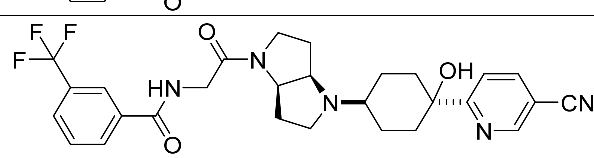

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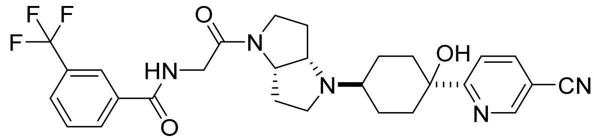
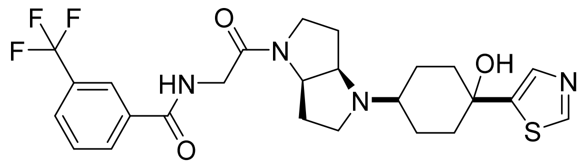
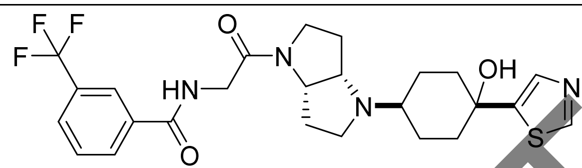
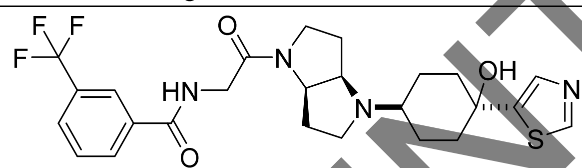
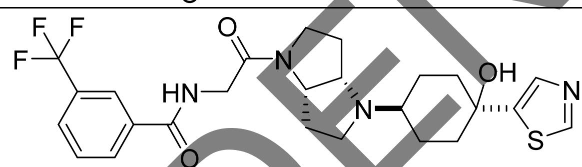
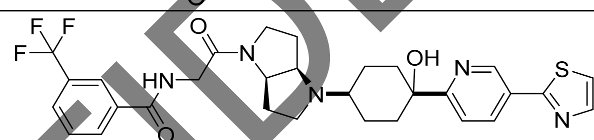
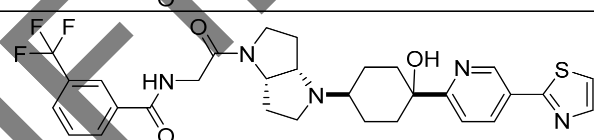
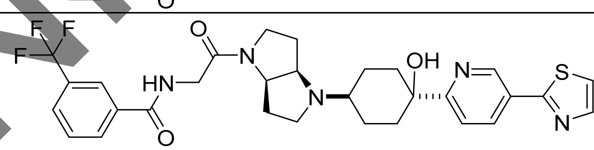
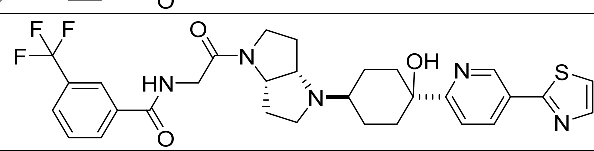
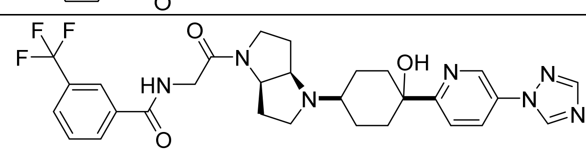
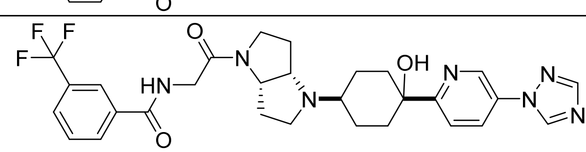

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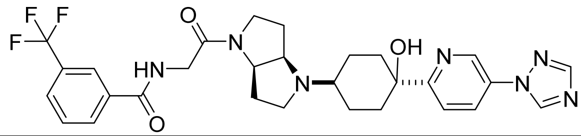
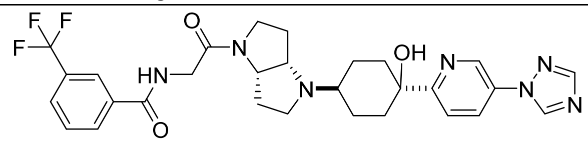
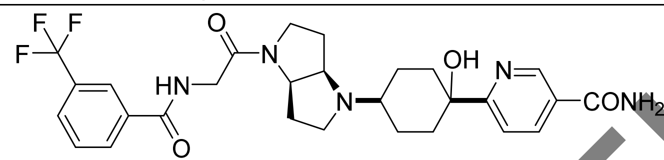
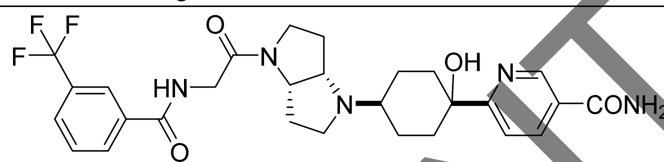
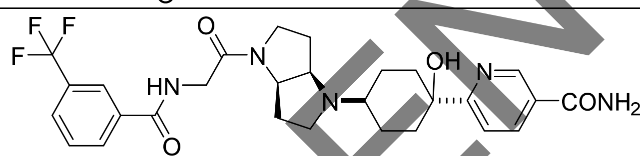
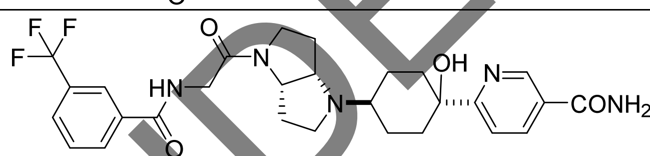
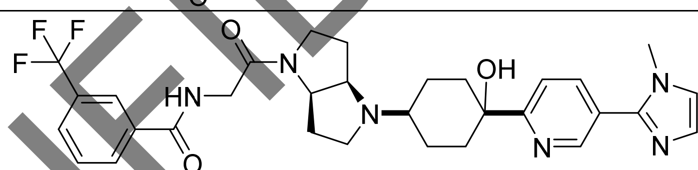
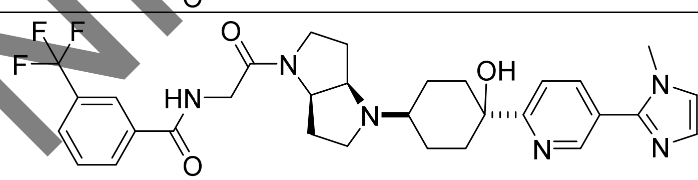
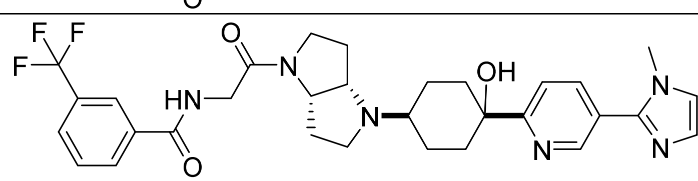
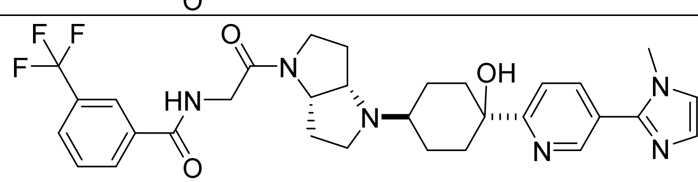

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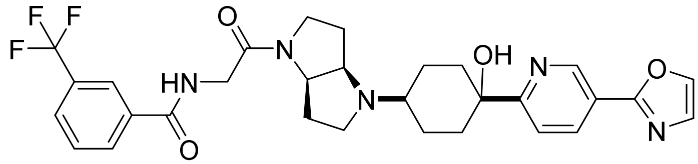
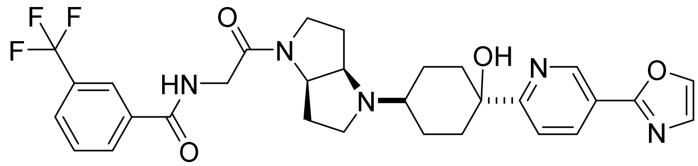
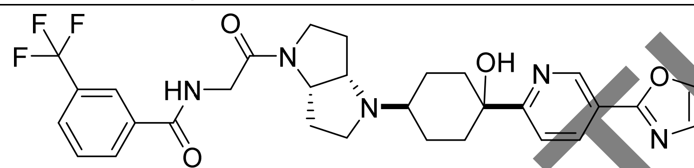
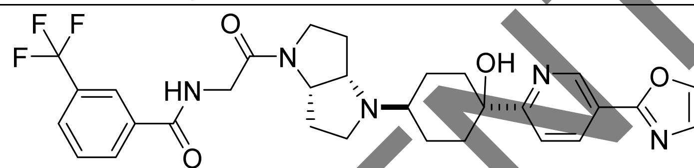
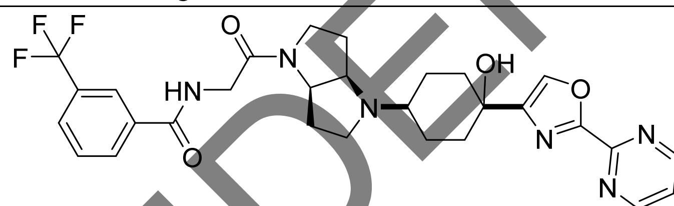
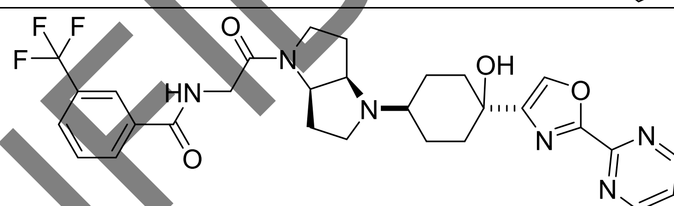
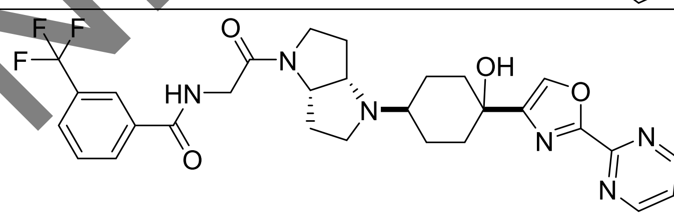
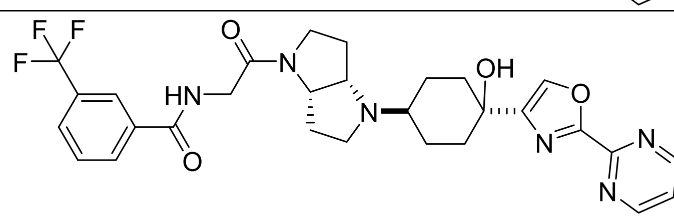

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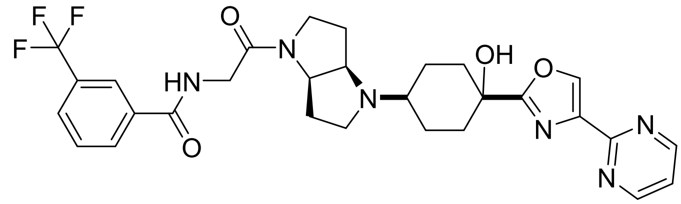
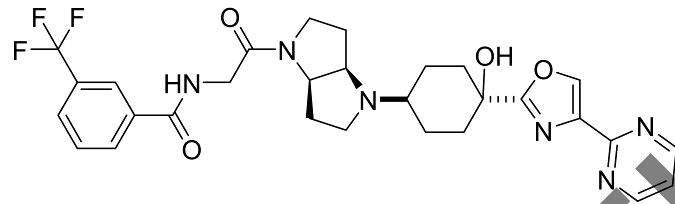
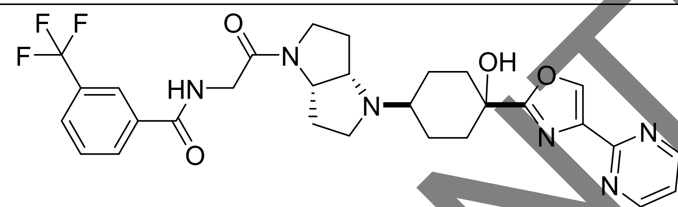
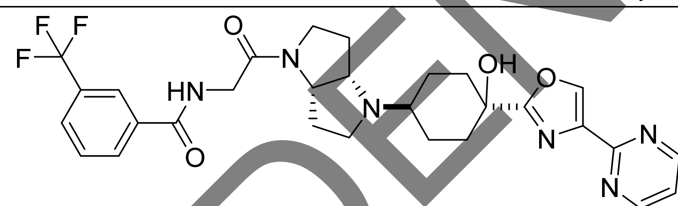
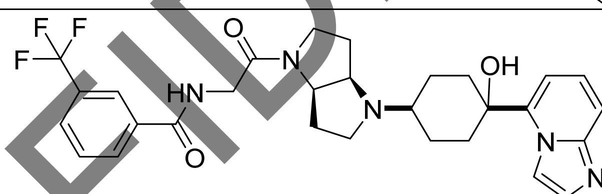
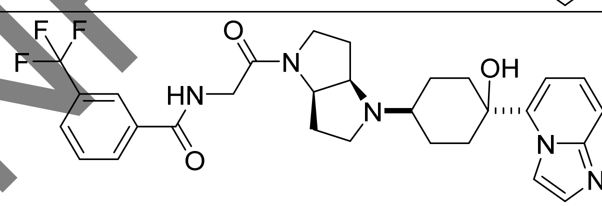
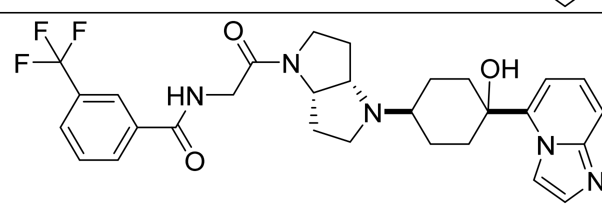
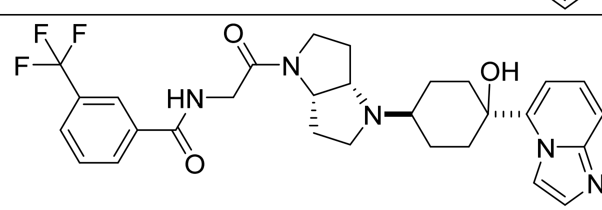

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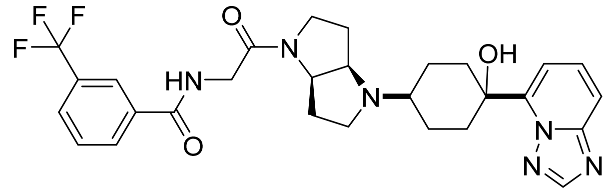
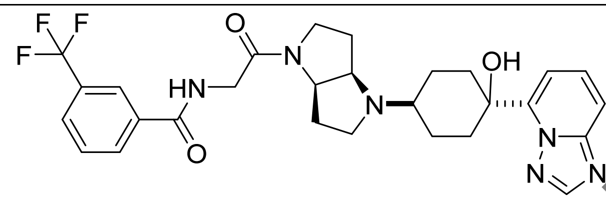
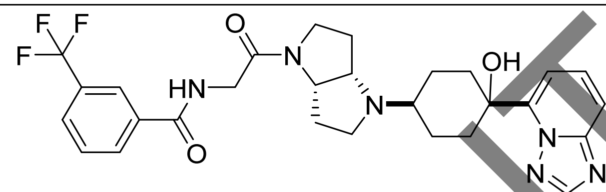
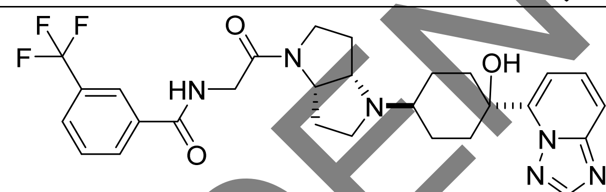
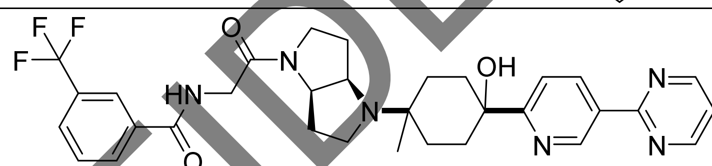
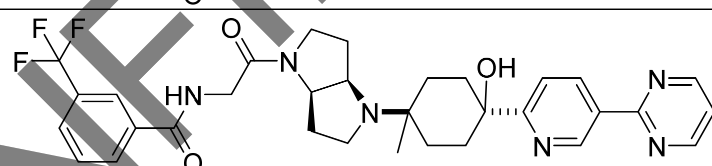
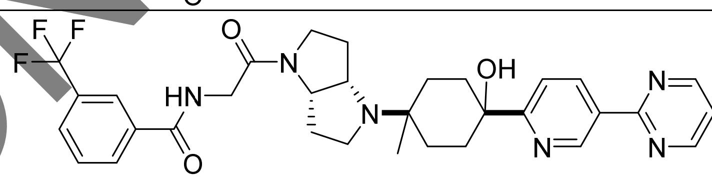
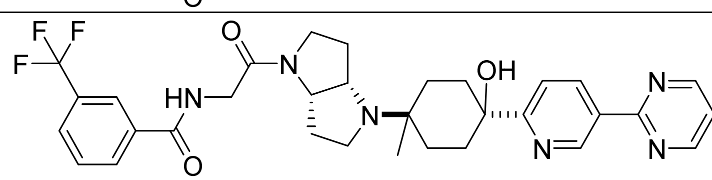
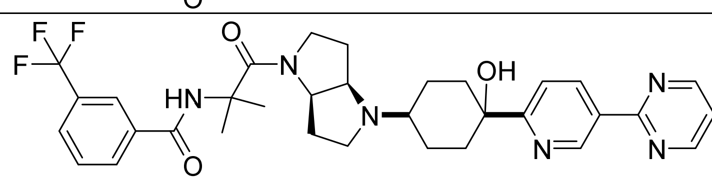

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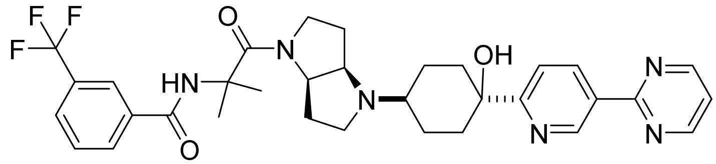
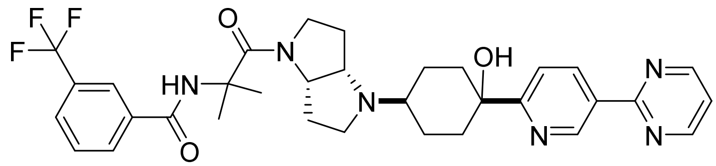
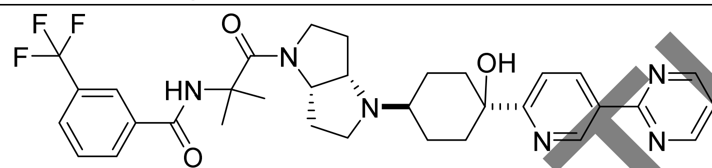
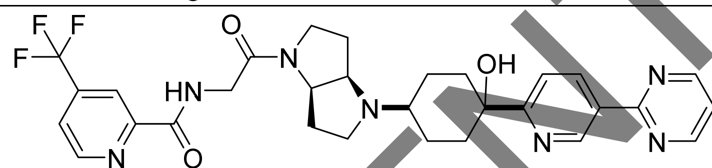
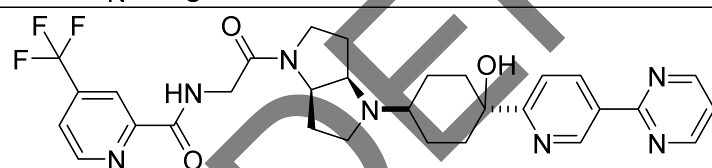
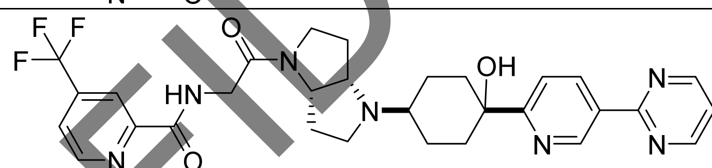
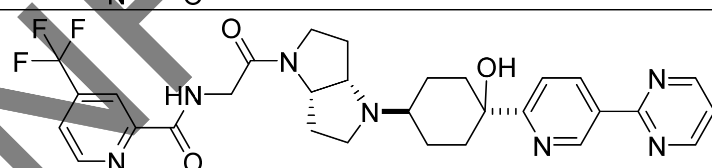
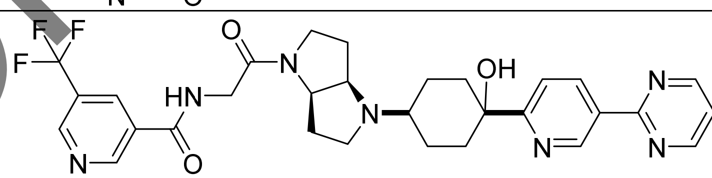
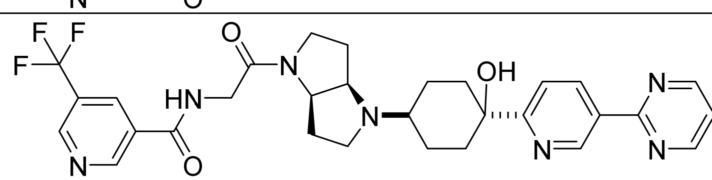
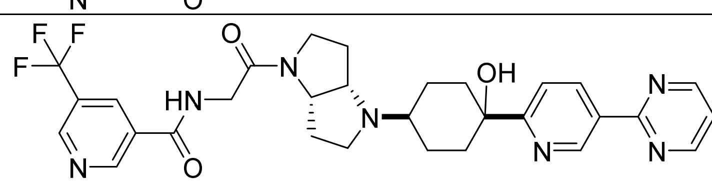

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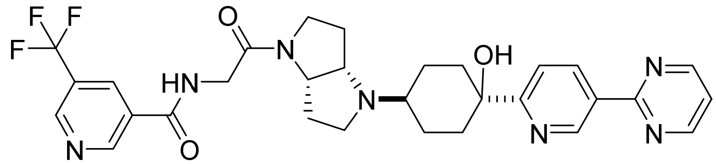
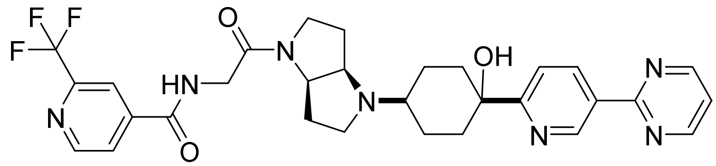
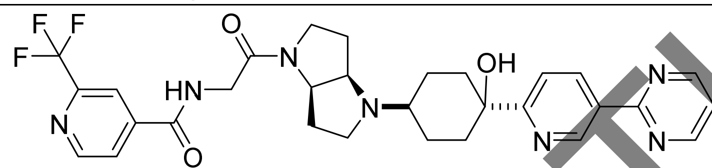
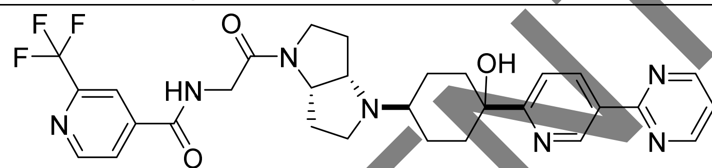
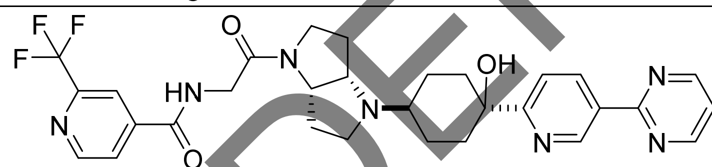
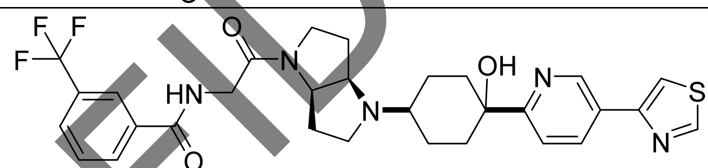
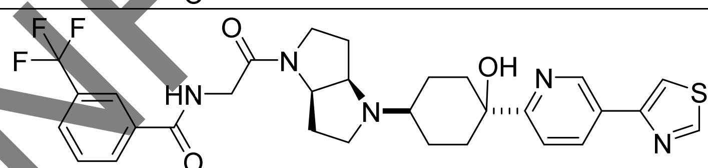
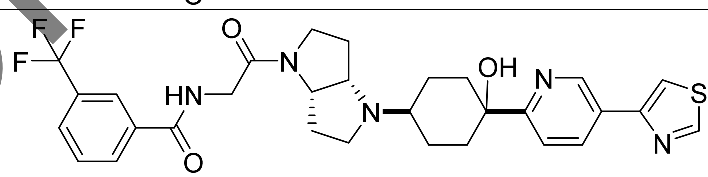
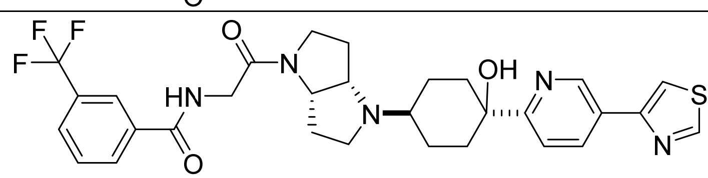

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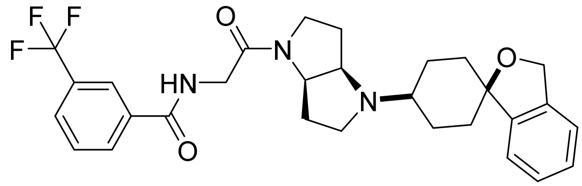
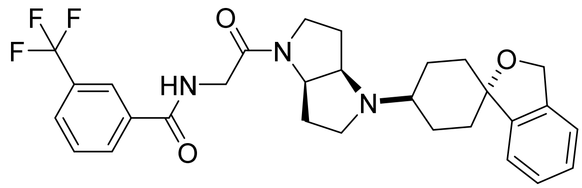
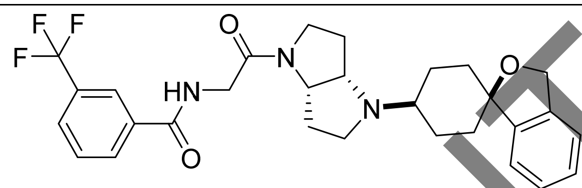
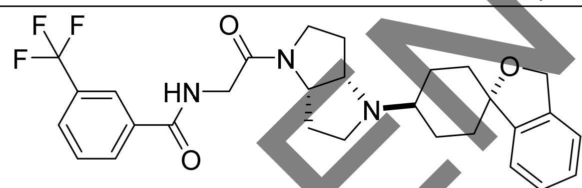
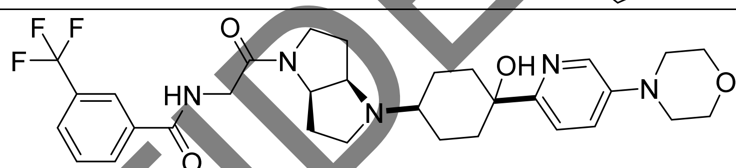
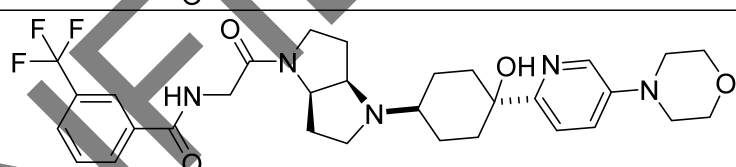
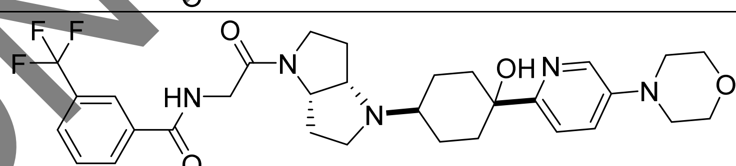
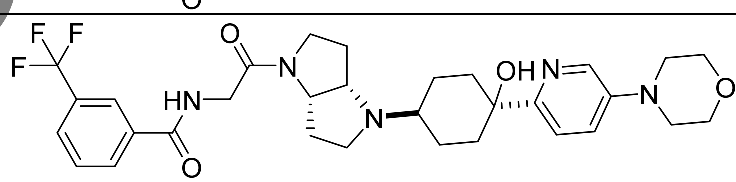
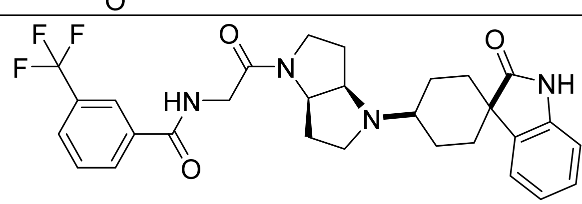

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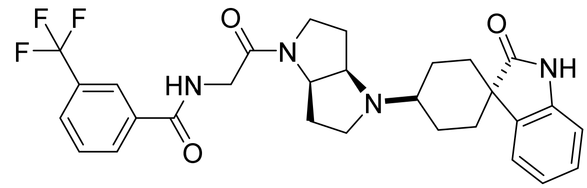
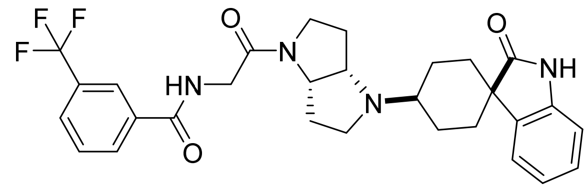
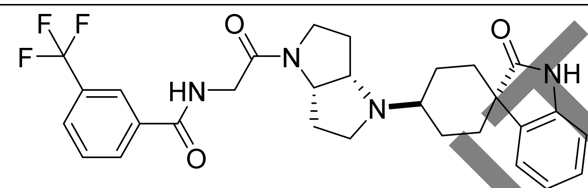
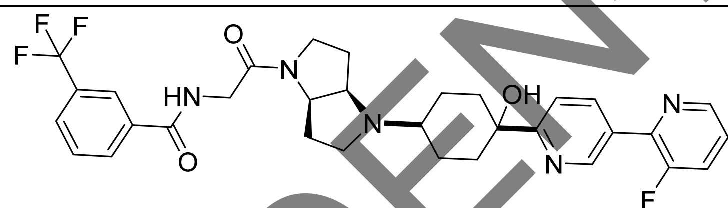
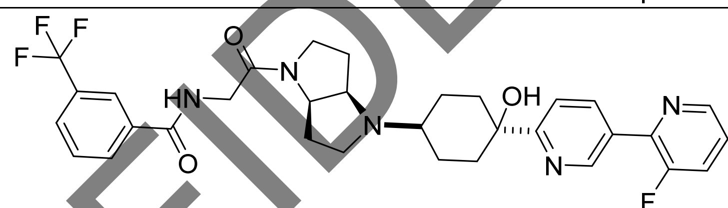
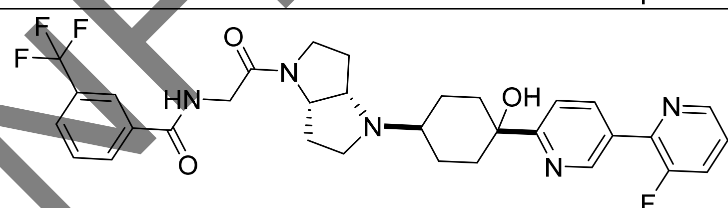
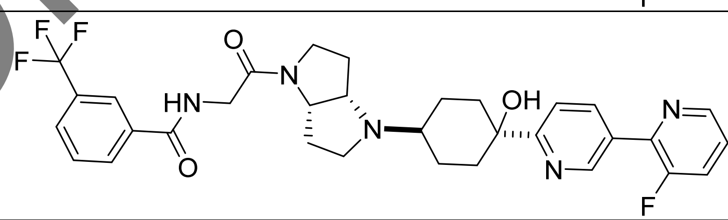
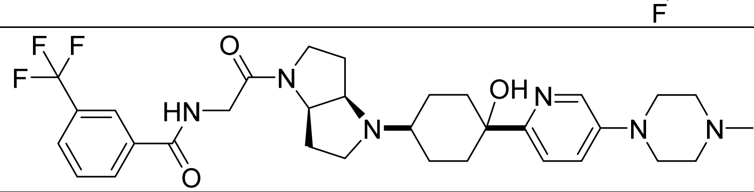

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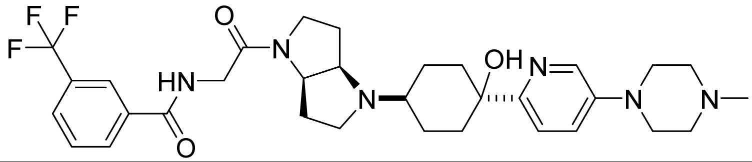
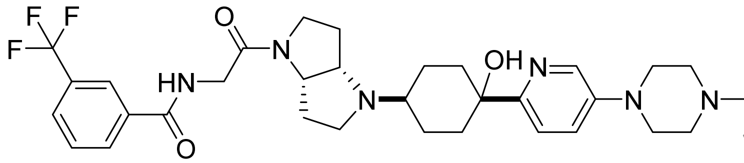
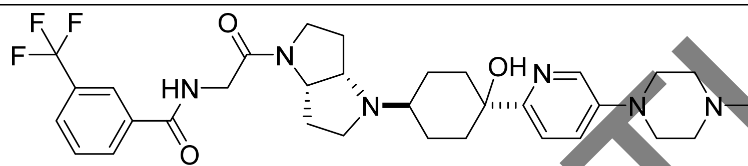
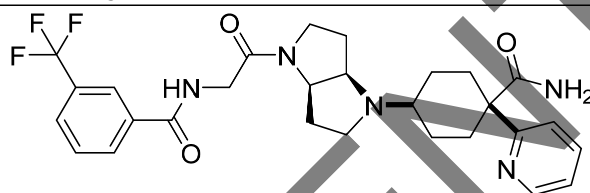
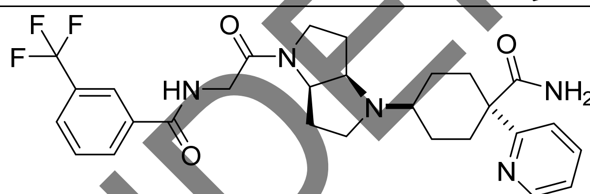
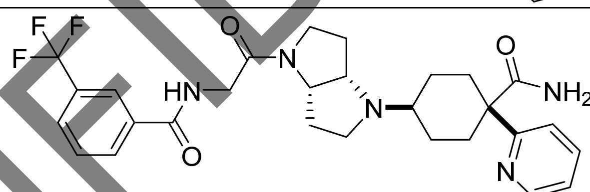
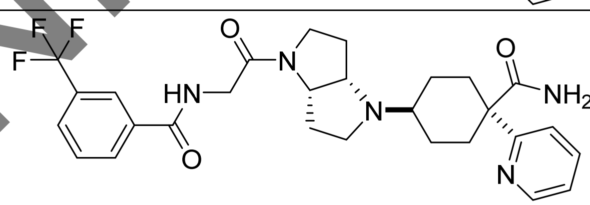
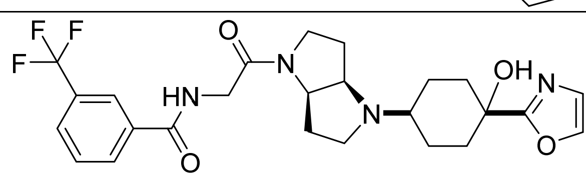
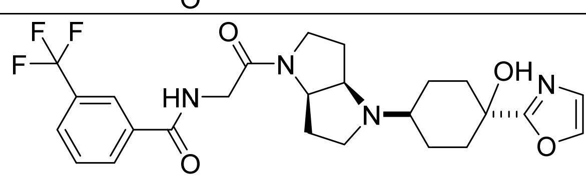

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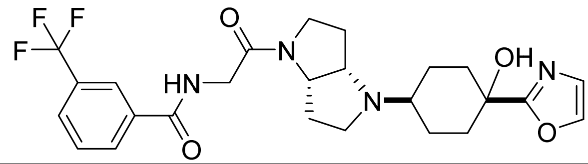
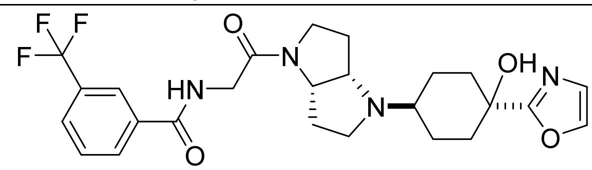
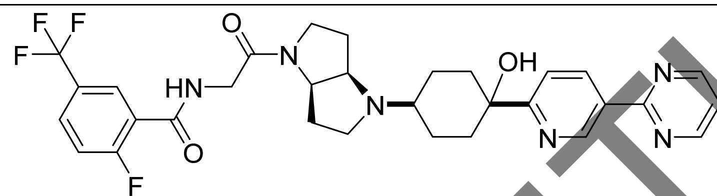
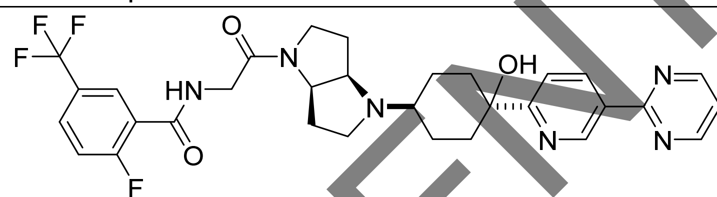
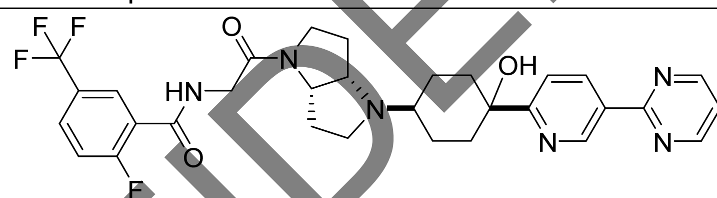
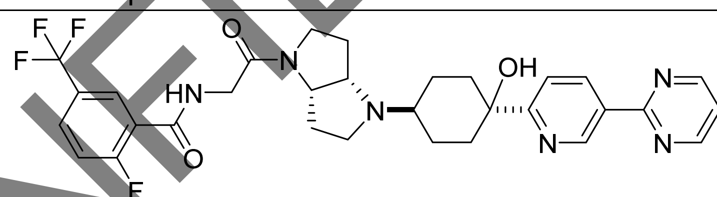
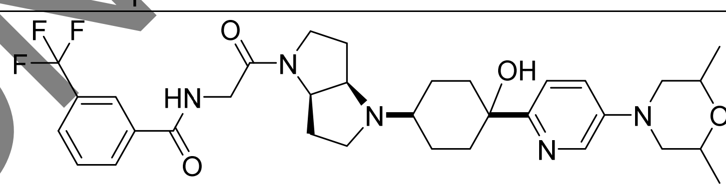
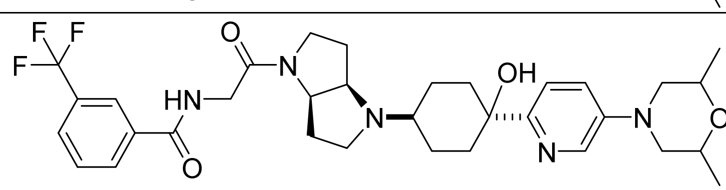
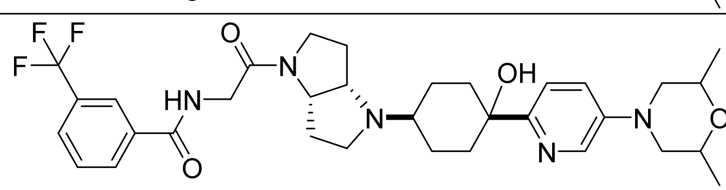

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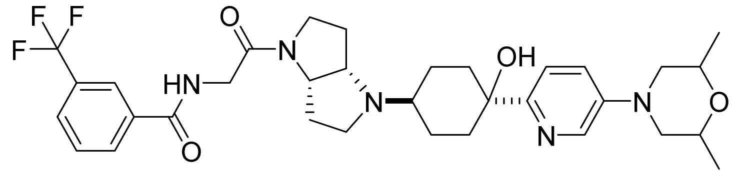
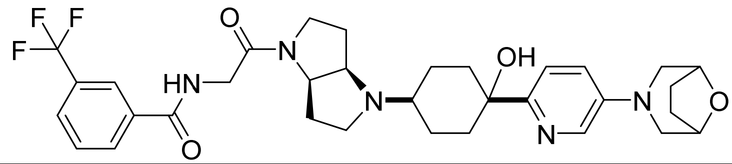
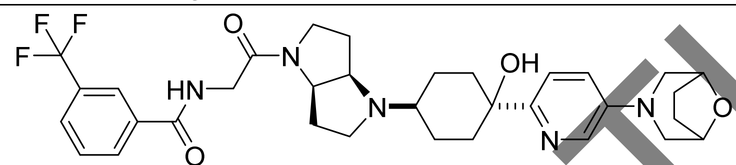
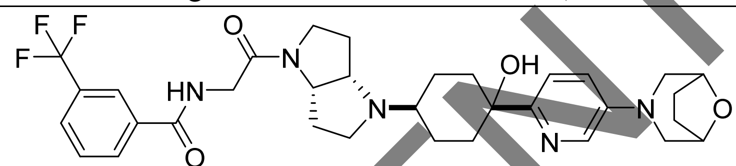
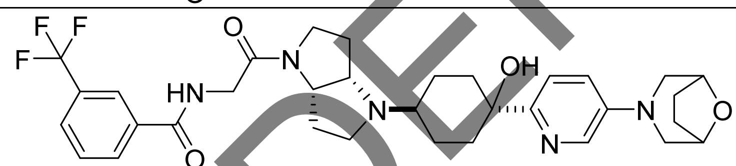
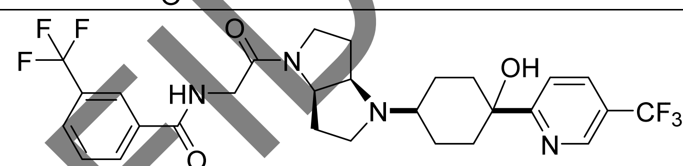
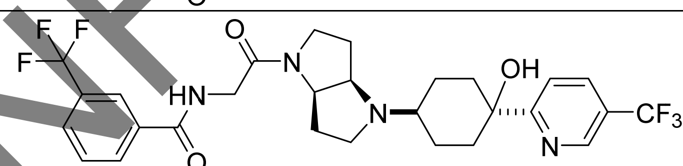
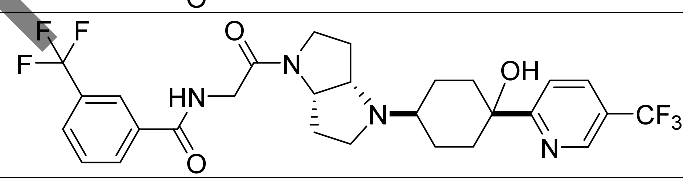
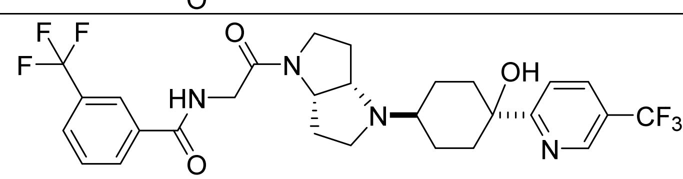
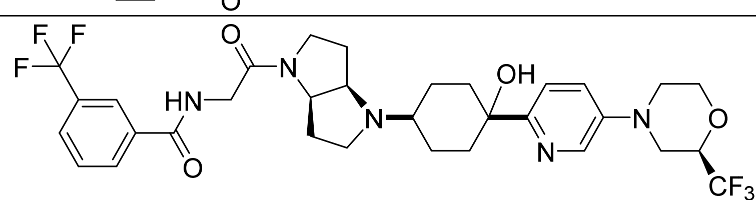

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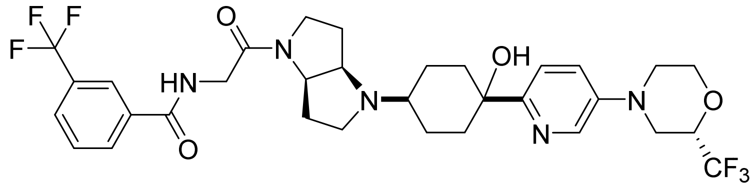
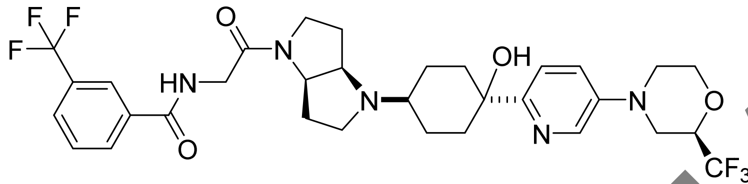
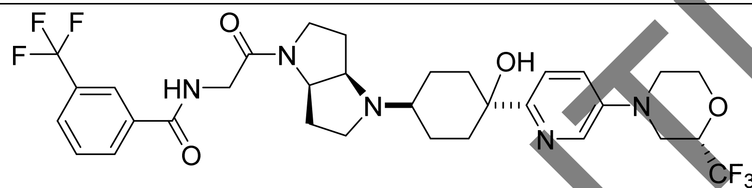
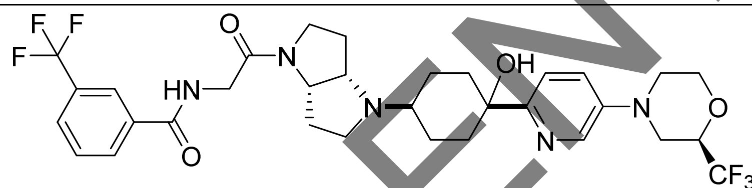
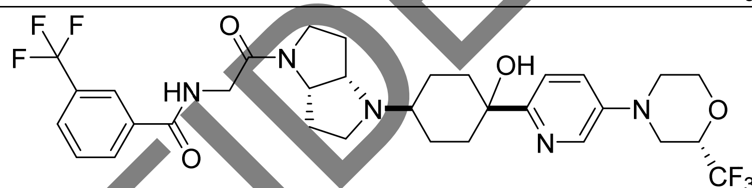
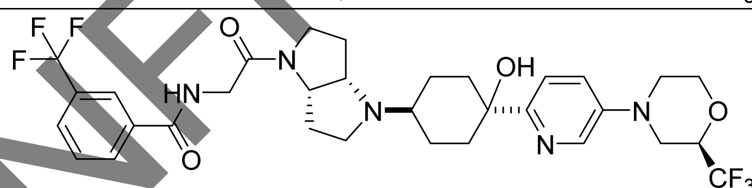
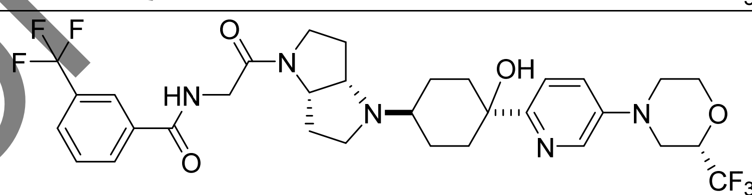
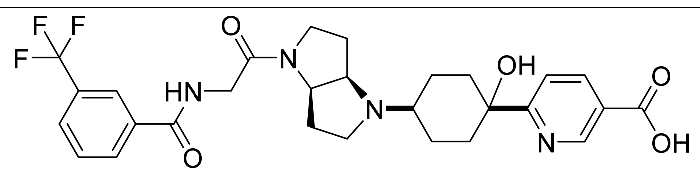
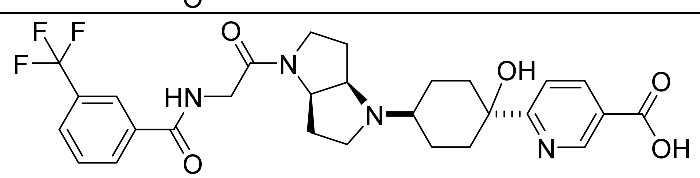

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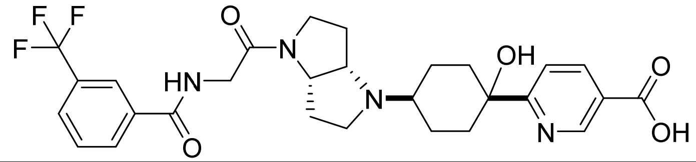
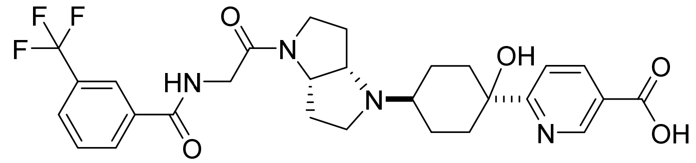
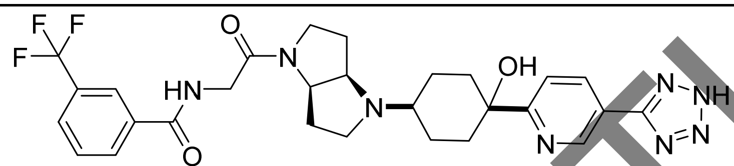
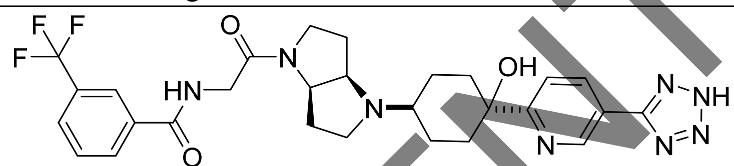
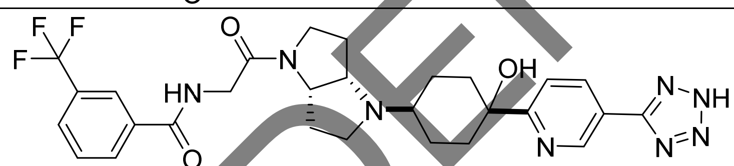
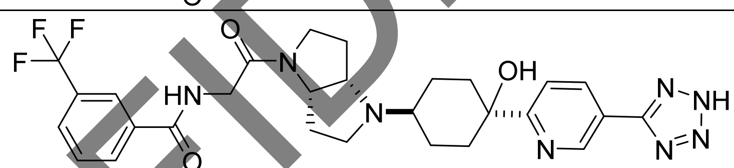
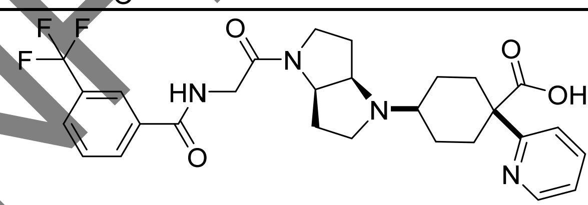
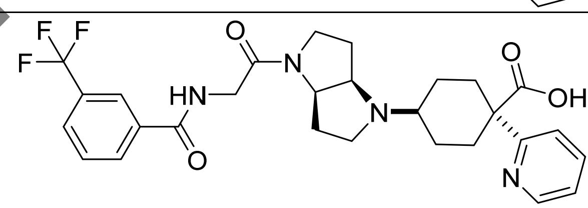
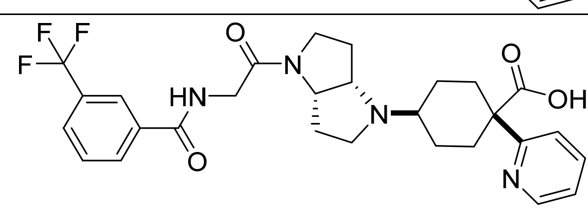

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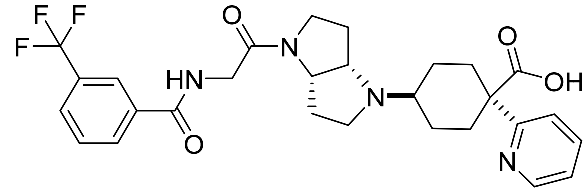
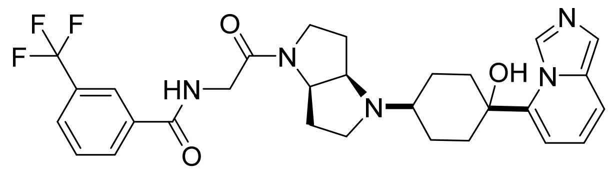
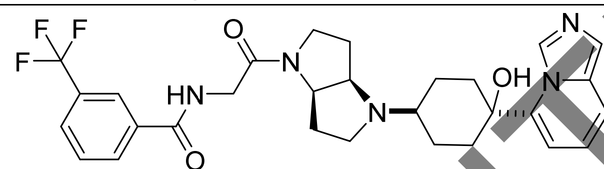
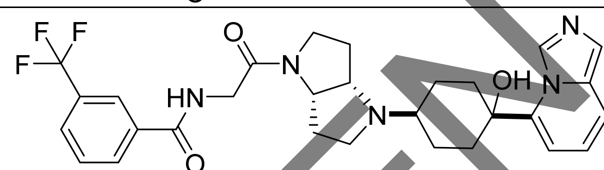
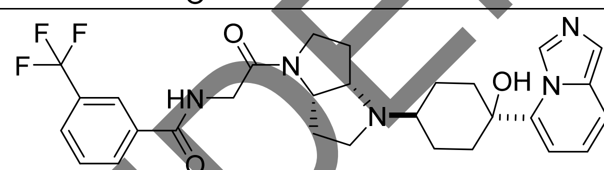
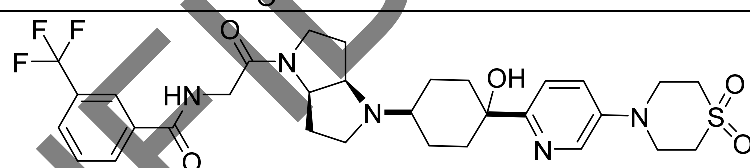
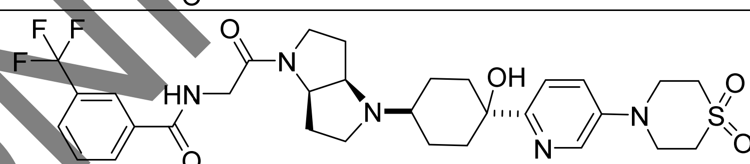
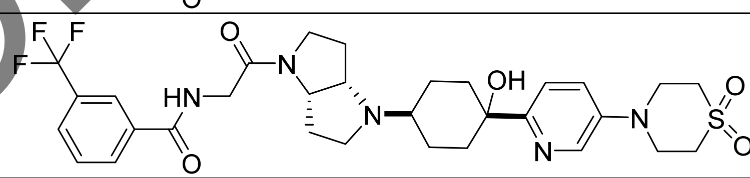
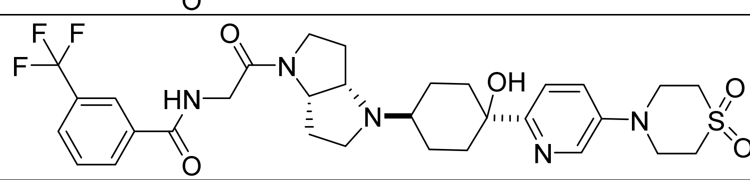

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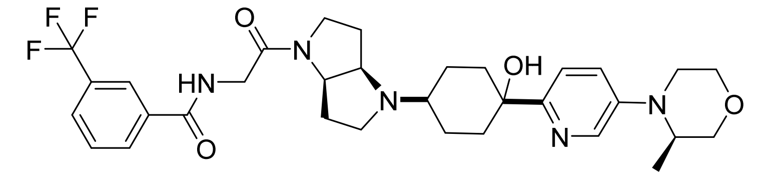
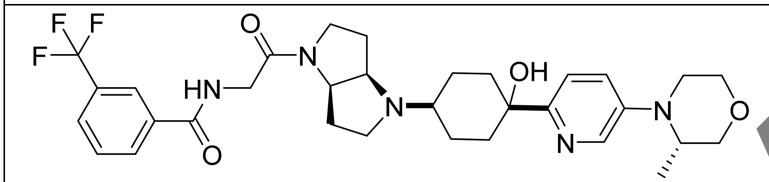
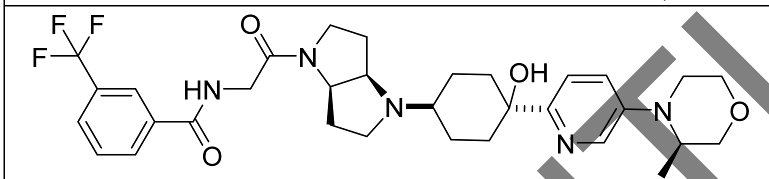
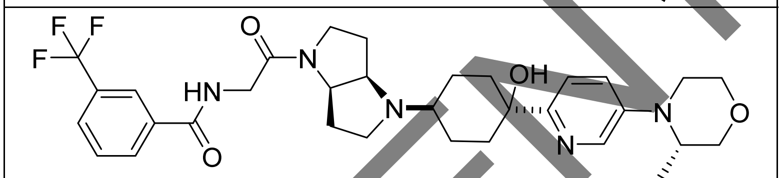
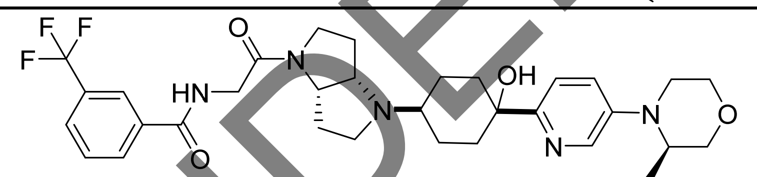
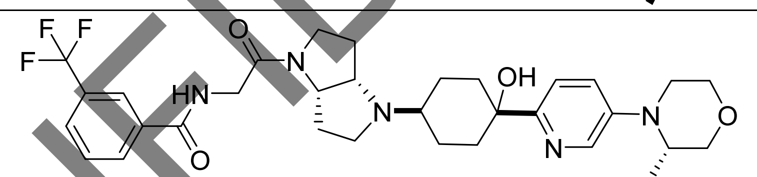
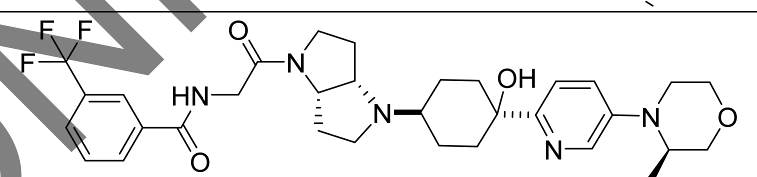
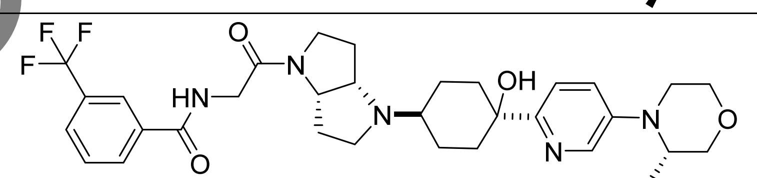
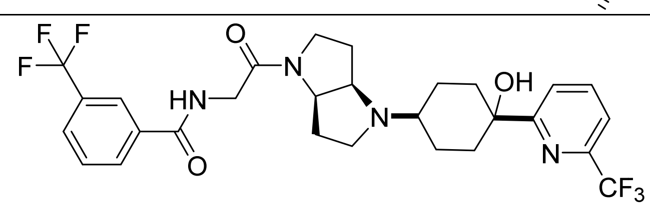

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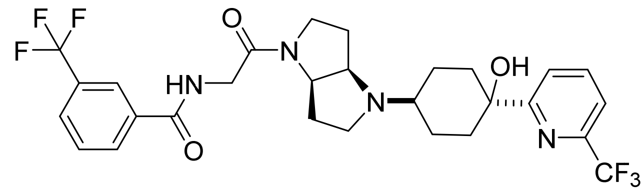
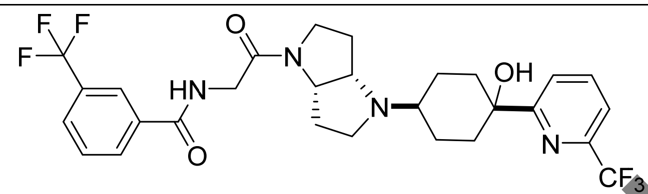
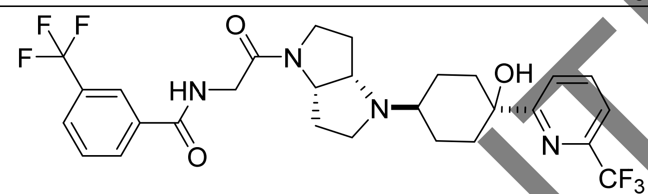
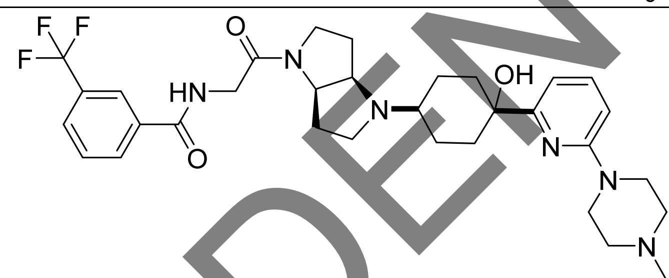
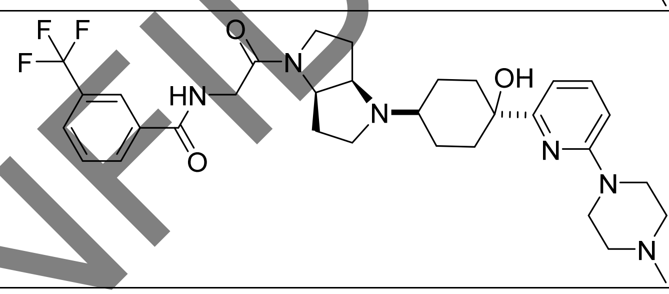
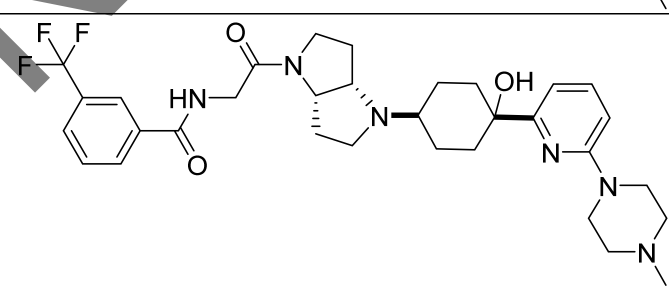
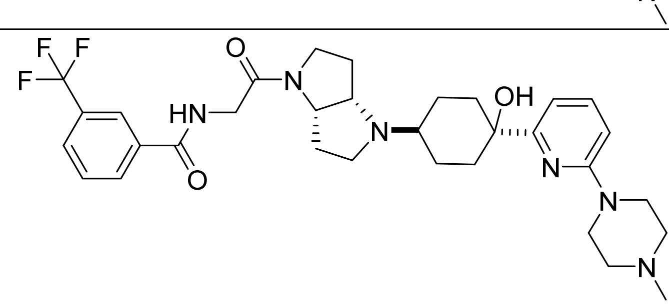

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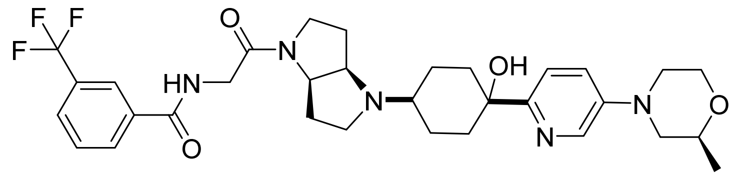
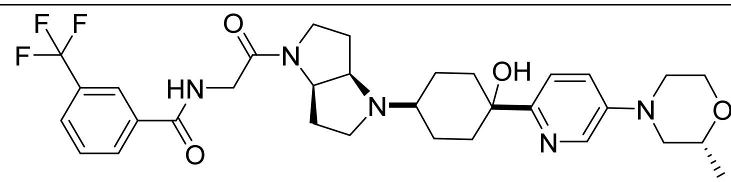
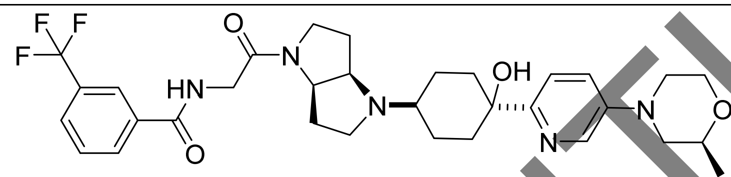
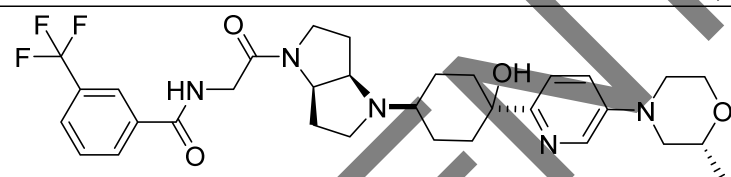
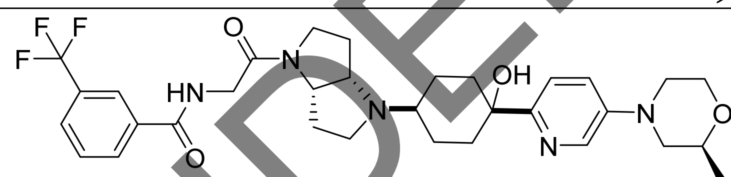
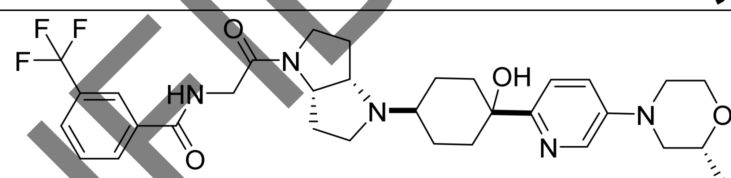
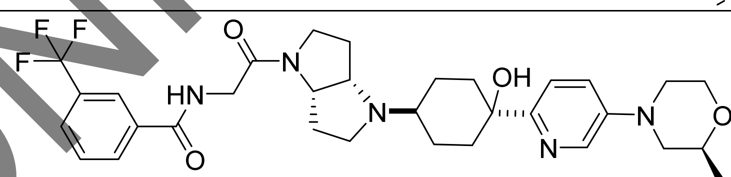
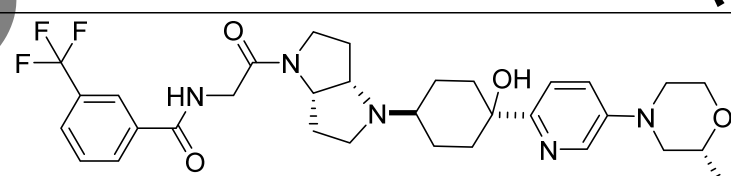
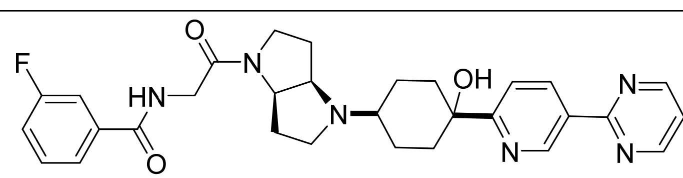

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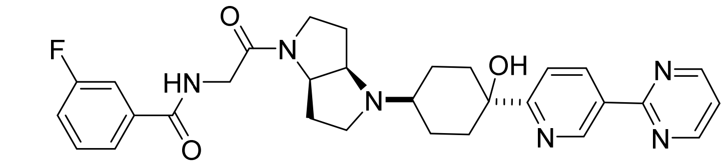
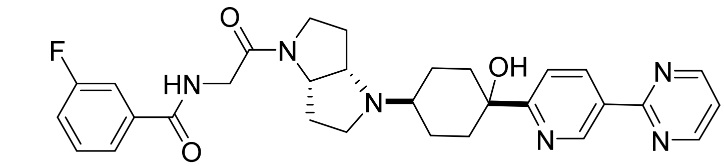
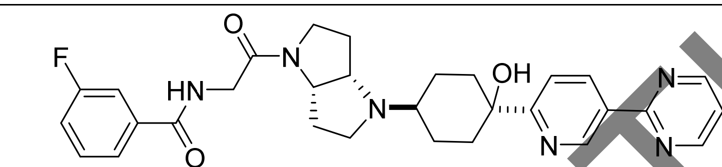
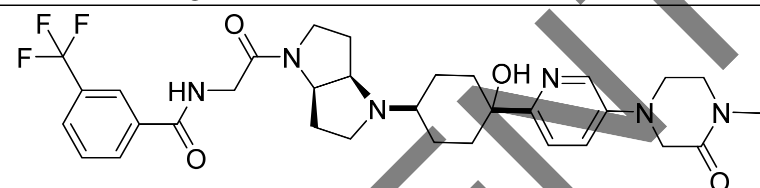
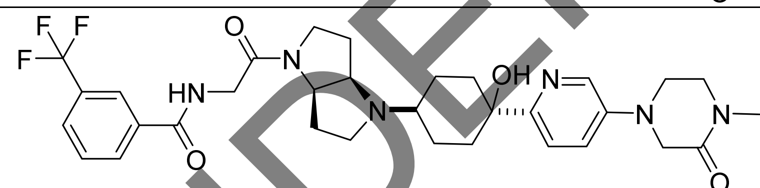
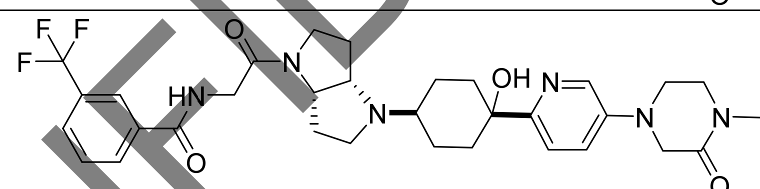
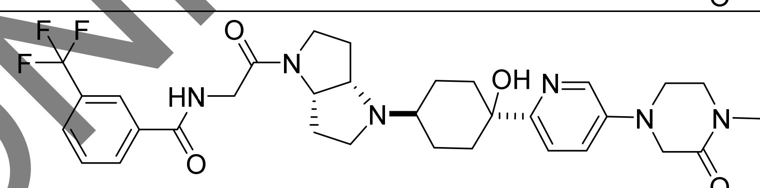
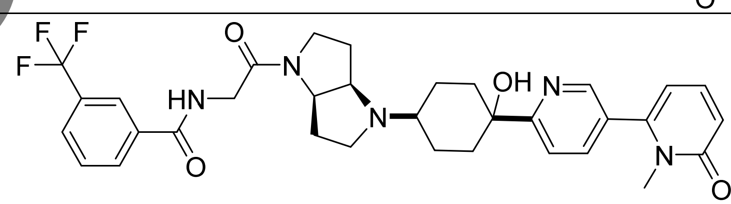
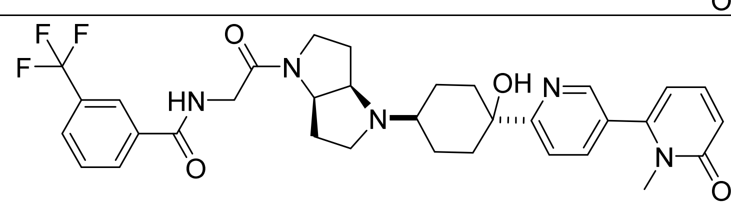

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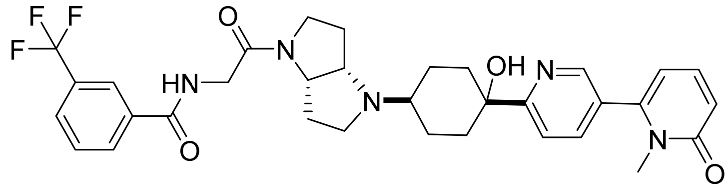
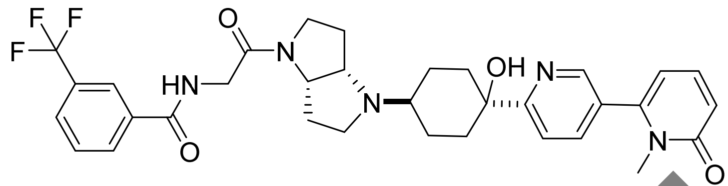
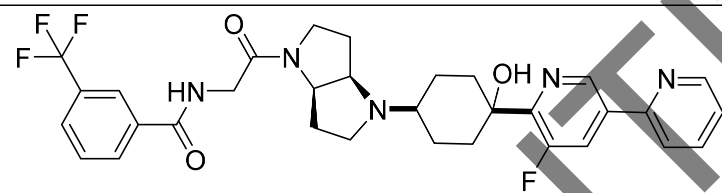
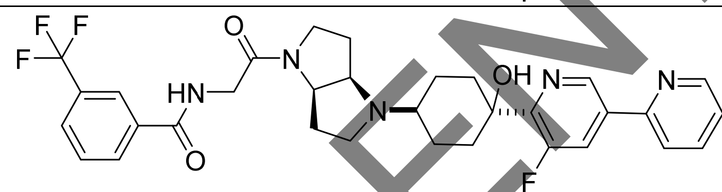
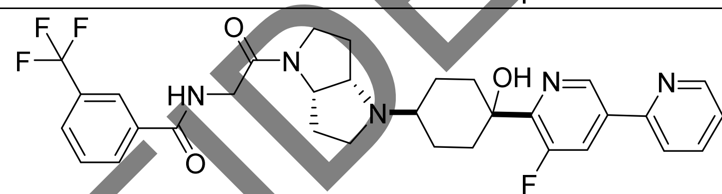
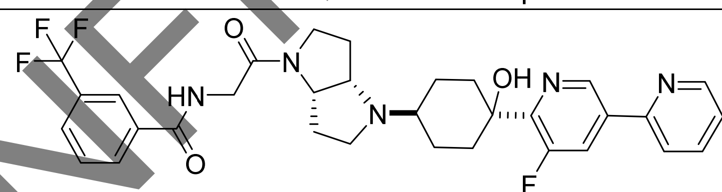
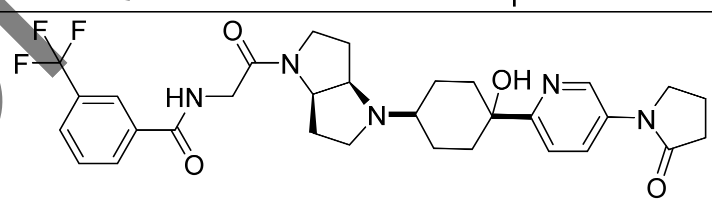
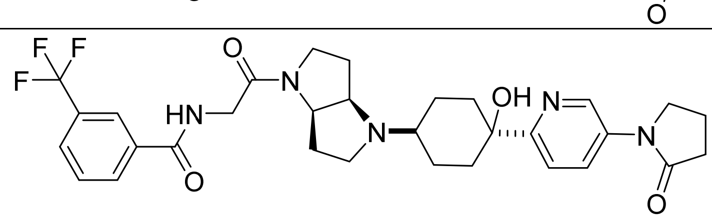

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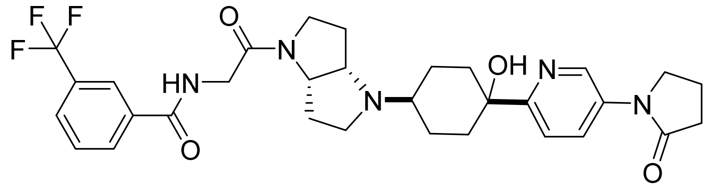
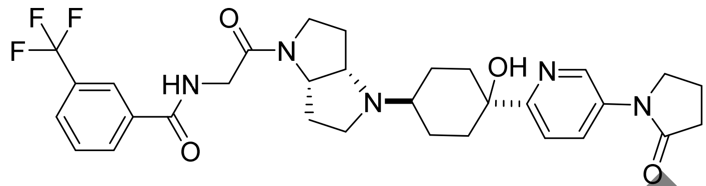
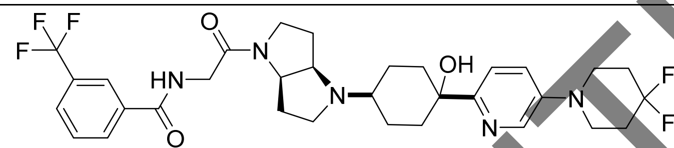
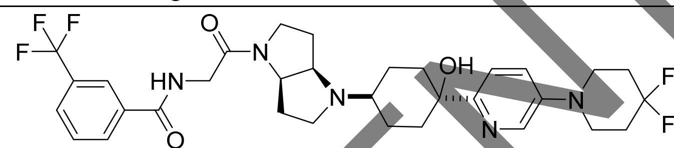
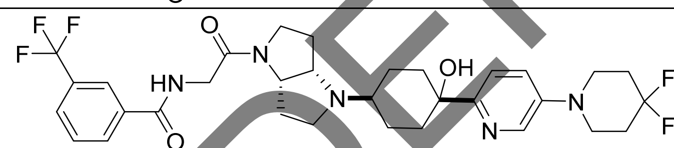
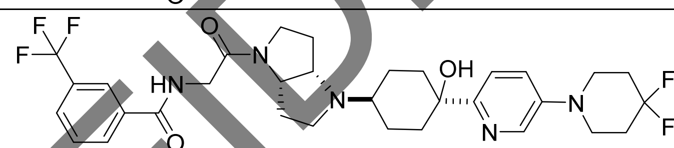
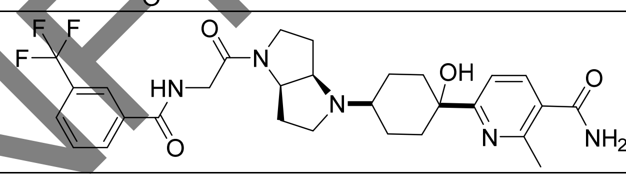
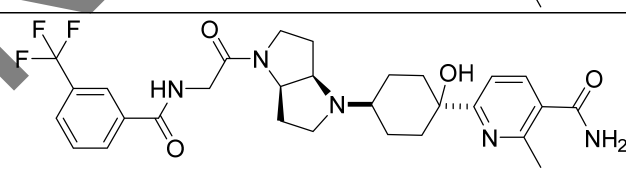
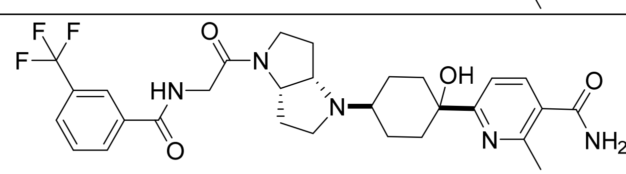
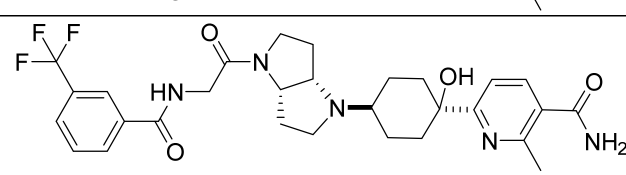

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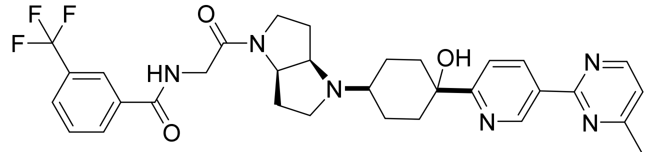
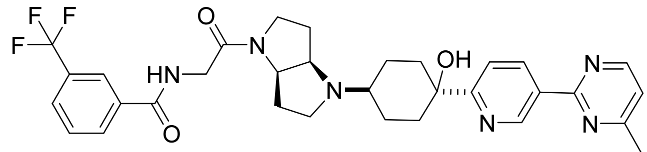
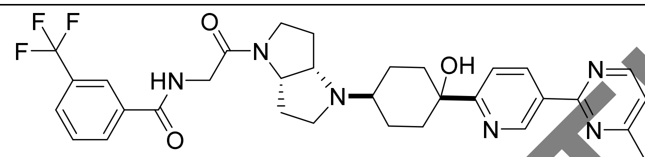
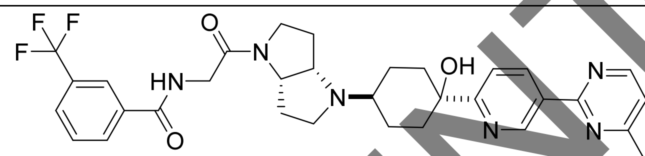
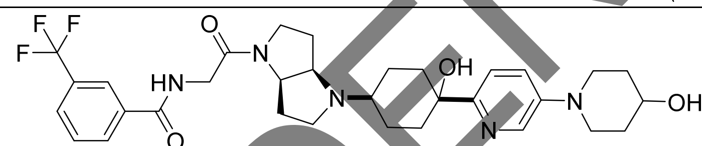
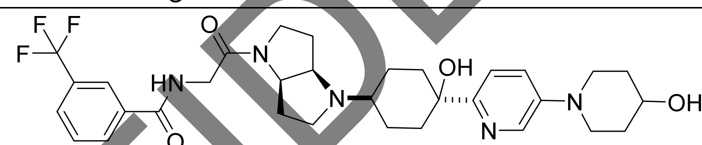
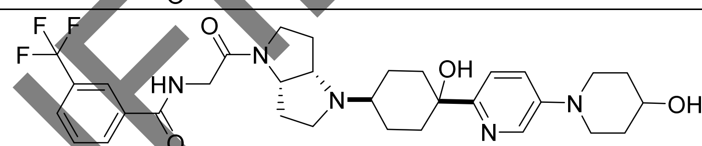
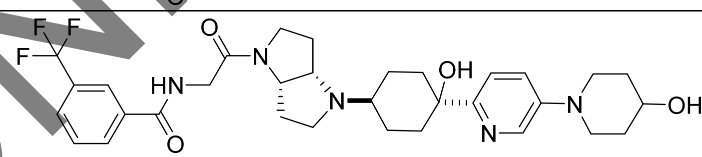
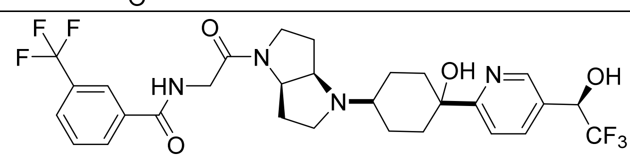
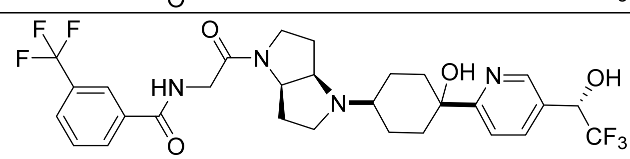
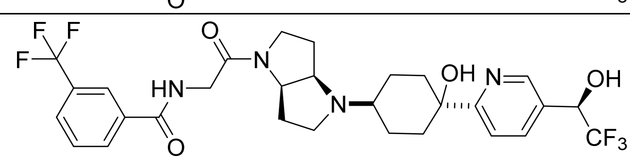

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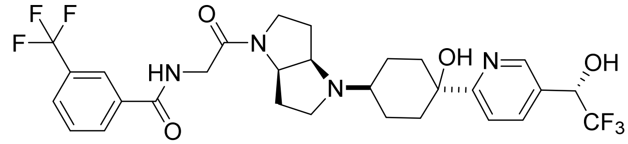
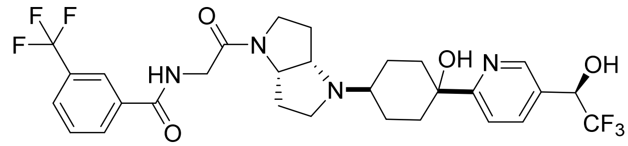
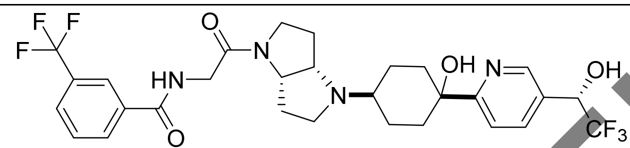
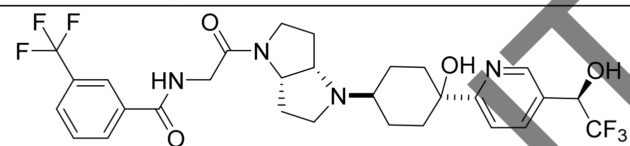
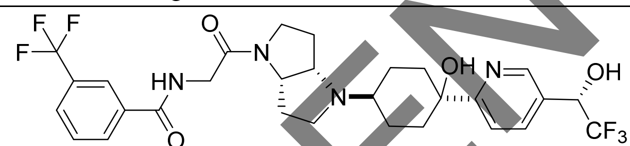
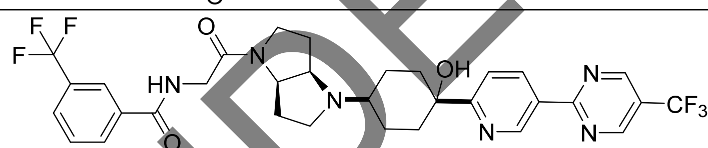
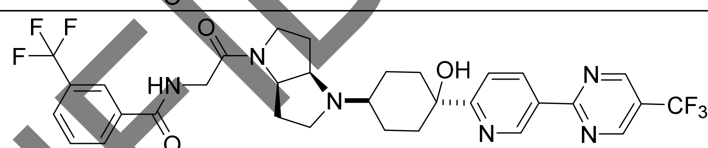
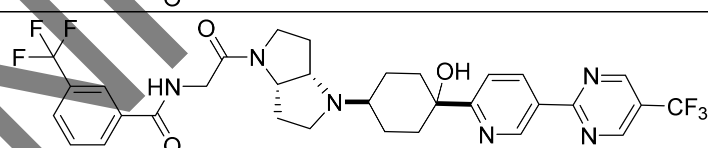
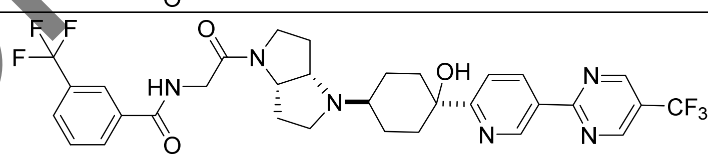
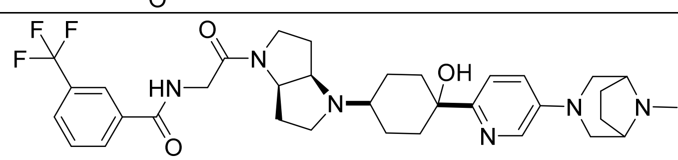
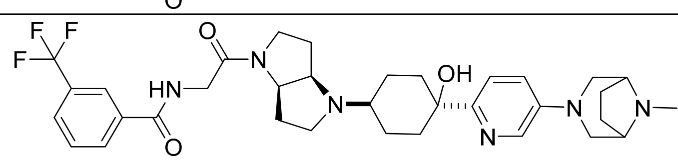

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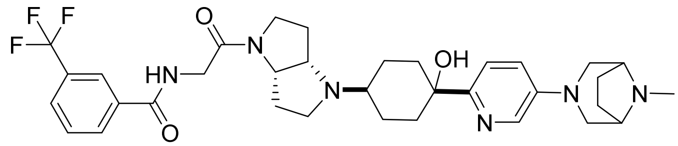
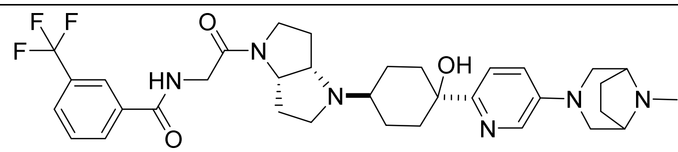
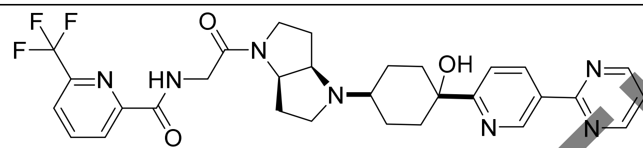
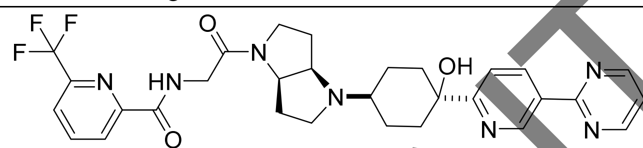
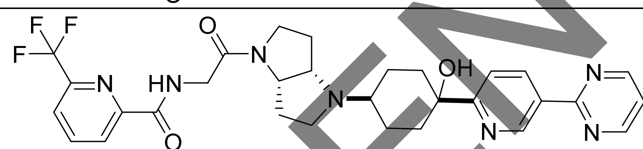
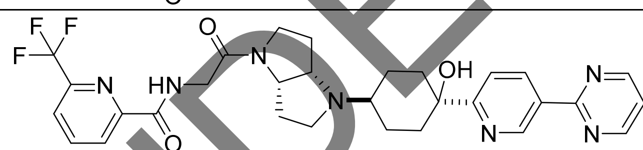
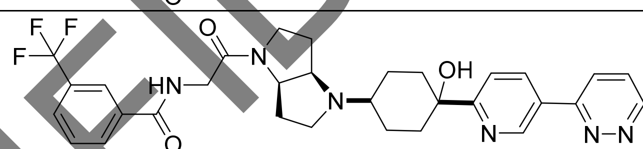
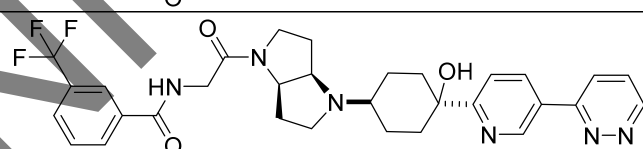
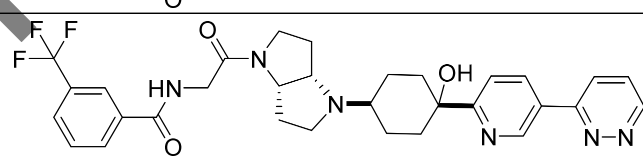
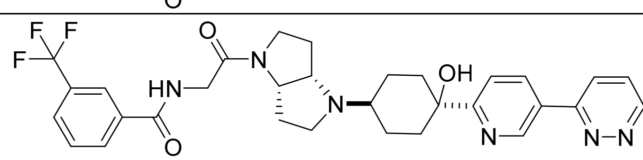
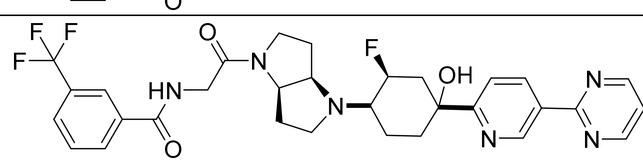

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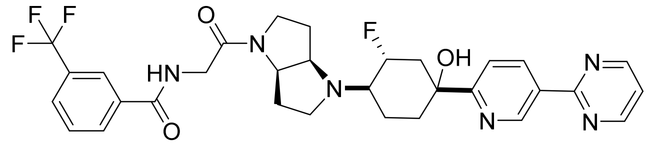
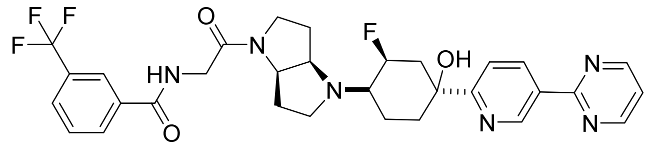
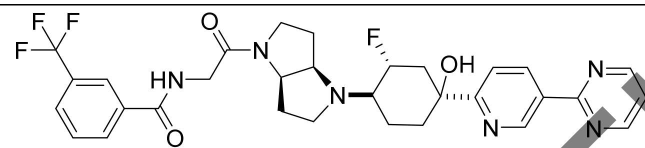
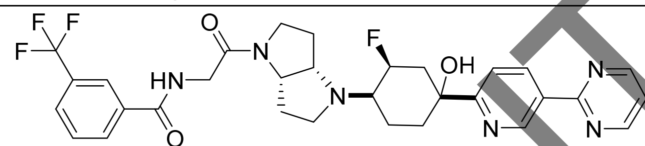
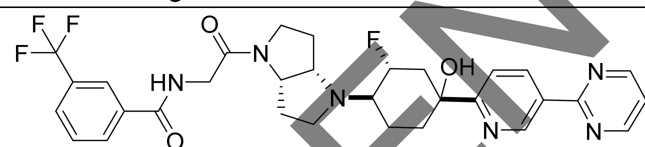
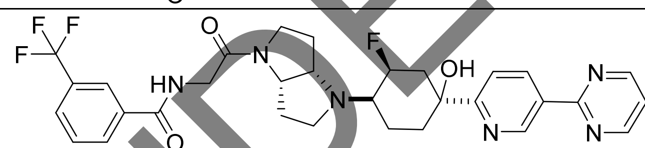
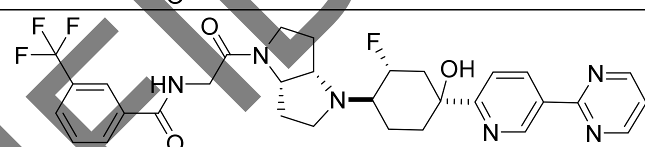
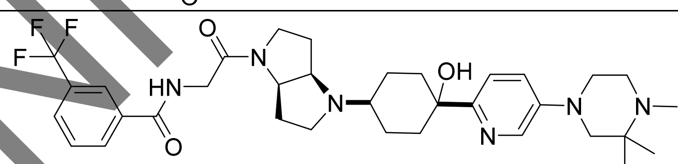
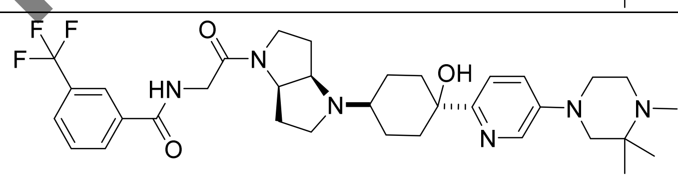
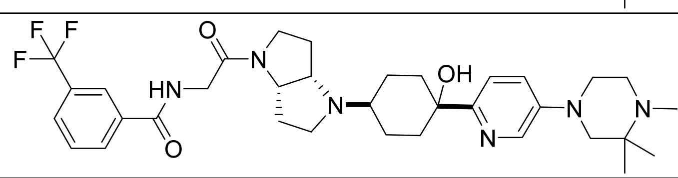
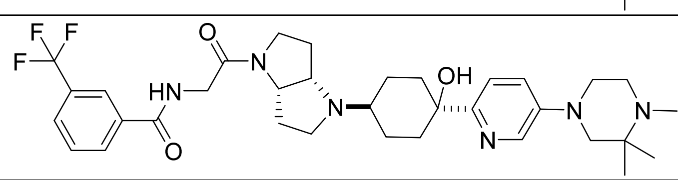

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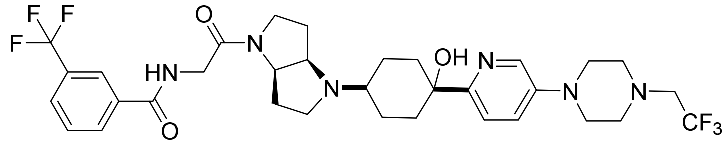
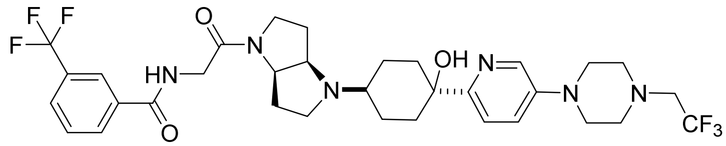
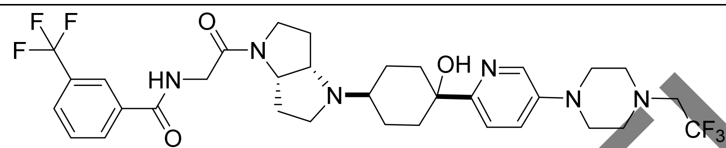
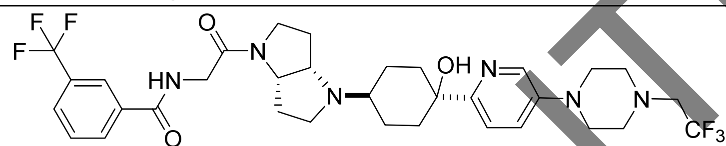
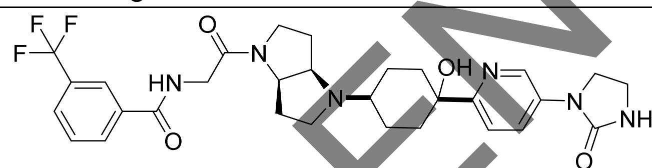
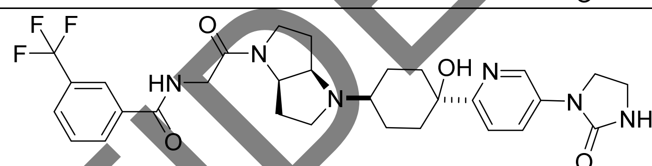
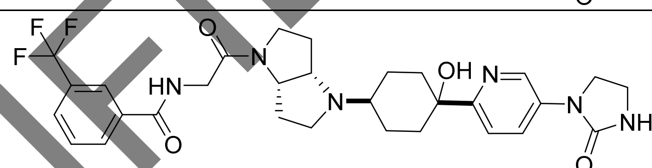
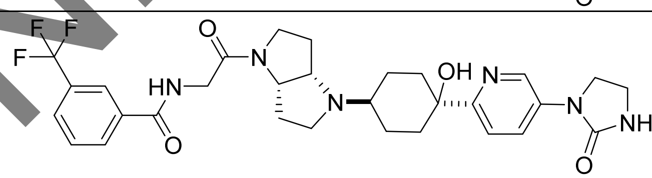
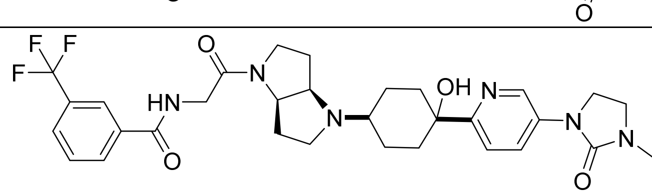
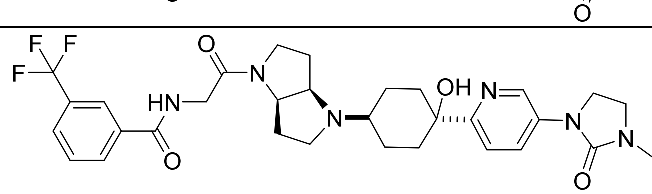

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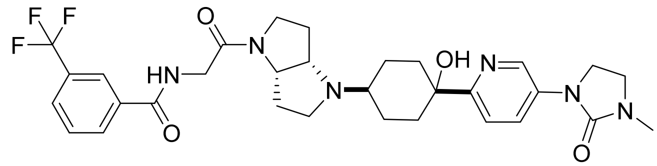
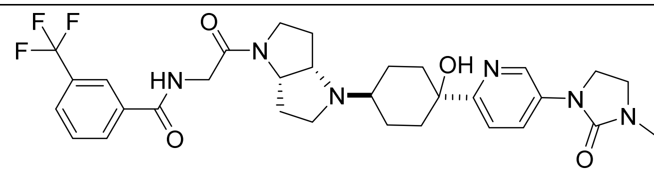
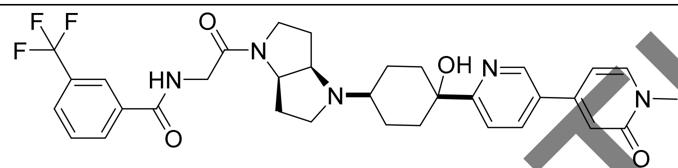
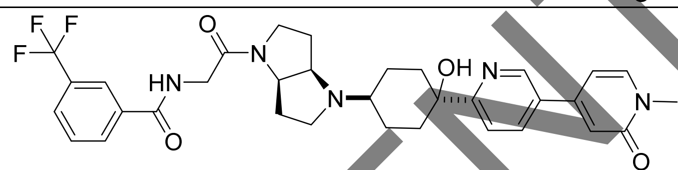
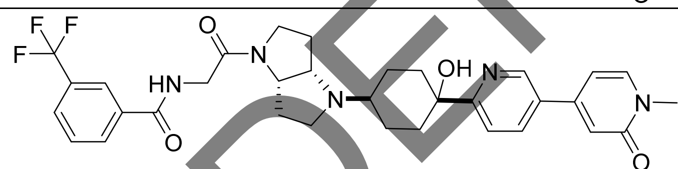
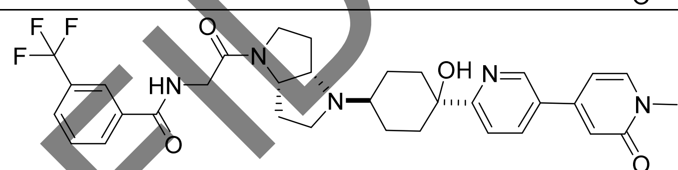
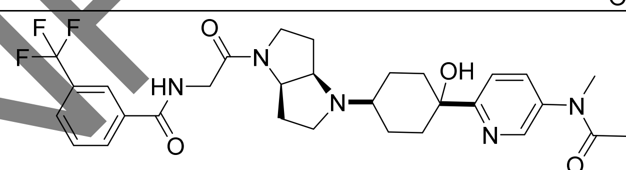
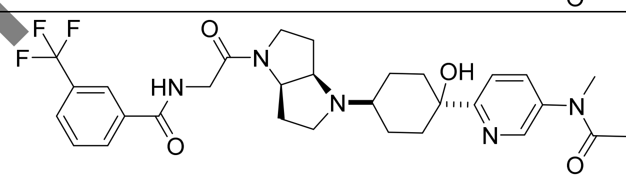
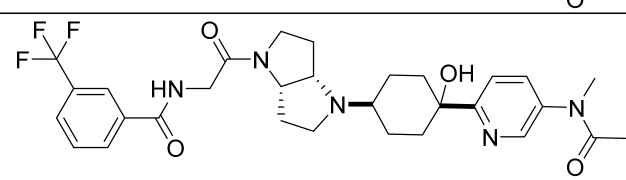
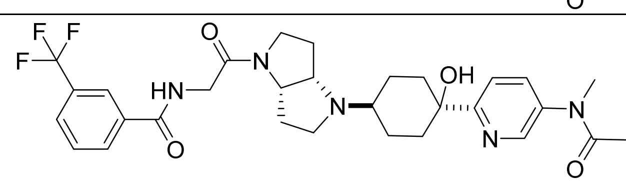

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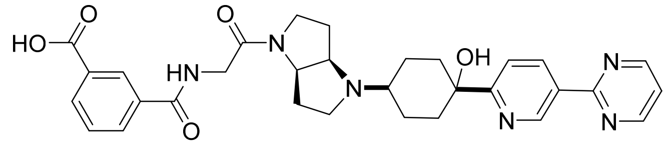
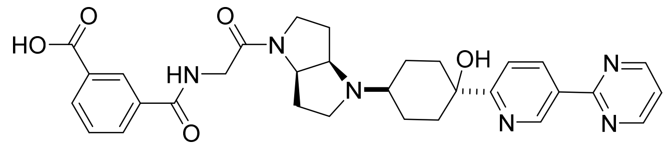
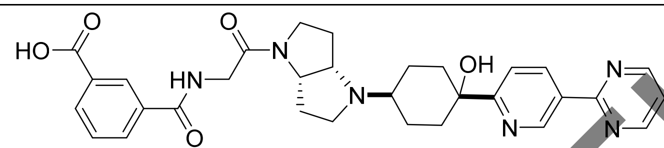
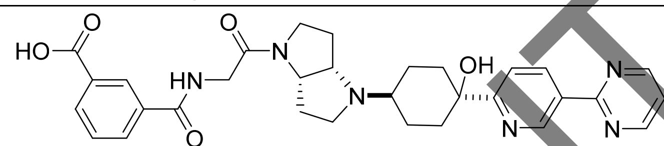
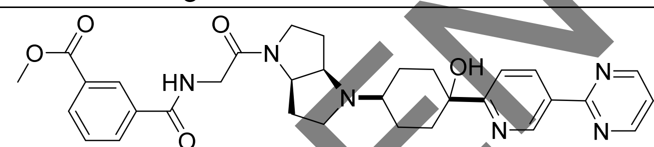
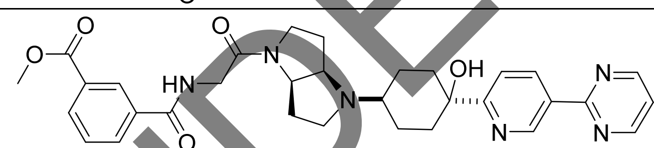
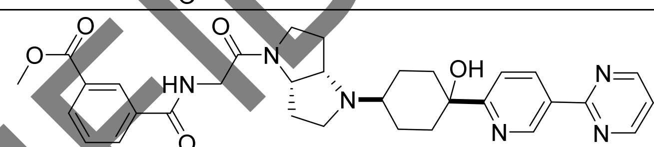
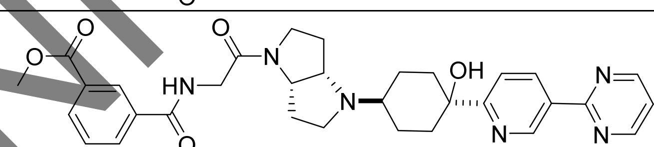
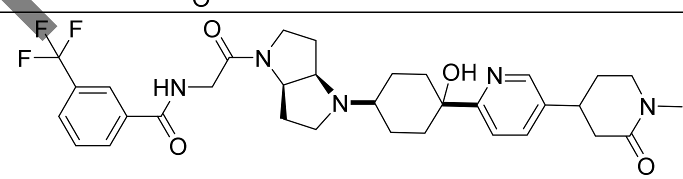
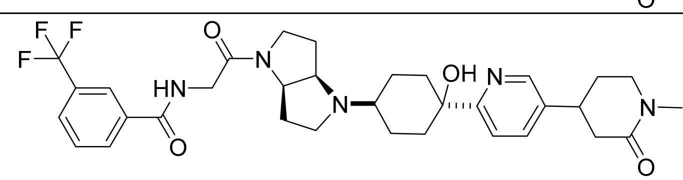
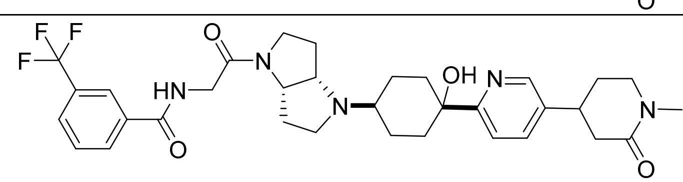

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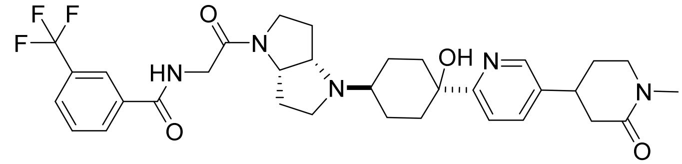
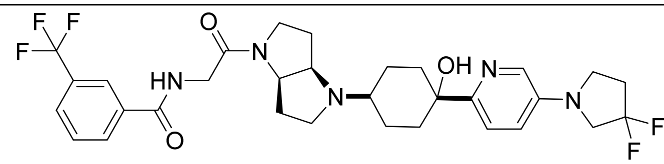
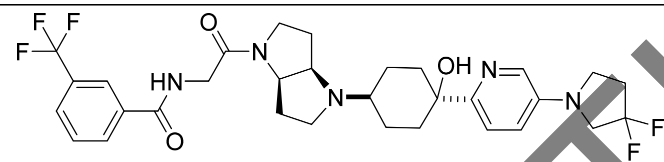
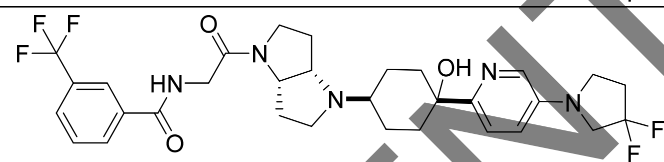
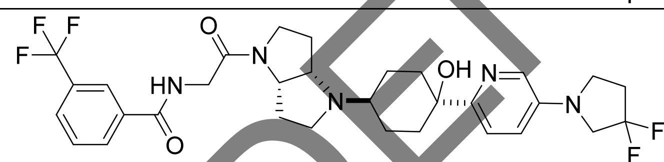
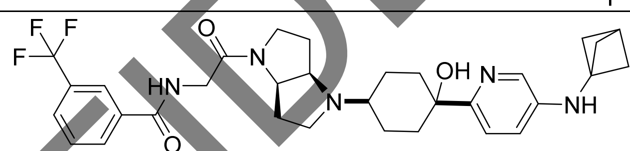
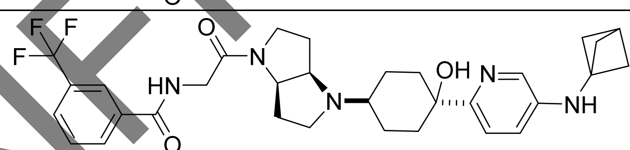
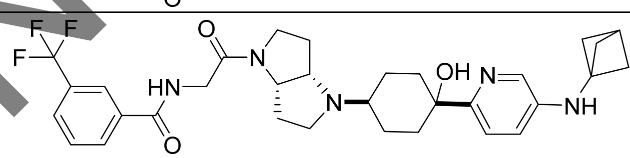
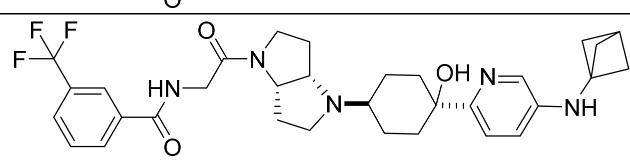
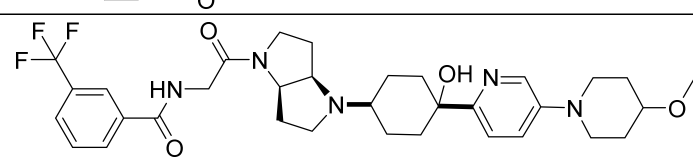
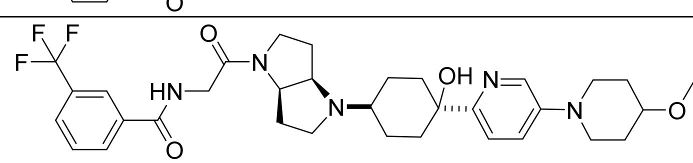

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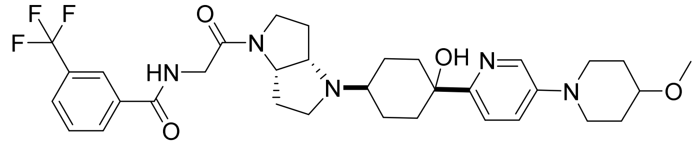
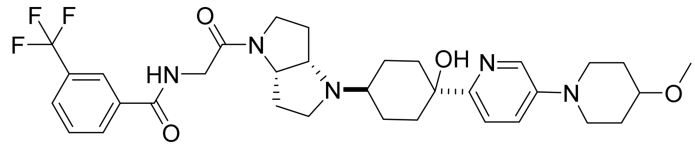
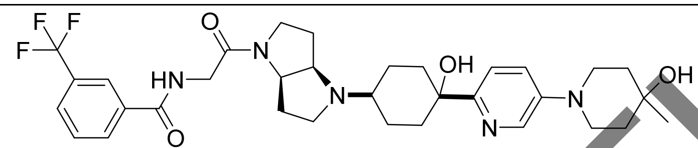
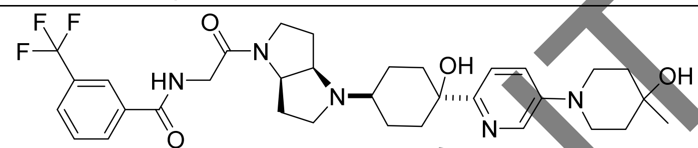
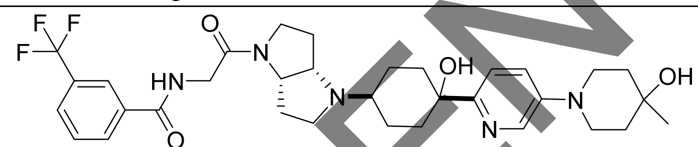
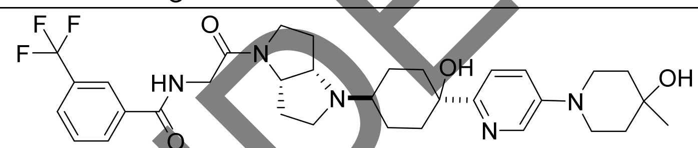
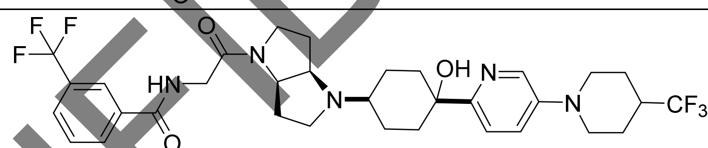
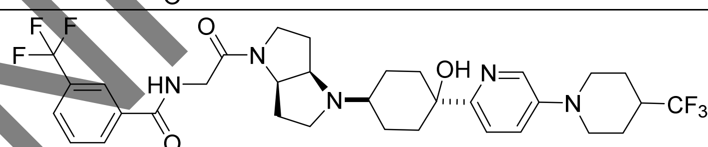
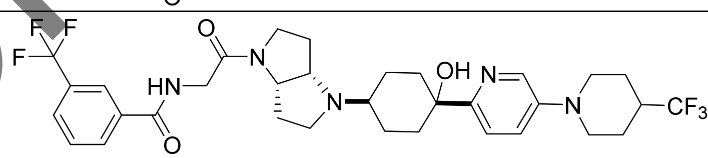
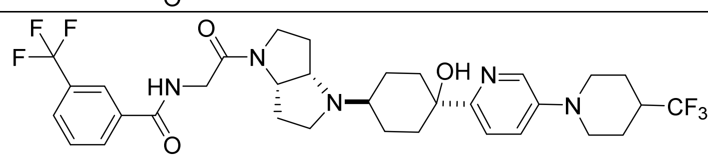
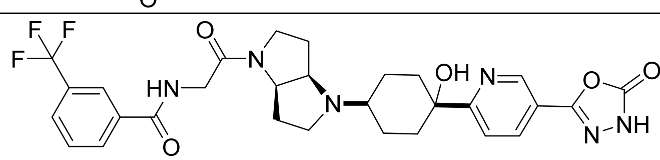

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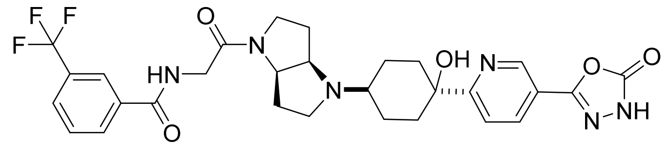
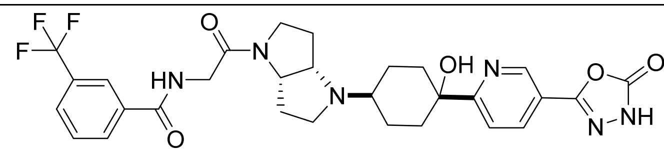
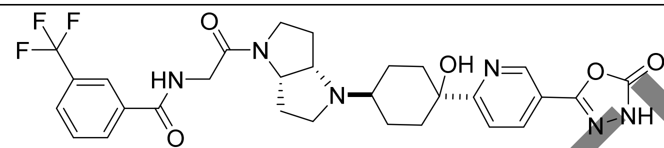
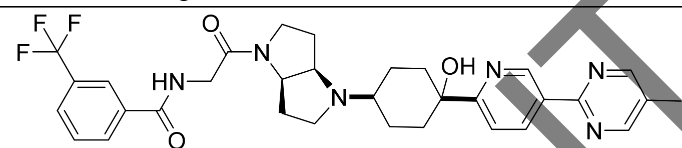
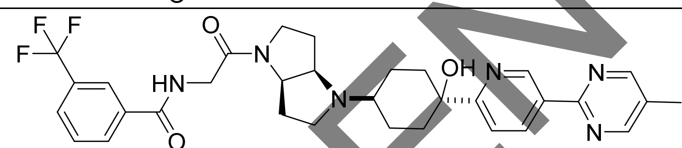
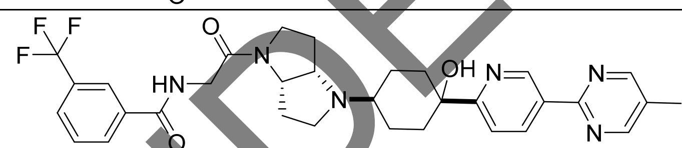
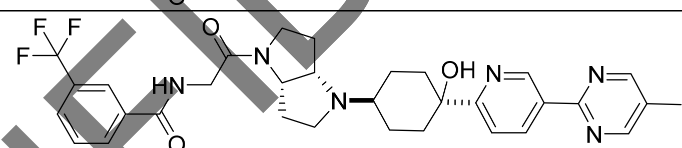
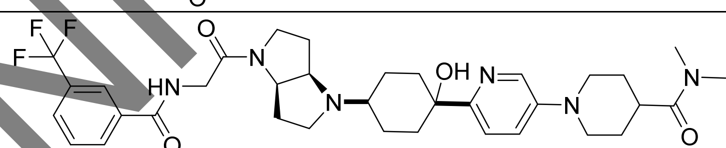
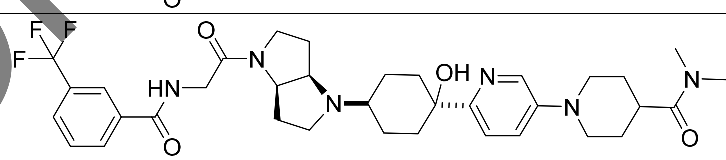
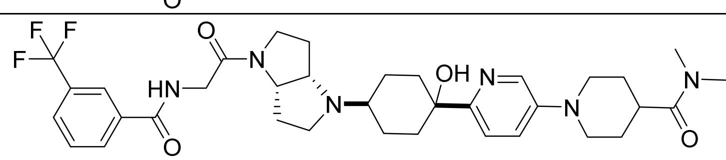
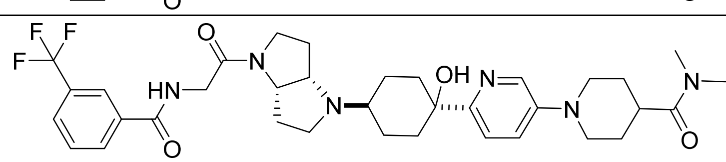

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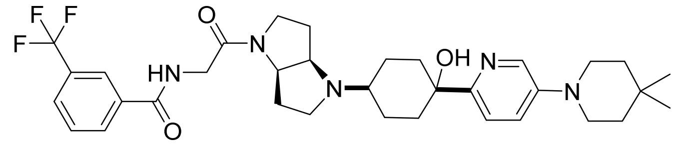
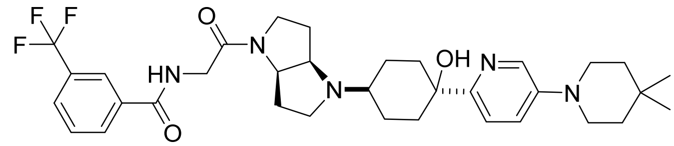
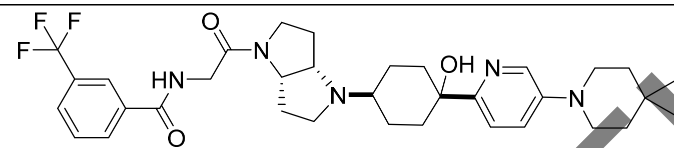
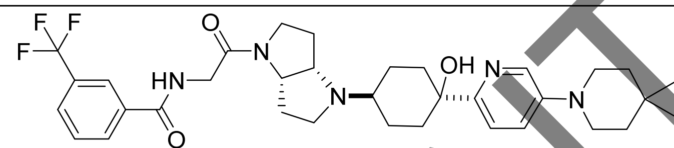
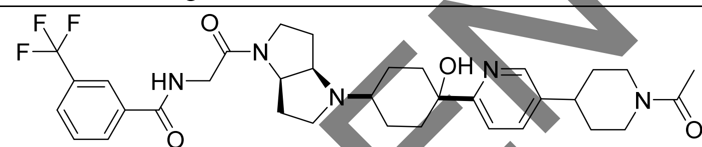
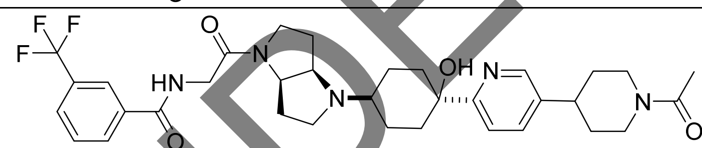
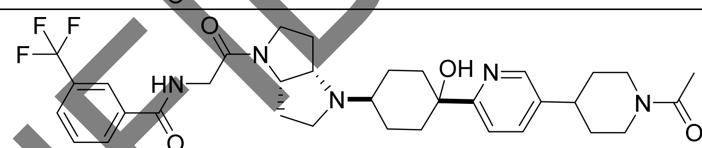
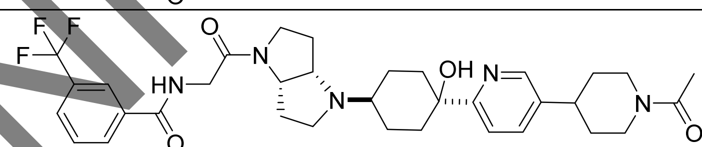
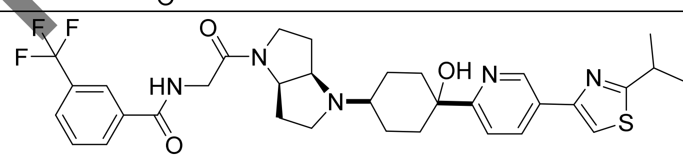
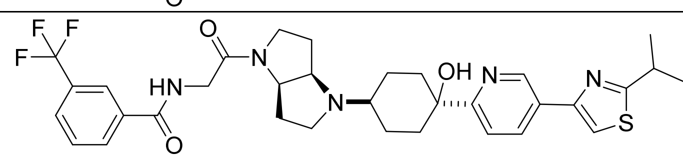
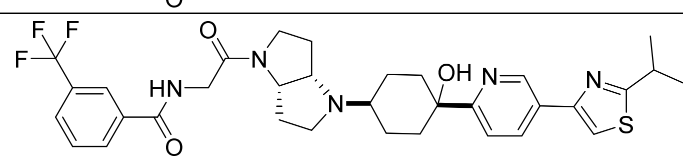

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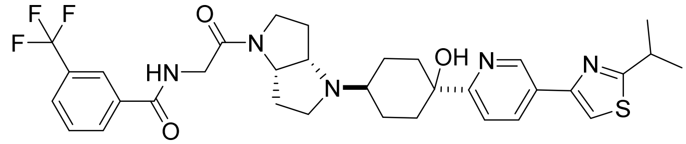
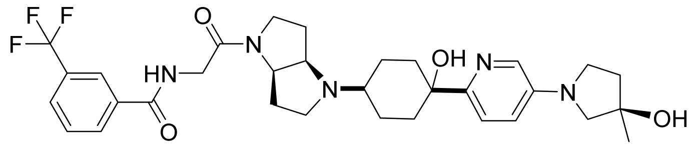
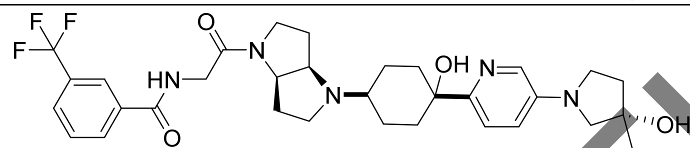
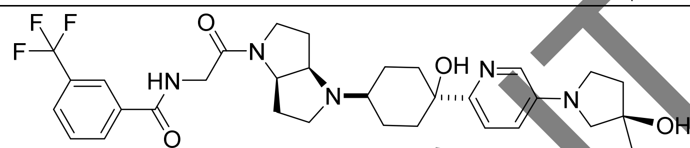
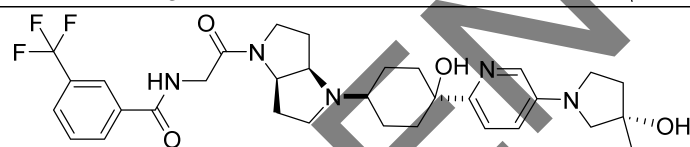
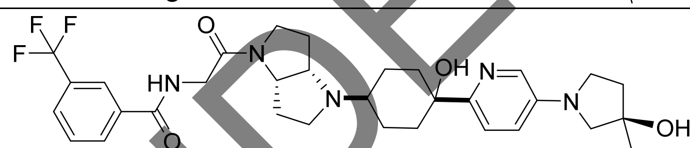
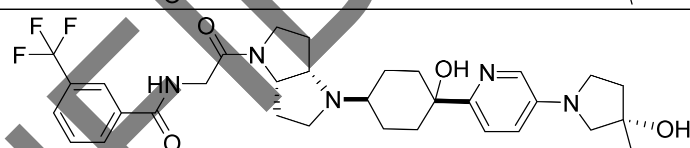
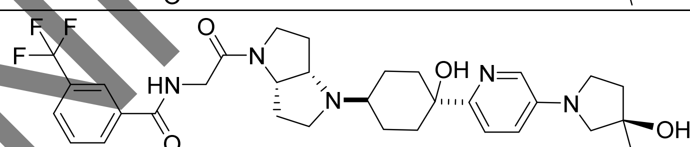
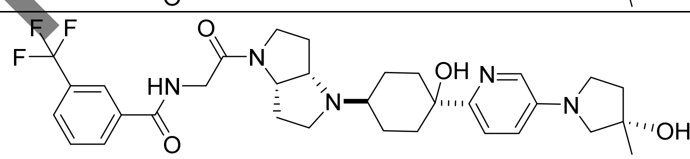
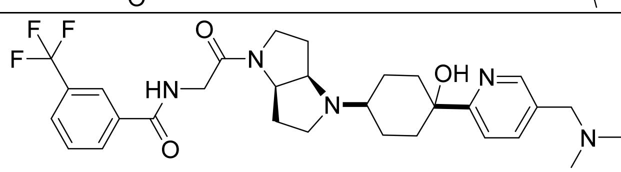
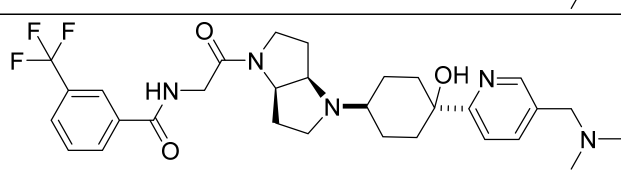

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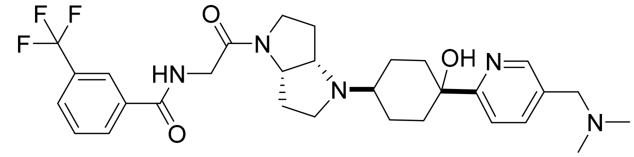
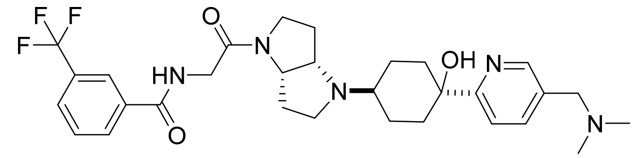
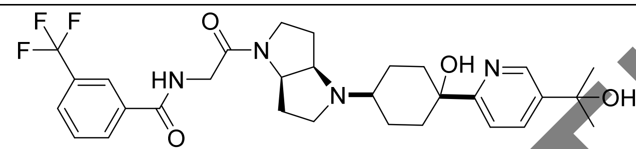
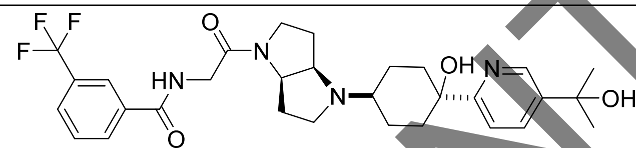
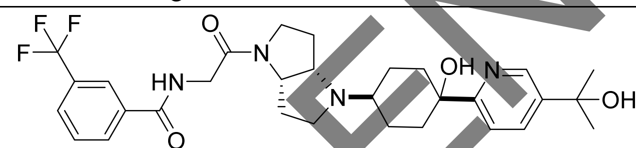
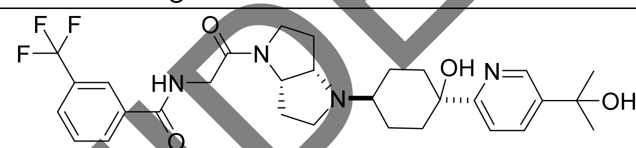
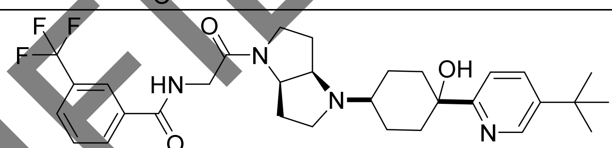
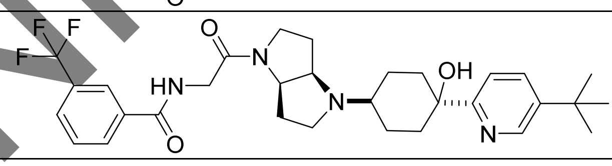
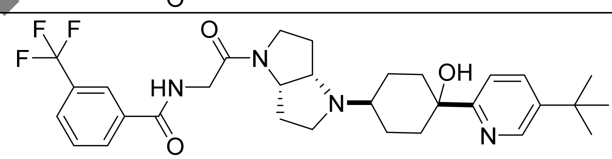
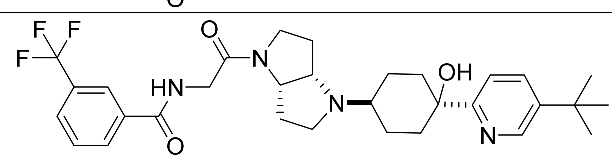
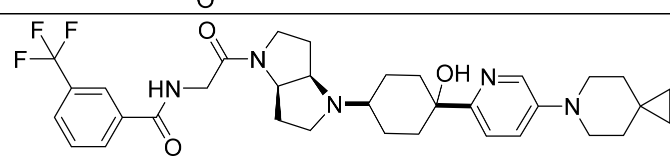

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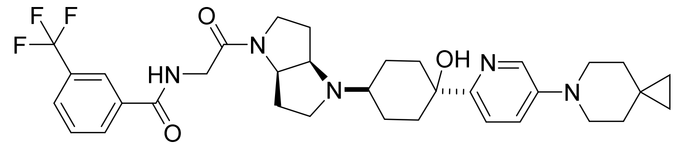
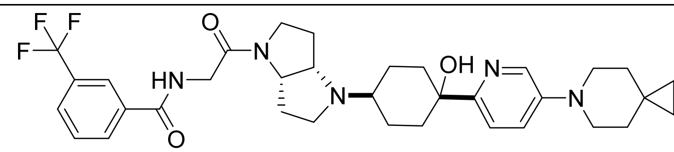
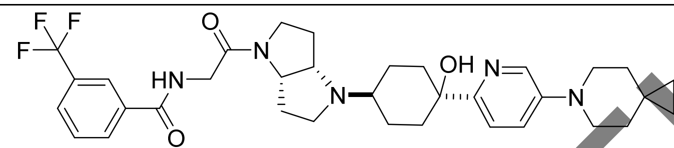
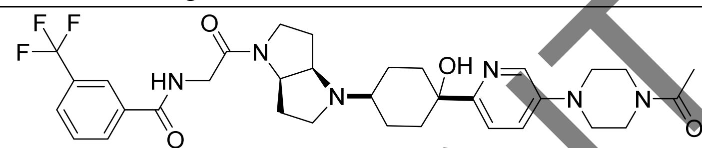
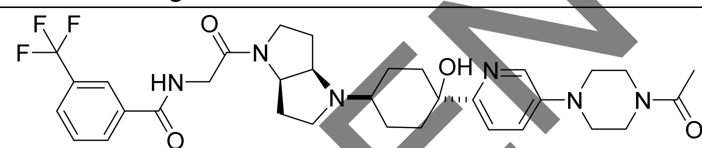
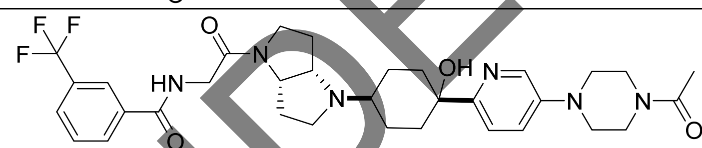
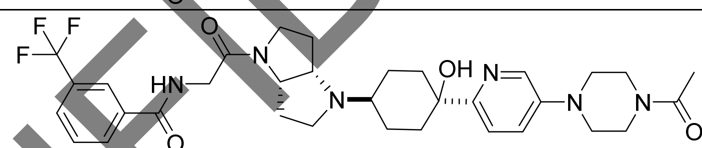
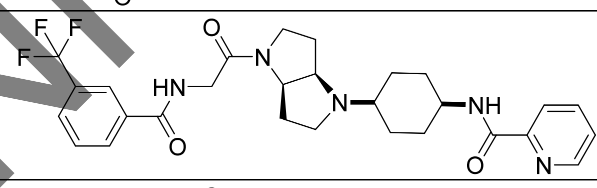
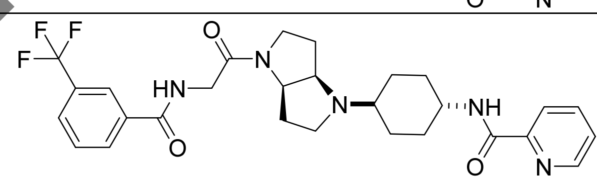
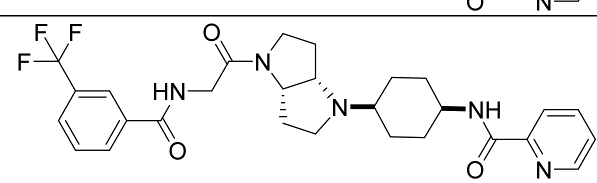

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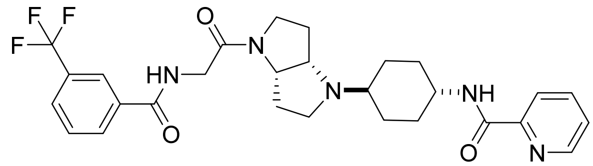
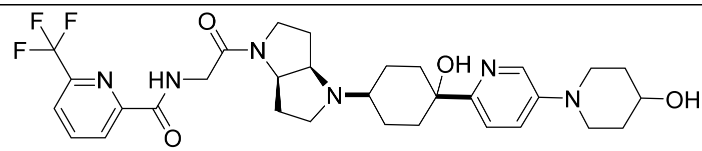
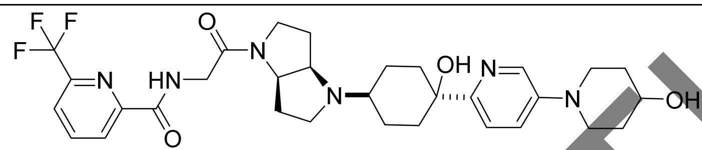
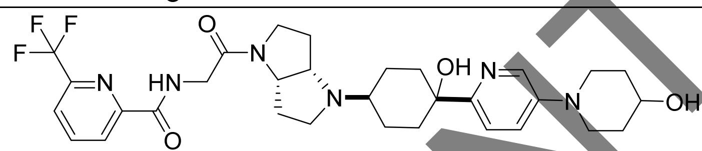
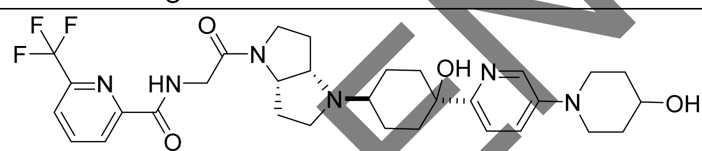
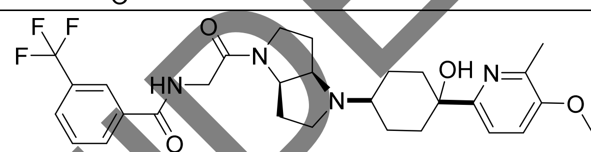
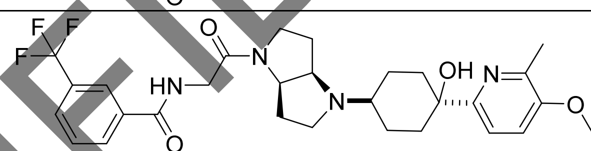
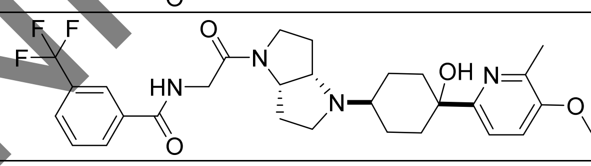
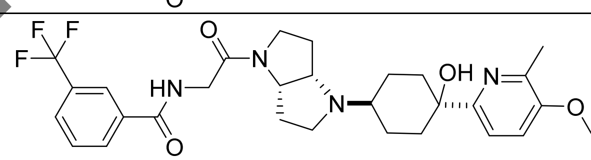
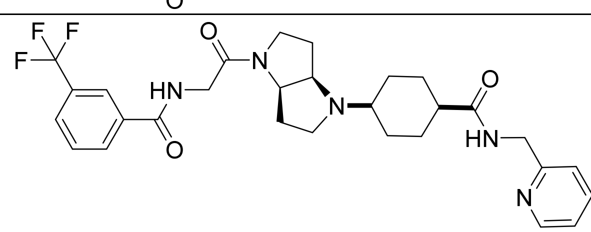

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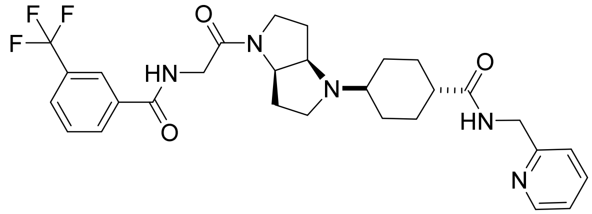
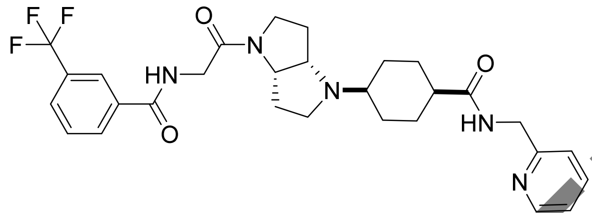
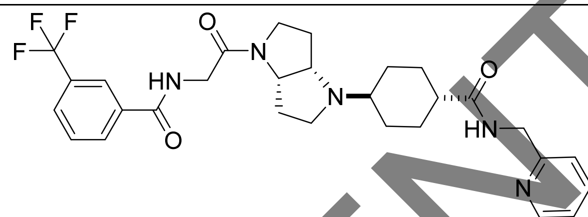
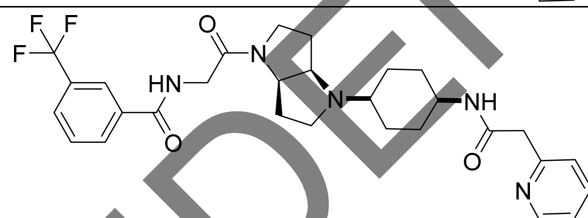
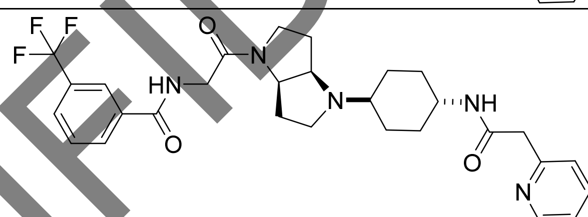
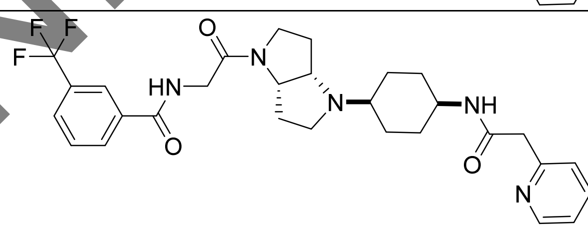
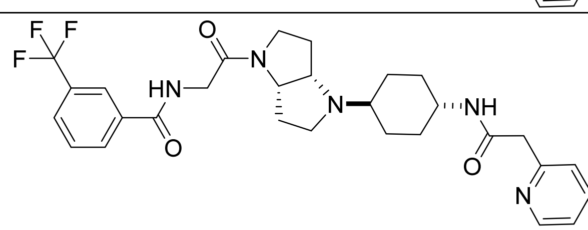

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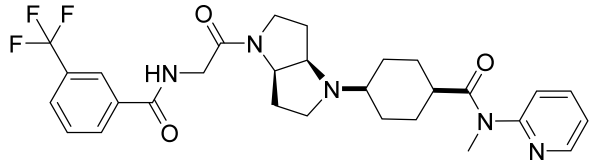
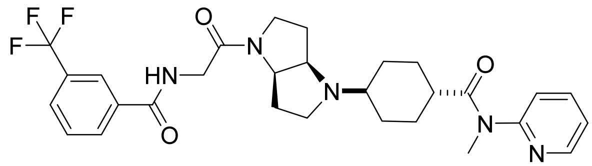
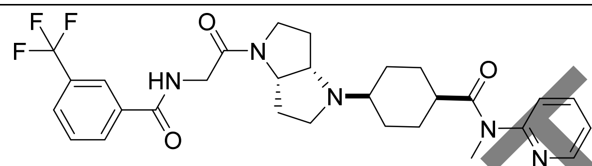
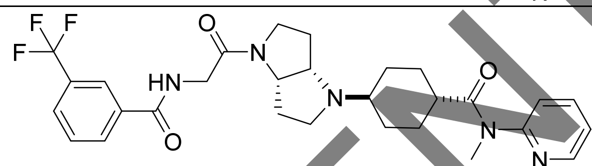
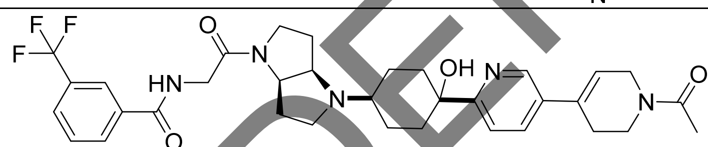
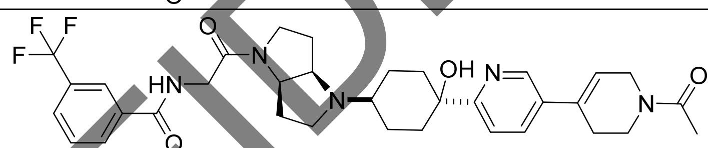
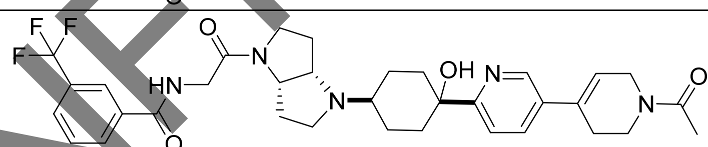
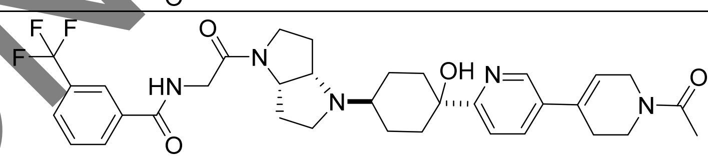
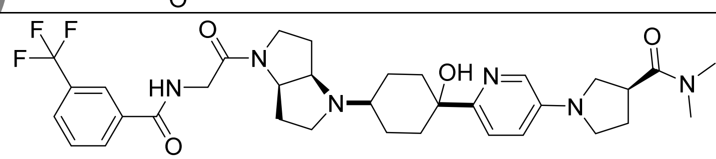
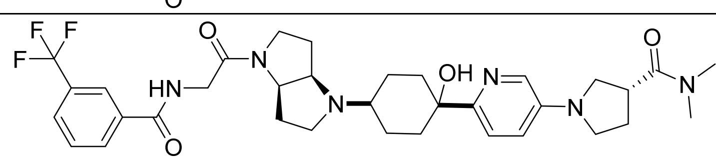

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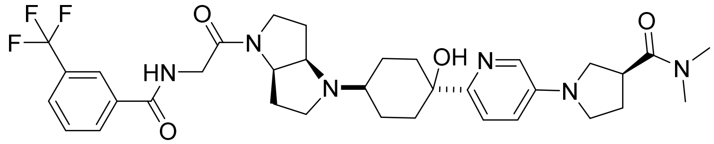
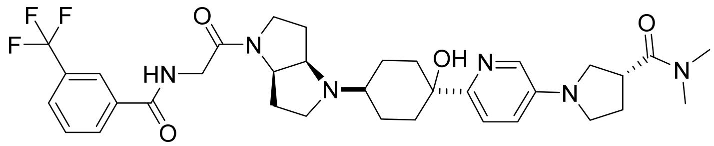
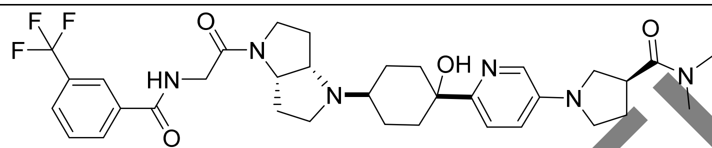
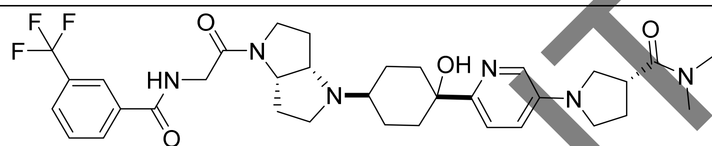
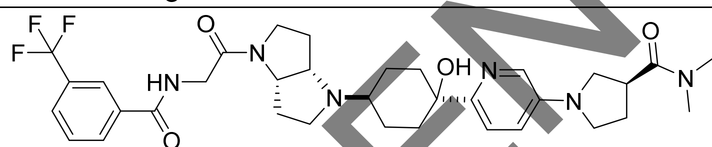
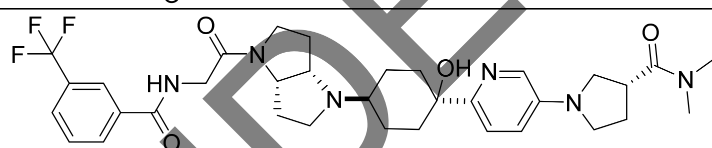
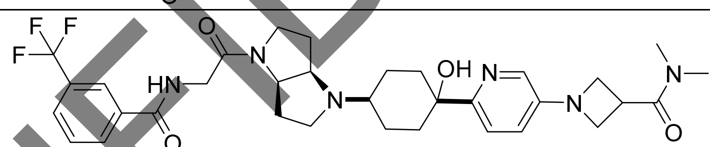
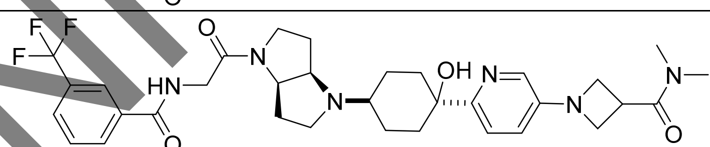
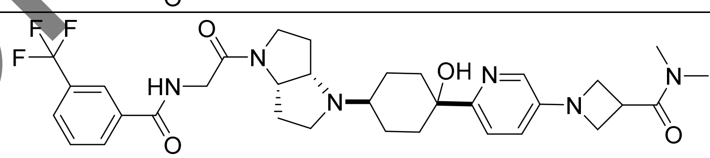
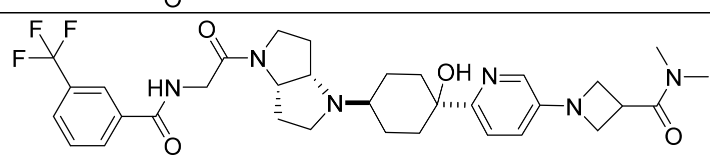
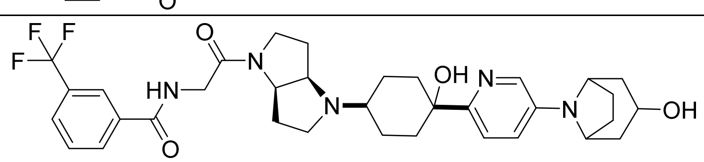

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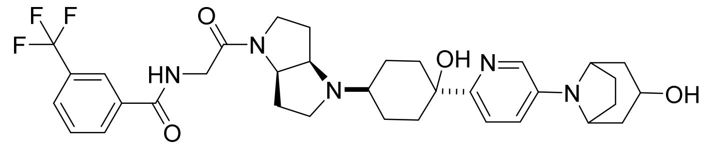
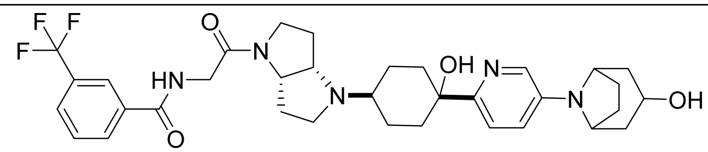
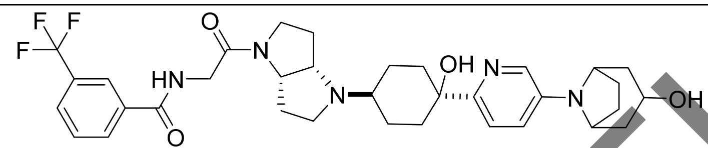
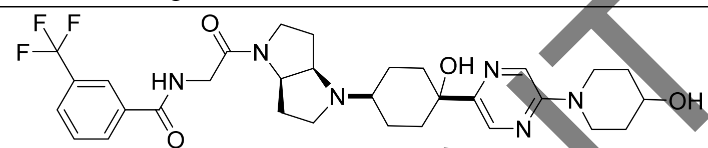
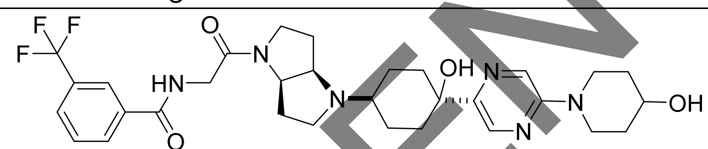
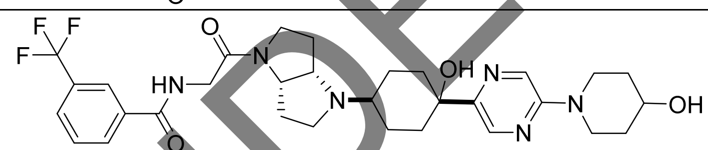
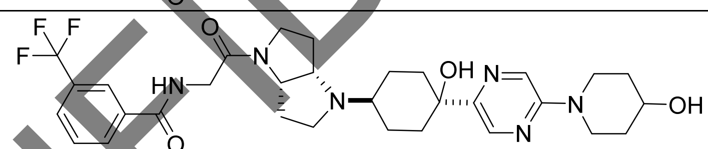
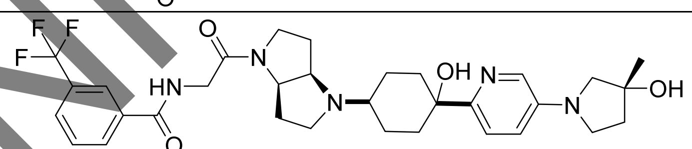
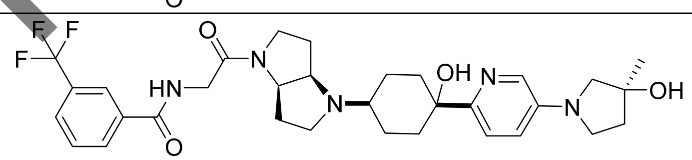
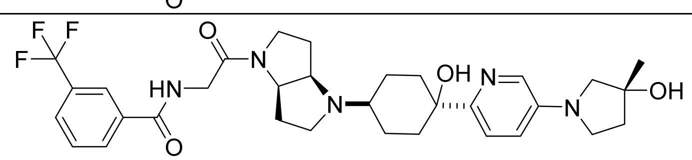
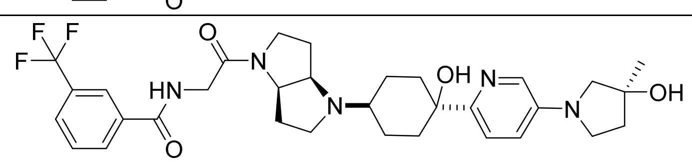

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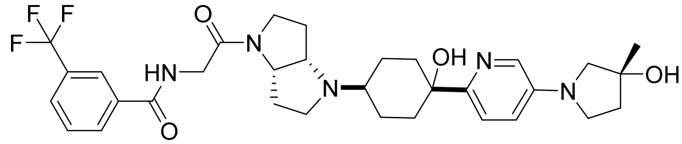
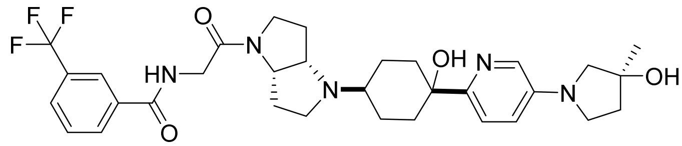
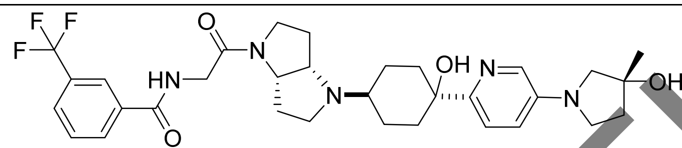
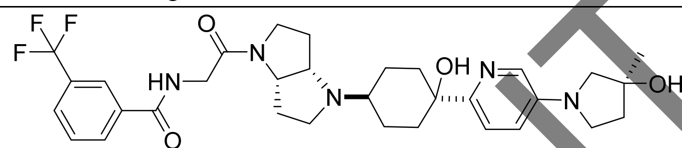
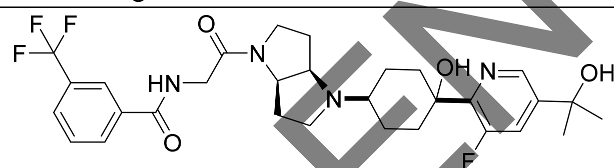
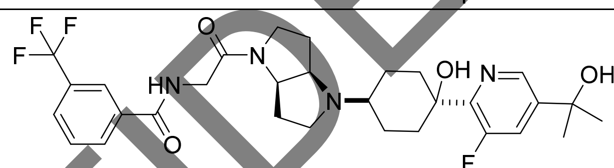
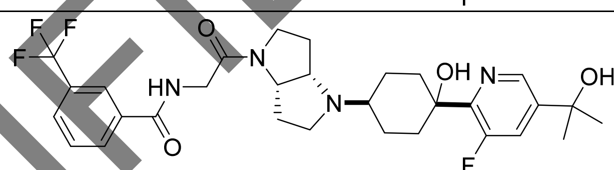
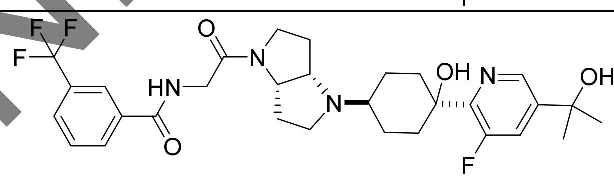
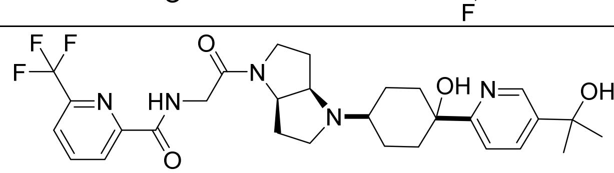
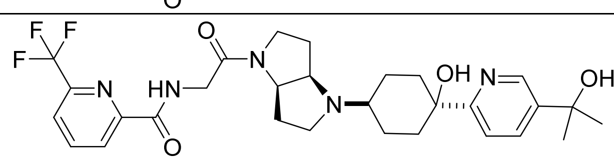

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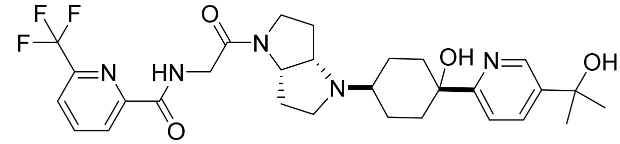
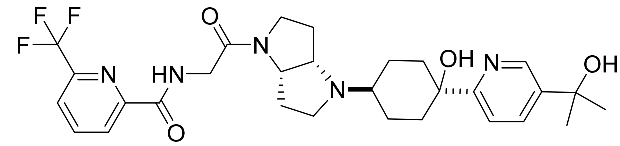
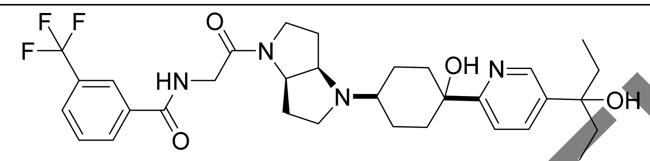
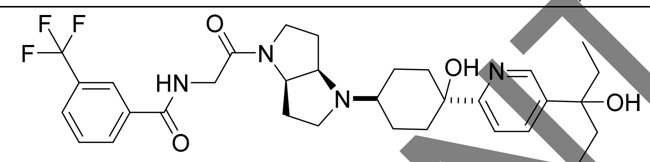
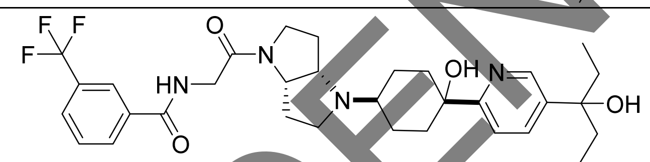
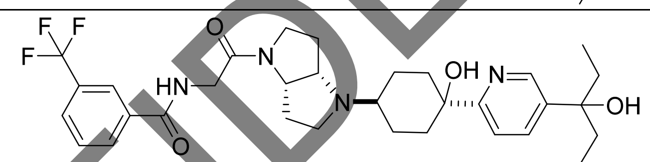
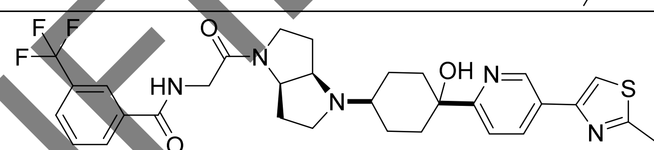
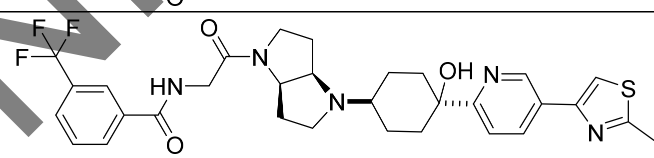
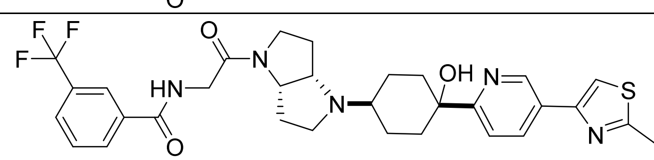
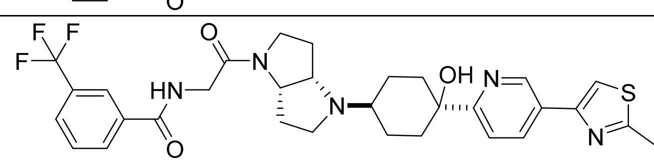
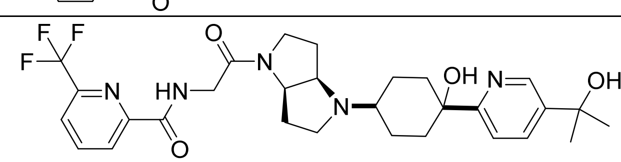

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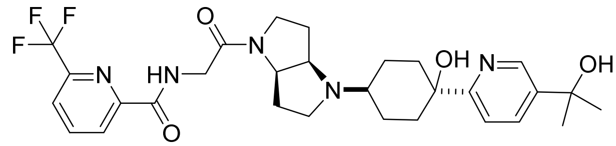
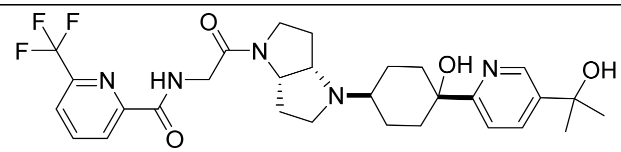
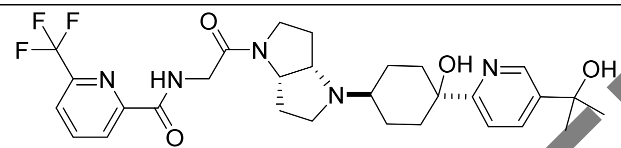
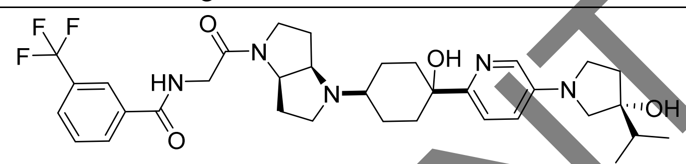
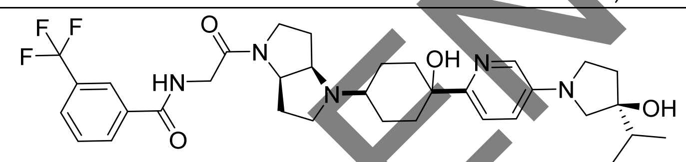
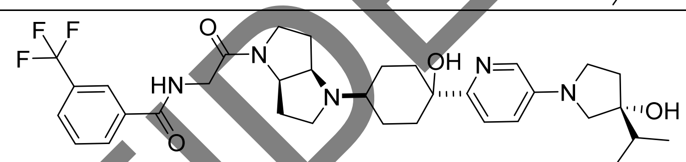
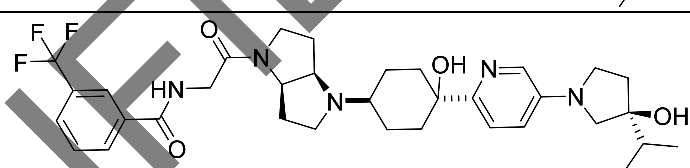
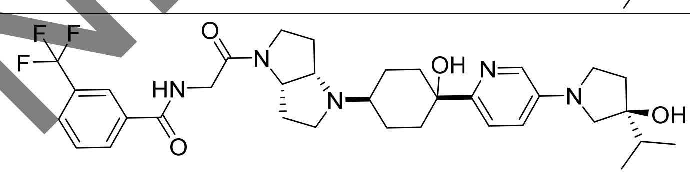
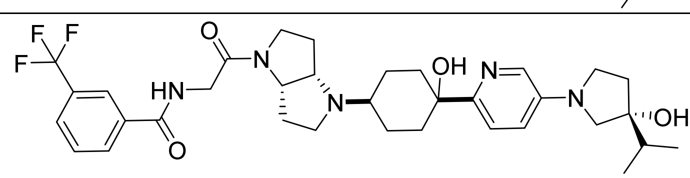
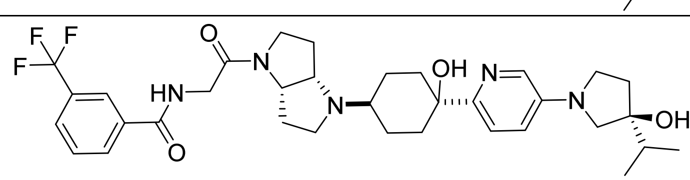

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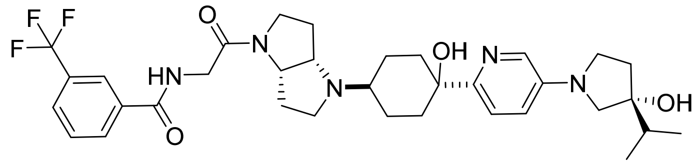


3. Methods

[0131] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life and/or prolonging survival. In one embodiment, treating does not encompass preventing.

[0132] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0133] "Subject" refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[0134] The term "therapeutically effective amount" or "effective amount" of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of a disease or condition of as described herein. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0135] The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. “*In vivo*” means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. “*Ex vivo*” means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo* to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[0136] In embodiments, the compounds disclosed herein can be used to treat or lessen a disease or condition mediated, at least in part, by CCR2, for example, by administering an effective amount of the compound disclosed herein to a subject in need thereof.

[0137] In certain embodiments, the compounds disclosed herein can be used to treat psoriasis, uveitis, rheumatoid arthritis, multiple sclerosis, restenosis, asthma, obesity, chronic obstructive pulmonary disease, pulmonary fibrosis, atherosclerosis, myocarditis, ulcerative colitis, nephritis (nephropathy), lupus, systemic lupus erythematosus, hepatitis, pancreatitis, sarcoidosis, organ transplantation, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, experimental autoimmune encephalomyelitis, and sepsis in which tissue infiltration of blood leukocytes, such as monocytes and lymphocytes, play a major role in the initiation, progression or maintenance of the disease.

[0138] In certain embodiments, the compounds disclosed herein can be used to treat autoimmune diseases. For example, the compounds disclosed herein can be used to treat multiple sclerosis, rheumatoid arthritis, lupus erythematosus, Guillain-Barré syndrome, retinal damage, among others.

[0139] In certain embodiments, the compounds disclosed herein can be used to treat an allergy.

[0140] In certain embodiments, the compounds disclosed herein can be used to treat metabolic syndrome and cardiovascular disease. For example, the compounds disclosed herein can be used to treat obesity and atherosclerosis.

[0141] In certain embodiments, the compounds disclosed herein can be used to treat inflammatory disorders.

[0142] In certain embodiments, the compounds disclosed herein can be used to treat cancers. It is contemplated that the compounds described herein can be used to treat any type of cancer, including, but not limited to, carcinomas, sarcomas, lymphomas, leukemias and germ cell tumors. Exemplary cancers include, but are not limited to, adrenocortical carcinoma, anal cancer, appendix cancer, basal cell carcinoma, cholangiocarcinoma, bladder cancer, bone cancer, osteosarcoma or malignant fibrous histiocytoma, brain cancer (e.g., brain stem glioma, astrocytoma (e.g., cerebellar, cerebral, etc.), atypical teratoid/rhabdoid tumor, central nervous system embryonal tumors, malignant glioma, craniopharyngioma, ependymoblastoma, ependymoma, medulloblastoma, medulloepithelioma, pineal parenchymal tumors of intermediate differentiation, supratentorial primitive neuroectodermal tumors and/or pineoblastoma, visual pathway and/or hypothalamic glioma, brain and spinal cord tumors, etc.), breast cancer, bronchial tumors, carcinoid tumor (e.g., gastrointestinal, etc.), carcinoma of unknown primary, cervical cancer, chordoma, chronic myeloproliferative disorders, colon cancer, colorectal cancer, embryonal tumors, cancers of the central nervous system, endometrial cancer, ependymoma, esophageal cancer, Ewing family of tumors, eye cancer (e.g., intraocular melanoma, retinoblastoma, etc.), gallbladder cancer, gastric cancer, gastrointestinal tumor (e.g., carcinoid tumor, stromal tumor (gist), stromal cell tumor, etc.), germ cell tumor (e.g., extracranial, extragonadal, ovarian, etc.), gestational trophoblastic tumor, head and neck cancer, hepatocellular cancer, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, islet cell tumors, Kaposi sarcoma, kidney cancer, large cell tumors, laryngeal cancer (e.g., acute lymphoblastic, acute myeloid, etc.), leukemia (e.g., myeloid, acute myeloid, acute lymphoblastic, chronic lymphocytic, chronic myelogenous, multiple myelogenous, hairy cell, etc.), lip and/or oral cavity cancer, liver cancer, lung cancer (e.g., non-small cell, small cell, etc.), lymphoma (e.g., AIDS-related, Burkitt, cutaneous Tcell, Hodgkin, non-Hodgkin, primary central nervous system, cutaneous T-cell, Waldenström macroglobulinemia, etc.), malignant fibrous histiocytoma of bone and/or osteosarcoma, medulloblastoma, medulloepithelioma, merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative diseases (e.g., myeloproliferative disorders, chronic, etc.), nasal cavity and/or paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oral cancer; oral cavity cancer, oropharyngeal cancer; osteosarcoma and/or malignant fibrous histiocytoma of bone; ovarian cancer (e.g., ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, etc.), pancreatic cancer (e.g., islet cell tumors, etc.), papillomatosis, paranasal sinus and/or nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal cell cancer, transitional cell cancer, respiratory tract carcinoma involving the nut gene on chromosome 15, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma (e.g., Ewing family of tumors, Kaposi, soft tissue, uterine, etc.), Sézary syndrome, skin cancer (e.g., non-melanoma, melanoma, merkel cell, etc.), small intestine cancer, squamous cell carcinoma, squamous neck cancer with occult primary, metastatic, stomach cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma and/or thymic carcinoma, thyroid cancer, transitional cell cancer of the renal, pelvis and/or ureter (e.g., trophoblastic tumor, unknown primary site carcinoma, urethral cancer, uterine cancer, endometrial, uterine sarcoma, etc.), vaginal cancer, visual pathway and/or hypothalamic glioma, vulvar cancer, Wilms tumor, and the like. Examples of noncancerous cellular proliferative disorders include, but are not limited to, fibroadenoma, adenoma, intraductal papilloma, nipple adenoma, adenosis, fibrocystic disease or changes of breast, plasma cell proliferative disorder (PCPD), restenosis, atherosclerosis, rheumatoid arthritis, myofibromatosis, fibrous hamartoma, granular lymphocyte proliferative disorders, benign hyperplasia of prostate, heavy chain diseases (HCDs), lymphoproliferative disorders, psoriasis, idiopathic pulmonary fibrosis, scleroderma, cirrhosis of the liver, IgA nephropathy, mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, hemangiomas, vascular and non-vascular intraocular proliferative disorders, and the like.

[0143] In certain embodiments, the compounds disclosed herein can be used to treat solid tumors. In certain embodiments, the compounds disclosed herein can be used to treat prostate cancer, breast cancer, and colorectal cancer. In certain embodiments, the compounds disclosed herein can be used to treat pancreatic cancer, gastric cancer, bladder cancer, chondrosarcoma, and skin cancer. In certain embodiments, the compounds disclosed herein can be used to inhibit metastasis formation. In certain embodiments, the compounds disclosed herein can be used to treat metastatic resistant prostate cancer. In certain embodiments, the compounds disclosed herein can be used to treat bone metastasis.

[0144] In certain embodiments, the compounds disclosed herein can be used to treat diseases of the nervous system. For example, ischemia, stroke, neurodegeneration, excitotoxic and mechanical injury, Neurological complications of HIV infections. In certain embodiments, the compounds disclosed herein are capable of inhibiting neuronal cell death, such as in prion disease. Generally, the method includes administering a therapeutically effective amount of a compound or composition as described herein, to a patient in need of. In some embodiments, the disorder is a neurodegenerative disease. The term “neurodegenerative disease” refers to a disease or condition in which the function of a subject's nervous system becomes impaired. Examples of neurodegenerative diseases include, e.g., Alexander’s disease, Alper’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt- Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, kuru, lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), multiple sclerosis, multiple system atrophy, narcolepsy, neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, primary lateral sclerosis, prion diseases, Refsum's disease, Sandhoffs disease, Schilder's disease, subacute combined degeneration of spinal cord secondary to pernicious anemia, schizophrenia, spinocerebellar ataxia (multiple types with varying characteristics), spinal muscular atrophy, Steele-Richardson-Olszewski disease, insulin resistance or Tabes dorsalis.

[0145] In embodiments, the compounds disclosed herein can be used to treat or lessen the severity of cancer, Alzheimer's disease, stroke, Type 1 diabetes, Parkinson disease, Huntington's disease, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, atherosclerosis, arrhythmias, or age-related macular degeneration.

[0146] In embodiments, the compounds disclosed herein can be used to treat or lessen inflammation, rheumatoid arthritis, atherosclerosis, neuropathic pain, lupus, lupus nephritis, systemic lupus erythematosus, restenosis, immune disorders, transplant rejection, neuroinflammation, acute brain injury, solid tumors, or cancer, for example, by administering an effective amount of the compound disclosed herein to a subject in need thereof.

[0147] In embodiments, the compounds disclosed herein can be used to treat or lessen systemic lupus erythematosus or lupus nephritis, for example, by administering an effective amount of the compound disclosed herein to a subject in need thereof.

[0148] In embodiments, provided here are the use of the compounds disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for treating a disease or condition mediated, at least in part, by CCR2. In embodiments, the disease or condition is inflammation, rheumatoid arthritis, atherosclerosis, neuropathic pain, lupus, systemic lupus erythematosus, lupus nephritis, fibrosis, immune disorders, transplant rejection, neuroinflammation, acute brain injury, solid tumors, metabolic disease, or cancer.

[0149] In embodiments, provided herein are compounds or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.

[0150] In embodiments, provided herein are compounds or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating systemic lupus erythematosus or lupus nephritis.

4. Kits

[0151] Provided herein are also kits that include a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and suitable packaging. In certain embodiments, a kit further includes instructions for use. In one aspect, a kit includes a compound of the disclosure, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a label and/or instructions for use of the compounds in the treatment of the indications, including the diseases or conditions, described herein.

[0152] Provided herein are also articles of manufacture that include a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe and intravenous bag.

5. Pharmaceutical Compositions and Modes of Administration

[0153] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds described herein a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0154] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0155] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0156] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0157] Some examples of suitable excipients include, e.g., lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0158] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0159] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0160] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

[0161] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

6. Dosing

[0162] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. In some embodiments, a dosage of from about 0.0001 to about 100 mg per kg of body weight per day, from about 0.001 to about 50 mg of compound per kg of body weight, or from about 0.01 to about 10 mg of compound per kg of body weight may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

7. Synthesis of the Compounds

[0163] The compounds may be prepared using the methods disclosed herein and routine modifications thereof, which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds described herein may be accomplished as described in the following examples. If available, reagents and starting materials may be purchased commercially, e.g., from Sigma Aldrich or other chemical suppliers.

[0164] It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

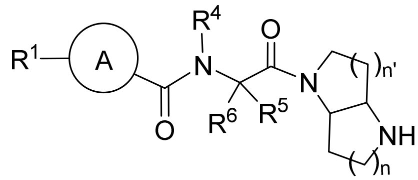
[0165] Additionally, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in Wuts, P. G. M., Greene, T. W., & Greene, T. W. (2006). Greene's protective groups in organic synthesis. Hoboken, N.J., Wiley-Interscience, and references cited therein.

[0166] Furthermore, the compounds of this disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

[0167] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

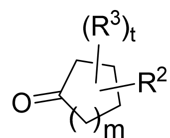
General Synthesis Method I

[0168] In certain embodiments, provided is a method of preparing a compound of Formula I, comprising coupling a compound of Formula 1-A, or salt thereof:



1-A

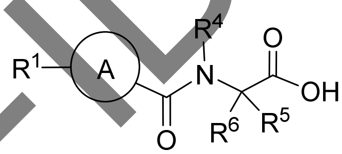
with a compound of Formula 1-B:



1-B

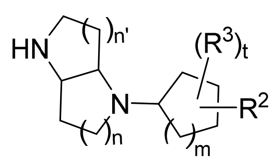
under conditions suitable to provide a compound of Formula I, wherein R^1, R^2, R^3, R^4, R^5, R^6, m, n, n′, and t are as defined herein.

[0169] In certain embodiments, provided is a method of preparing a compound of Formula I, comprising coupling a compound of Formula 10-A:



10-A

with a compound of Formula 10-B:

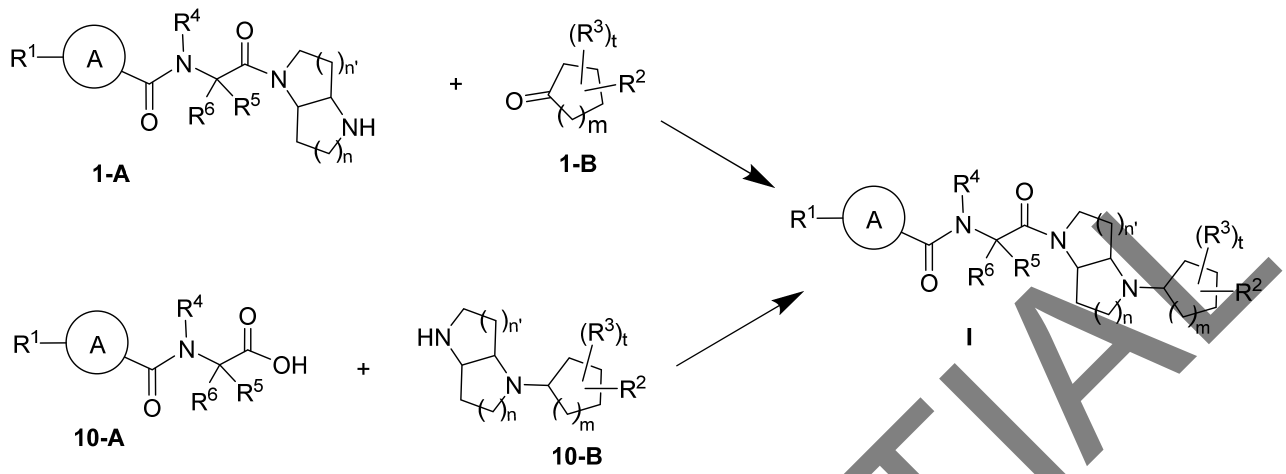


10-B

under conditions suitable to provide a compound of Formula I, wherein R^1, R^2, R^3, R^4, R^5, R^6, m, n, n′, and t are as defined herein.

[0170] The following reaction shown in Scheme I illustrates a general method which can be employed for the synthesis of compounds disclosed herein. In Scheme I, R^1, R^2, R^3, R^4, R^5, R^6, m, n, n′, and t are as defined herein.

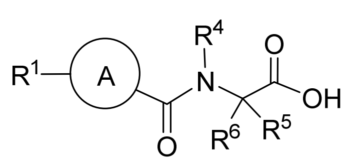
Scheme I



[0171] Referring to Scheme I, a solution of compound of Formula 1-A, or salt thereof, is cooled down to low temperature (e.g., 0 °C). A compound of Formula 1-A (1 *eq*) and an excess amount of base (e.g., triethylamine, 6 *eq*) are added to the solution. After agitation for about 0.5 h, a chemical reductant (e.g., sodium bis(acetyloxy)boranuidyl acetate, 2 *eq*) is introduced in portions. The reaction mixture is maintained at room temperature with agitation for several more hours until completion is indicated by chromatography results. The reaction mixture is then concentrated, quenched, and extracted. The combined organic layer, after suitable workups, provides the compound of Formula I. In certain embodiments, the compound of Formula 1-A is used as the hydrochloric salt in the reaction. In other embodiments, the compound of Formula 1-A is used as the free base in the reaction.

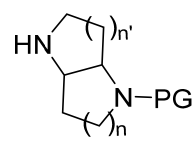
[0172] Alternatively, a solution of compound of Formula 10-A (1.1 *eq*) is cooled down to low temperature (e.g., 0 °C). A peptide coupling agent (e.g., [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium;hexafluoro-λ^5-phosphanuide (HATU) or the like) is added at 0°C along with the compound of 10-B (1 *eq*). Thereafter, a Hünig's base (e.g., ethylbis(propan-2-yl)amine (DIPEA), 3 *eq*) is introduced to the reaction mixture. The reaction mixture is stirred at room temperature for several hours and the progress is monitored by chromatography means. At the completion of the reaction, the reaction mixture is quenched and extracted. The combined organic layer, after suitable workups, provides the compound of Formula I.

[0173] In certain embodiments, the compound of Formula 1-A is prepared by coupling a compound of Formula 10-A:



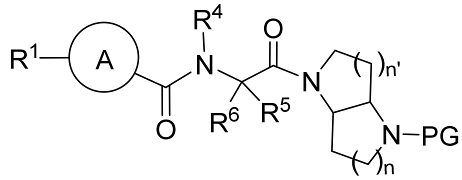
10-A

with a compound of Formula 2-A:



2-A

under conditions suitable to provide a compound of Formula 3-A:

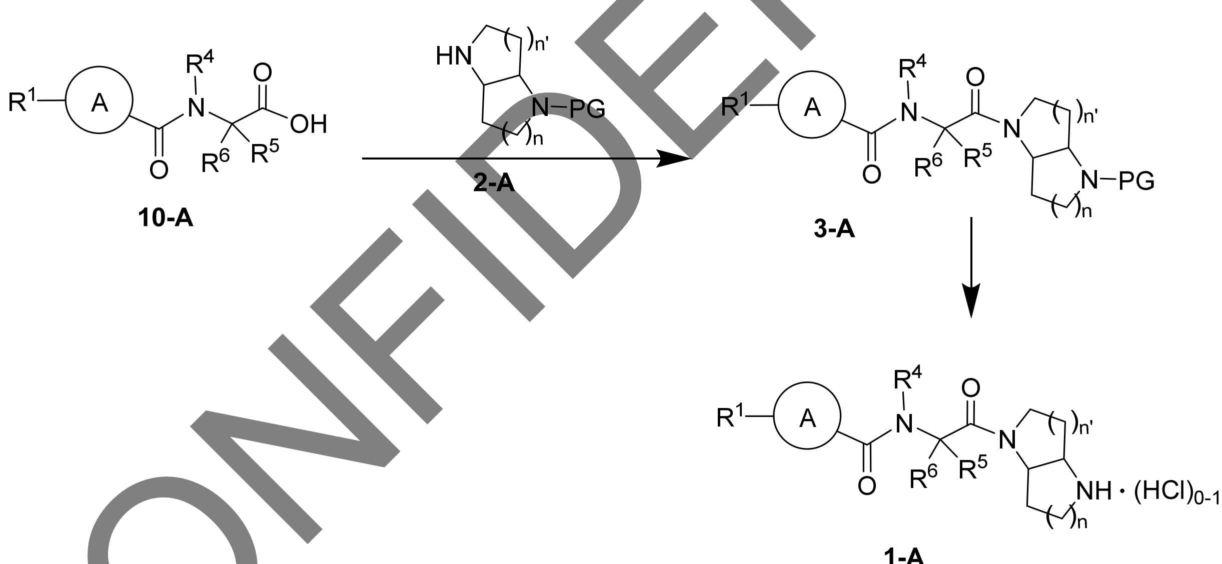


3-A,

wherein R^1, R^2, R^3, R^4, R^5, R^6, m, n, n′, and t are as defined herein, and PG is a protecting group (e.g., tert-butoxycarbonyl (BOC) protecting group, or similar). Subsequently, the compound of Formula 3-A is deprotected to provide the compound of 1-A.

[0174] The following reaction shown in Scheme IA illustrates a general method which can be employed for the synthesis of the compound of Formula 1-A.

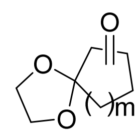
Scheme IA



[0175] Referring to Scheme IA, the compound of Formula 10-A (1 *eq*) is dissolved in a suitable organic solvent and stirred. A peptide coupling reagent (e.g. HATU, 2 *eq*) is added in portion-wise, along with the compound of Formula 2-A (1.2 *eq*). Thereafter, a Hünig's base (e.g., DIPEA, 4 *eq*) is introduced to the reaction mixture. The reaction mixture is stirred at room temperature for about 10 h to about 18 h or until chromatography result indicates the completion of the reaction. The reaction mixture is then quenched and extracted. The combined organic layer, after suitable workups, provides the compound of Formula 3-A.

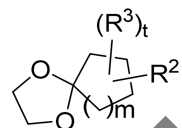
[0176] The compound of Formula 3-A (1 *eq*) is then redissolved in a suitable organic solvent (e.g., dichloromethane). The solution is acidified at low temperature (e.g., 0 °C), for example, using a 1,4-dioxane solution of hydrogen chloride (4N). The reaction mixture is maintained with stirring at room temperature for about 6 h to 10 h, or until chromatography results suggest completion of the reaction. Crude product is obtained following evaporation of the solvents. After subsequent suitable workups, the compound of Formula 1-A is received.

[0177] In certain embodiments, the compound of Formula 1-B is prepared by first contacting a compound of Formula 2-B:



2-B

with a brominated compound R^2-Br in presence of an organolithium compound under conditions suitable to provide a compound of Formula 3-B:

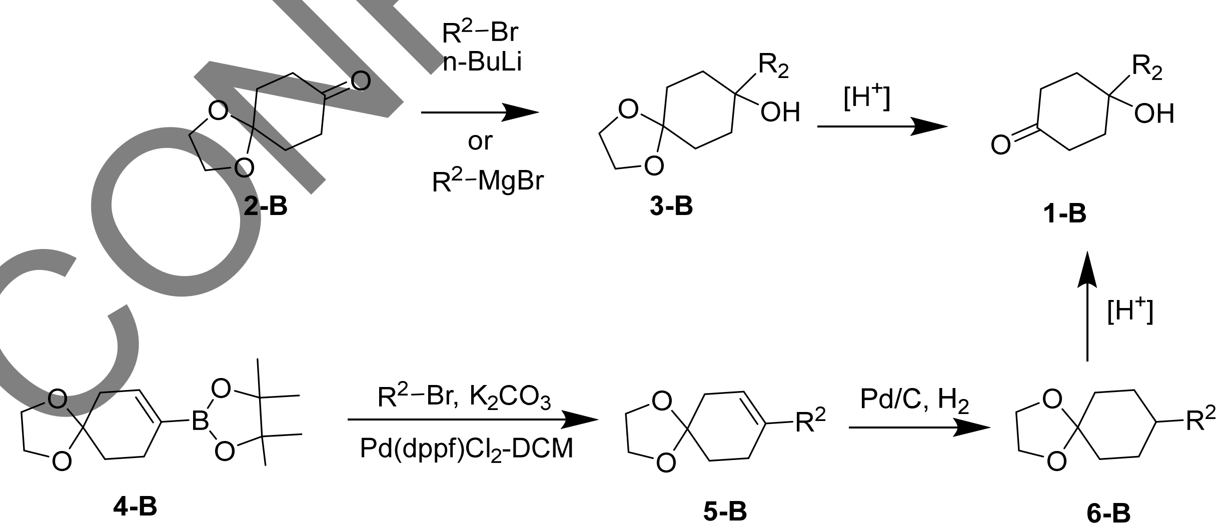


3-B.

Alternatively, the compound of Formula 3-B can also be prepared by contacting the compound of Formula 2-B with a Grignard reagent R^2MgBr under conditions suitable to provide a compound of Formula 3-B. The prepared compound of Formula 3-B is then acidified under conditions suitable to provide a compound of Formula 1-B.

[0178] The following reaction shown in Scheme IB illustrates a general method which can be employed for the synthesis of some compounds of Formula 1B.

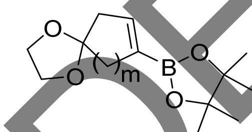
Scheme IB



[0179] Referring to Scheme IB, a compound of Formula 2-B (1 *eq*) is dissolved in a suitable organic solvent (such as tetrahydrofuran) and cooled down to a low temperature (such as about -78° C). A brominated compound R^2-Br (1 *eq*) and an organolithium compound are introduced while maintaining the temperature and stirring of the reaction mixture. After a reaction of about 1 h to about 3 h, the compound of Formula 3-B is received. The reaction progress is monitored by chromatography means and terminated when completion is observed. Following purification of the compound of Formula 3-B, the solution thereof may be acidified (e.g. using aqueous hydrochloric acid, 4N) and stirred at room temperature for about 1 h to about 3 h to afford the compound of Formula 1-B. In some circumstances, the purification of the compound of Formula 3-B may be omitted.

[0180] Alternatively, a Grignard reagent of R^2 (e.g., R^2MgBr) may instead be used to provide the compound of Formula 3-B. For example, contacting the compound of Formula 1-B with the Grignard reagent at a temperature of about 0° C for about 0.5 h to about 2 h in a suitable solvent provides the compound of Formula 3-B. Subsequently, the solution of the compound of Formula 3-B is acidified (e.g., using aqueous solution of hydrogen chloride) at room temperature for several hours to provide the compound of Formula 1-B.

[0181] In certain embodiments, the compound of Formula 1-B may be formed by first contacting the compound of Formula 4-B:



4-B

with a brominated compound R^2-Br in a suitable solvent (such as water or a mixture of 1,4-dioxane and water) in presence of a base and a catalytic amount of catalyst (such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane ($Pd(dppf)Cl_2 \cdot DCM$)). The product (a compound of Formula 5-B) is then hydrogenated in presence of a catalyst to provide the compound of Formula 6-B. The compound of Formula 6-B is then acidified to form the compound of Formula 1-B.

[0182] Still referring to Scheme IB, a compound of Formula 4-B (1 *eq*) is dissolved in a suitable organic solvent (such as a mixture of tetrahydrofuran and water). A brominated compound R^2-Br (1 *eq*) and a base (e.g., dipotassium carbonate, 3 *eq*) are added in. The reaction mixture is sufficiently purged with an inert gas, after which, a catalytic amount (e.g., about 0.02 *eq* to about 0.2 *eq*) of ($Pd(dppf)Cl_2 \cdot DCM$) is added in portion-wise. The reaction mixture is stirred at a temperature of about 95º C to about 120º C for about 45 min to about 18 h. When chromatography result indicates the completion of the reaction, water is introduced to quench the reaction. After suitable workup, the compound of Formula 5-B is received.

[0183] The compound of Formula 5-B (1 *eq*) is redissolved in a suitable organic solvent (such as ethylacetate). A hydrogenation catalyst (e.g., 10% palladium on carbon, with 50% moisture, 1 *eq*) is introduced. The reaction mixture is stirred at room temperature in hydrogen, at a pressure of about 0 psi to about 150 psi, for about 2 h to about 48 h to provide the compound of Formula 6-B. The compound of Formula 6-B is acidified (e.g. using aqueous hydrochloric acid, 4N) and stirred at room temperature for about 1 h to about 3 h to afford the compound of Formula 1-B.

[0184] Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art.

EXAMPLES

[0185] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

General Experimental Methods

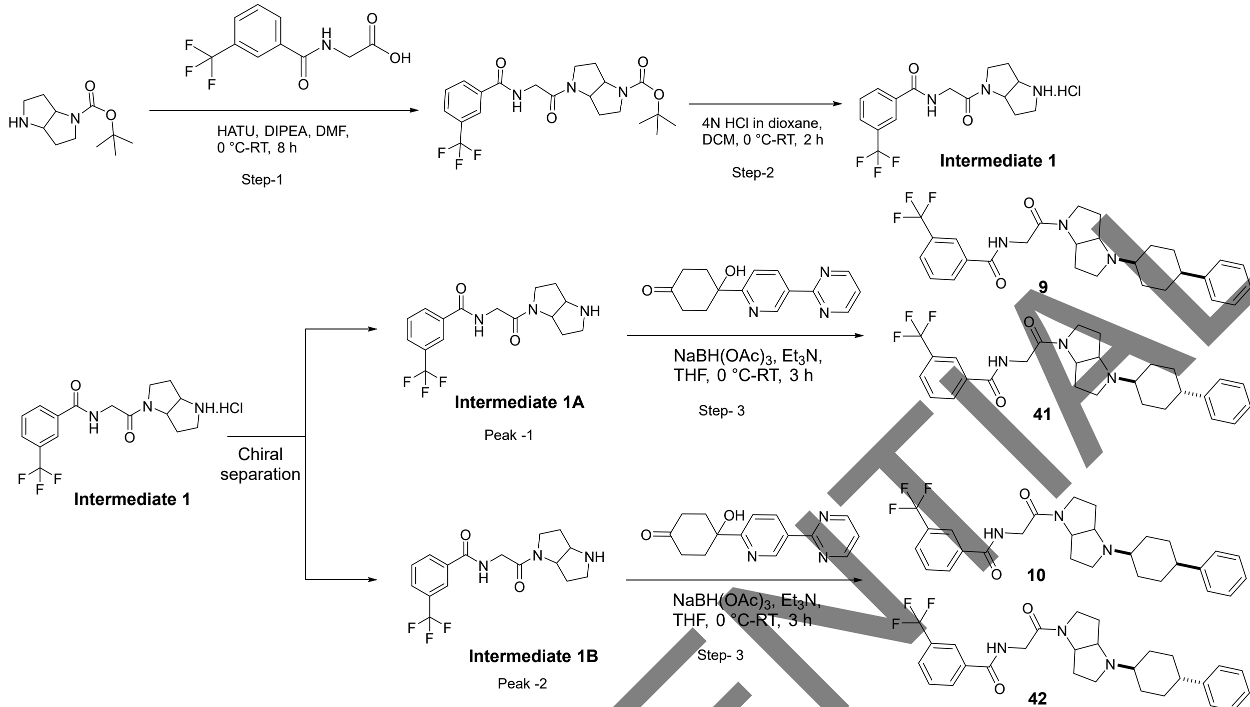
[0186] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[0187] NMR Spectroscopy: All NMR data was collected on Bruker 400 MHz instruments using the deuterated solvent as mentioned in the procedures described below. The peak frequencies are expressed in δ ppm.

[0188] Thin Layer Chromatography (TLC): Analytical TLC plates from Merck were used for reaction monitoring using solvent system as mentioned in the procedures described below. For preparative TLC (prep TLC) for compound purifications, silica-loaded preparative TLC plates were used, and solvent systems used are mentioned in the procedures described below.

[0189] Liquid Chromatography-Mass Spectrometry (LC-MS) and High-Pressure Liquid Chromatography (HPLC) Analysis: LC-MS and HPLCs data were generated using instruments from Water both for LCMS and HPLC (preparative and analytical).

Procedure 1: Synthesis of Examples 9, 10, 41, and 42



[0190] Preparation of (3-(trifluoromethyl)benzoyl)glycine-*tert*-butyl 4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrole-1(2H)-carboxylate-*tert*-butyl hexahydropyrrolo[3,2-b]pyrrole-1(2H)-carboxylate: To a stirred solution of 2-{[3-(trifluoromethyl)phenyl]formamido}acetic acid (0.6 g, 2.43 mmol, 1 eq) in DMF (10 mL) were added *tert*-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.68 g, 2.91 mmol, 1.2 eq) and [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (1.85 g, 4.85 mmol, 2 eq) portionwise, then ethylbis(propan-2-yl)amine (1.73 mL, 9.71 mmol, 4 eq) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 12 h, and reaction progress was checked by TLC monitoring. After completion of the reaction, the reaction mixture was quenched with ice cold water (15 mL), extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified using 60% ethyl acetate in *n*-heptane as an eluent to give the *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (1 g, 93%). LC-MS (ES) m/z: 442 $[M+H]^+$.

[0191] Preparation of N-(2-(hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride: To a stirred solution of *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.8 g, 0.747 mmol, 1 eq) in dichloromethane (15 mL) at 0 °C was added 4 N HCl in 1,4-dioxane (6 mL) dropwise and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was evaporated under reduced pressure. The reaction mixture was then triturated with diethyl ether (20 mL) and pentane (20 mL), and dried under reduced pressure to afford N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (1.2 g, crude). LC-MS (ES) m/z : 342 $[M+H]^+$ Free base mass was observed. Further (1.2 g) crude was submitted to chiral separation following: Column: CHIRALPAK IC (100 mm X 4.6 mm X 3 µm); Mobile phase: n-hexane:IPA with 0.1% DEA (50:50); Flow rate: 1.0 mL/min.

[0192] Peak-1 (**Intermediate 1A**): LC-MS (ES) m/z : 342 [M+H]+. After chiral separation peak-1 yield is 0.5 g; Peak-1: Retention Time (RT) = 3.237 minutes.

[0193] Peak-2 (**Intermediate 1B**): LC-MS (ES) m/z : 342 [M+H]+. After chiral separation peak-2 yield is 0.428 g; Peak-2: RT = 4.036 minutes.

[0194] Preparation of compounds 9 and 41: N-(2-oxo-2-(4-((1s,4s)-4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (Peak-1; Intermediate 1A) (0.050 g, 0.146 mmol, 1 eq) in THF (5 mL) at 0 °C were added 4-phenylcyclohexan-1-one (0.025 g, 0.146 mmol, 1 eq) and triethylamine (0.119 mL, 0.879 mmol, 6 eq). The reaction mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C, then sodium triacetoxy borohydride (0.061 g, 0.293 mmol, 2 eq) was added portionwise and stirred at room temperature for 3 h. Progress of the reaction mixture was checked by TLC (1% methanolic ammonia in ethyl acetate) monitoring. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, quenched with saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate (2 x 25 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by preparative TLC using 1% methanolic ammonia in 70% ethyl acetate in *n*-heptane as eluent to give the N-{2-[(3aR,6aR)-4-(4-phenylcyclohexyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (3 mg, 4.3%) (non-polar isomer) and N-{2-[(3aR,6aR)-4-(4-phenylcyclohexyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]-2-oxoethyl}-3-(trifluoromethyl)benzamide (3 mg , 4.5%) (polar isomer).

[0195] Example 9: Non-polar on TLC. LC-MS (ES) m/z: 500 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 8.98 - 8.89 (m, 1 H), 8.22-8.17 (m, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.31 - 7.15 (m, 5 H), 4.50 - 4.30 (m, 1 H), 4.25 - 4.00 (m, 2 H), 3.75 - 3.47 (m, 3 H), 2.86 - 2.78 (m, 1 H), 2.70 - 2.55 (m, 1 H), 2.25 - 1.85 (m, 8 H), 1.75 - 1.50 (m, 5 H), 1.35 (s, 1 H). HPLC purity: 99.93% at 240 nm.

[0196] Example 41: polar on TLC. LC-MS (ES) m/z: 500 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.94 - 8.89 (m, 1 H), 8.22 - 8.17 (m,, 2 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.30 - 7.15 (m, 5 H), 4.28 - 4.06 (m, 1 H), 4.05 - 3.96 (m, 2 H), 3.69- 3.42 (m, 3 H), 3.35 - 3.25 (m, 1 H), 2.98- 2.89 (m, 1 H), 2.33 - 2.16 (m, 8 H), 1.60 - 1.26 (m, 5 H), 1.40-1.30 (m, 1 H). HPLC purity: 99.94% at 240 nm.

[0197] Preparation of compounds 10 and 42: N-(2-oxo-2-(4-(4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (Peak-2; Intermediate 1B) (0.050 g, 0.146 mmol, 1 eq) in THF (5 mL) at 0 °C were added 4-phenylcyclohexan-1-one (0.025 g, 0.146 mmol, 1 eq) and triethylamine (0.119 mL, 0.879 mmol, 6 eq). The reaction mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C, and sodium bis(acetyloxy)boranuidyl acetate (0.061 g, 0.293 mmol, 2 eq) was added portionwise and stirred at room temperature for 3 h. Progress of the reaction mixture was checked by TLC (2% methanolic ammonia in ethyl acetate) monitoring. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, quenched with saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate (2 x 25 mL), and the combined organic layer were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by prep TLC using 1% methanolic ammonia in ethyl acetate as eluent to obtain N-(2-oxo-2-(4-(4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (3.3 mg, 4.5%) and N-(2-oxo-2-(4-(4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (0.011 g, 15%).

[0198] Example 10: Non- polar on TLC. LC-MS (ES) m/z : 500 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 - 8.95 (m, 1 H), 8.28 (s, 1 H), 8.25 - 8.23 (m, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.80 (t, *J* = 7.6 Hz, 1 H), 7.36 - 7.20 (m, 5 H), 4.55 - 4.30 (m, 1 H), 4.25 - 4.00 (m, 2 H), 3.75 - 3.4 (m, 3 H), 2.95 - 2.8 (m, 1 H), 2.70 - 2.55 (m, 1 H), 2.25 - 1.85 (m, 8 H), 1.75 - 1.50 (m, 5 H), 1.3 (s, 1 H). HPLC purity: 99.61% at 230 nm.

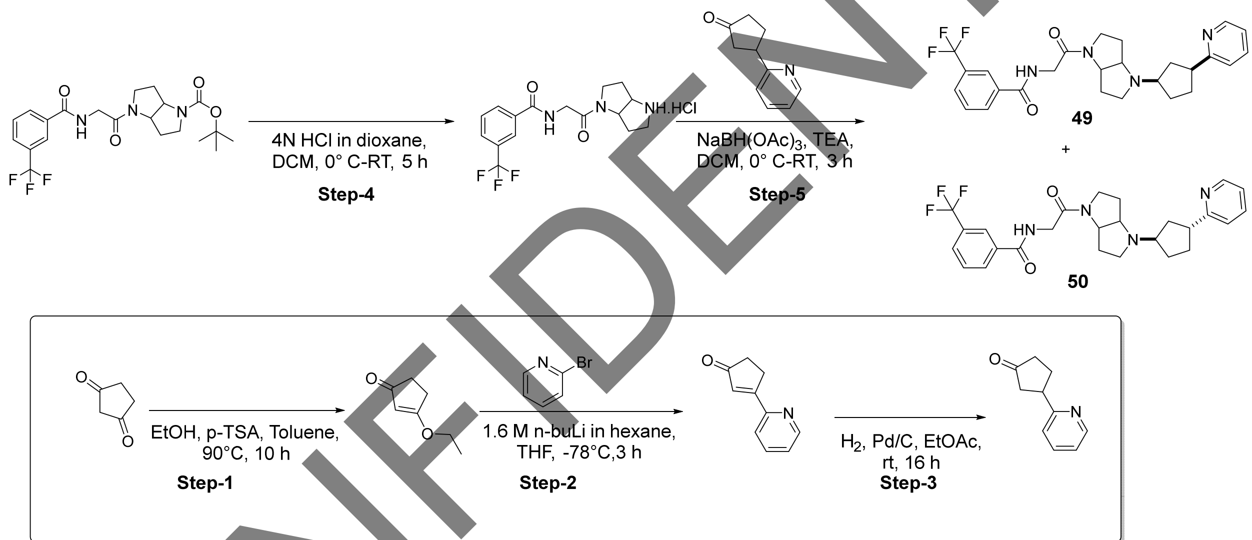
[0199] Example 42: polar on TLC. LC-MS (ES) m/z: 500 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.98 - 8.90 (m, 1 H), 8.20 (s, 1 H), 8.17 - 8.15 (m, 1 H), 7.91 (d, *J* = 7.2 Hz, 1 H), 7.73 (t, *J* = 8 Hz, 1 H), 7.28 - 7.13 (m, 5 H), 4.55 - 4.25 (m, 1 H), 4.22 - 3.85 (m, 2 H), 3.75 - 3.9 (m, 3 H), 3.35 - 3.15 (m, 2 H), 3.05 - 2.85 (m, 1 H), 2.3 - 2.4 (m, 1 H), 2.25 - 1.7 (m, 7 H), 1.65 - 1.25 (m, 5 H).

[0200] The following compounds were synthesized according to Procedure 1 using Intermediate 1B as a starting material as in the synthesis of Examples **10** and **42**.

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm	LC-MS (m/z) [M+H]$^+$
31	N-(2-oxo-2-(4-((1s,4s)-4-phenoxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.96 - 8.90 (m, 1 H), 8.27 - 8.12 (m, 2 H), 7.99 - 7.92 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 6.95 - 6.89 (m, 3 H), 4.75 - 4.40 (m, 2 H), 4.30 - 3.9 (m, 3 H), 3.75 - 3.40 (m, 4 H), 3.05 - 2.75 (m, 1 H), 2.35 - 2.1 (m, 1 H), 1.80 - 1.40 (m, 8 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 2 H).	516.2
32	N-(2-oxo-2-(4-((1r,4r)-4-phenoxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.96 - 8.90 (m, 1 H), 8.28 - 8.13 (m, 2 H), 7.99 - 7.92 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 6.96 - 6.88 (m, 3 H), 4.75 - 4.40 (m, 2 H), 4.30 - 3.9 (m, 3 H), 3.75 - 3.40 (m, 4 H), 3.05 - 2.75 (m, 1 H), 2.35 - 2.1 (m, 1 H), 1.80 - 1.40 (m, 8 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 2 H).	516.2
33	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.45 - 9.44 (m, 1H), 8.96 - 8.94 (m, 2 H), 8.90 - 8.83 (m, 1 H), 8.67 - 8.65 (m, 1 H), 8.22 (s, 1 H), 8.19 - 8.17 (m, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.76 - 7.74 (m, 1 H), 7.50 (t, *J* = 4.8 Hz, 1 H), 5.11 (s, 1 H), 4.40 - 4.45 (m, 1H), 4.30 - 4.00 (m, 2 H), 3.75 - 3.75 (m, 3 H), 2.45 - 2.35 (m, 3 H), 2.30 - 2.1 (m ,1 H), 2.00 - 1.75 (m, 5 H), 1.25 - 1.1 (m, 4 H), 1.50 - 1.40 (m, 2 H).	595.3
37	N-(2-(4-((1r,4r)-4-fluoro-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00 - 8.90 (m, 1 H), 8.59 - 8.52 (m, 1 H), 8.22 - 8.17 (m, 2 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.88 - 7.83 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.36 - 7.33 (m, 1 H), 4.51 - 4.47 (m, 0.5 H), 4.35 - 4.29 (m, 0.5 H), 4.19 - 3.99 (m, 2 H), 3.68 - 3.52 (m, 3 H), 2.89 - 2.75 (m, 1 H), 2.65 - 2.55 (m, 2 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 11 H).	519.5

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm	LC-MS (m/z) [M+H]$^+$
38	N-(2-(4-((1s,4s)-4-fluoro-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1 H), 8.53 - 8.52 (m, 1 H), 8.20 - 8.15 (m, 2 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.83 (t, *J* = 7.8 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.54 - 7.52 (m, 1 H), 7.33 - 7.30 (m, 1 H), 4.50 - 4.10 (m, 2 H), 4.09 - 3.90 (m, 2 H), 3.65 - 240 (m, 3 H), 3.15 - 3.3 (m, 1 H), 2.65 - 2.5 (m, 2 H), 2.30 - 1.4 (m, 11 H).	519.5

Procedure 2: Synthesis of Examples 49 and 50



[0201] Preparation of 3-ethoxycyclopent-2-en-1-one: To a stirred solution of cyclopentane-1,3-dione (1 g, 10.2 mmol, 1 *eq*) in ethanol (6.3 mL, 108 mmol, 10 eq) were added ethanol (6.3 mL, 108 mmol, 10 *eq*) and 4-methylbenzene-1-sulfonic acid hydrate (38.8 mg, 0.204 mmol, 0.02 *eq*) and the reaction mixture was stirred for 16 h at 90 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated and purified by combiflash using EA/heptane to afford 3-ethoxycyclopent-2-en-1-one (1.1 g, 8.72 mmol). LC-MS (ES) m/z = 127.1 [M+H]$^+$

[0202] Preparation of 3-(pyridin-2-yl)cyclopent-2-en-1-one: To a solution of 2-bromopyridine (756 µL, 7.93 mmol, 1 *eq*) in THF (25 mL) at -78 °C was added lithium(1+) butan-1-ide (5.95 mL, 9.51 mmol, 1.2 *eq*) dropwise over 10 min. The reaction was stirred for an additional 30 min at -78 °C and the solution of 3-ethoxycyclopent-2-en-1-one (1 g, 7.93 mmol) in THF (3 mL) was added dropwise over 10 min. After addition the reaction was stirred for an additional 1.5 h at -78 °C, then quenched with saturated aqueous ammonium chloride (10 mL) and warmed to room temperature, diluted with water (100 mL), and extracted using ethyl acetate (100 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude compound which was purified by combiflash using 30% ethyl acetate/heptane as eluent to afford 3-(pyridin-2-yl)cyclopent-2-en-1-one (0.75 g, 63.4%). LC-MS (ES) m/z = 160.1 $[M+H]^+$

[0203] Preparation of 3-(pyridin-2-yl)cyclopentan-1-one: To a stirred solution of 3-(pyridin-2-yl)cyclopent-2-en-1-one (0.8 g, 5.03 mmol,1 *eq*) in ethyl acetate (10.4 mL) was added Pd/C (267 mg, 2.51 mmol, 0.5 *eq*) and the reaction mixture was stirred for 5 h at room temperature under hydrogen atmosphere. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was filtered by using a sintered funnel with a celite bed. The filtrate was concentrated under vacuum to provide 3-(pyridin-2-yl)cyclopentan-1-one (0.35g, 43.2%). LCMS (ES) m/z = 162.1$[M+1]^+$

[0204] Preparation of N-(2-(hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride: To a solution *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.3 g, 0.680 mmol, 1 *eq*) in dichloromethane (5 mL) was added 4N HCl in 1,4-dioxane (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was evaporated yield the crude and washed with the diethyl ether and *n*-pentane to afford N-(2-{hexahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.22g, 94.84%). LCMS m/z = 342.2 $[M+1]^+$.

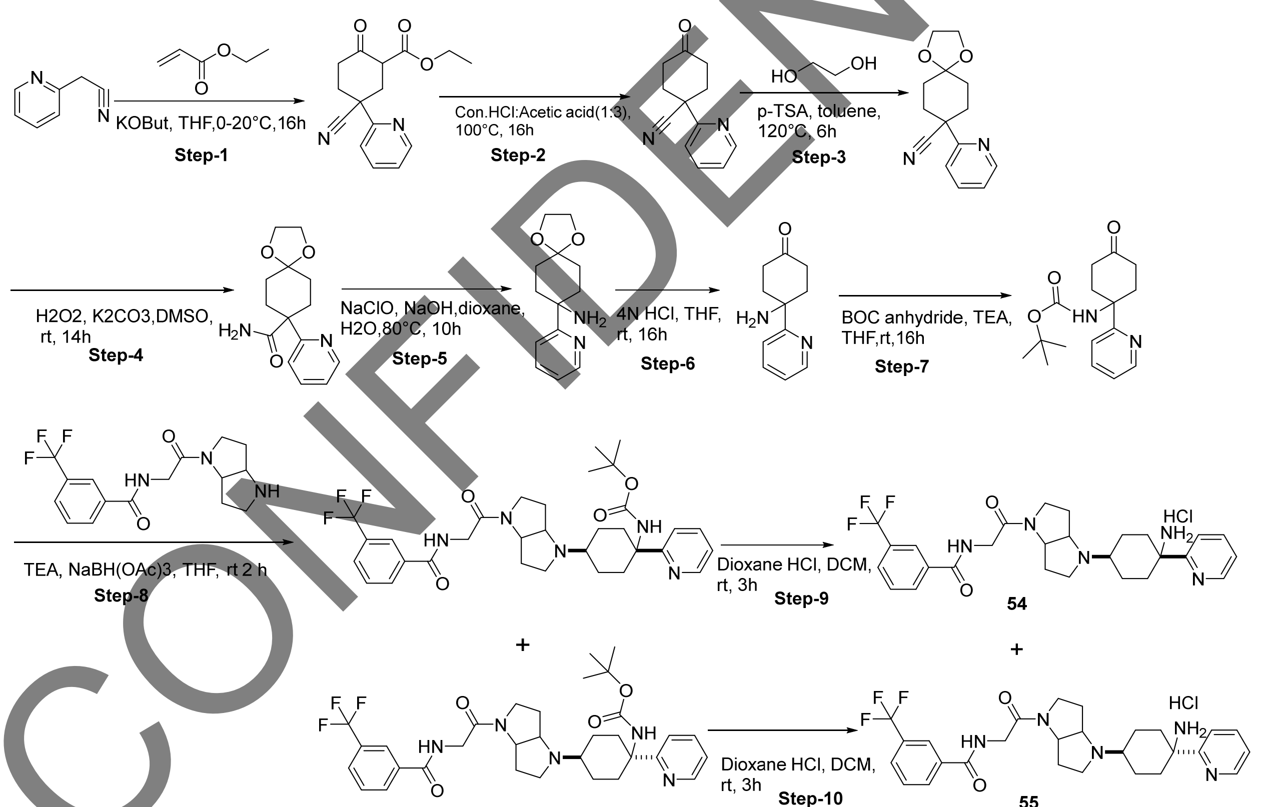
[0205] Preparation of N-(2-oxo-2-{4-[(3R)-3-(pyridin-2-yl)cyclopentyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (49) and N-(2-oxo-2-{4-[(3S)-3-(pyridin-2-yl)cyclopentyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (50): To a solution of N-(2-{hexahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (55 mg, 146 µmol, 0.8 *eq*) in THF (5 mL) was added triethylamine (0.154 mL, 1.1 mmol, 6 *eq*), and after stirring for 5 minutes 3-(pyridin-2-yl)cyclopentan-1-one (29.5 mg, 0.183 mmol, 1.2 *eq*) was added. The resulting mixture was stirred at room temperature for 30 minutes, then sodium bis(acetyloxy)boranuidyl acetate (77.6 mg, 0.366 mmol, 2 *eq*) was added and stirred at room temperature for 2 h. the reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude which was purified through chiral prep-HPLC. Non polar and polar band of compound were separated and isolated to afford both geometrical isomers i.e. N-(2-oxo-2-{4-[(3R)-3-(pyridin-2-yl)cyclopentyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (1 mg, 1.1%) and N-(2-oxo-2-{4-[(3S)-3-(pyridin-2-yl)cyclopentyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (9 mg, 10.1%).

[0206] Separation Conditions: Column: Inertsil C18 (20 X 250) mm, 5 µm; Mobile phase(A): 0.1% ammonia in water; Mobile phase(B): acetonitrile; Flow rate: 19 mL/min.

[0207] Analytical data of Example 49: [Enantiomer-01] (By chiral HPLC): LC-MS (ES) m/z : 487.2 [M+H]+ = 99.50. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.96-8.90(m, 1 H), 8.50(m, 1 H), 8.22 (s, 1 H), 8.19-8.17(d, *J* =8Hz, 1H), 7.94(m, 1 H) 7.74 (m, 1 H), 7.68 (m, 1 H), 7.28 (m, 1 H), 7.18 (m, 1 H), 4.48 (m, 1H), 4.01 (m, 2 H), 3.65 (m, 2 H), 3.17 (m, 2 H), 2.97 (m, 2 H), 2.40 (m, 1 H), 2.18 (m, 1 H), 1.99 (m, 5 H), 1.76 (m, 2 H), 1.64 (m, 1 H), 1.51 (m, 1 H). HPLC purity: 99.5 % at 230 nm.

[0208] Analytical data of Example 50: [Enantiomer-02] (By chiral HPLC): LC-MS (ES) m/z : 487.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.97-8.88 (m, 1 H), 8.50 (m, 1 H), 8.22 (s, 1 H), 8.19-8.17 (d, *J* =8Hz, 1 H), 7.94 (m, 1 H) 7.74 (m, 1 H), 7.68 (m, 1 H), 7.29 (m, 1 H), 7.18 (m, 1 H), 4.48 (m, 1 H), 4.01 (m, 2 H), 3.96 (m, 2 H), 3.22 (m, 2 H), 3.01 (m, 1 H), 2.33 (m, 2H), 1.96 (m, 6 H), 1.76 (m, 1H), 1.54 (m, 3 H). HPLC purity: 99.5 % at 230 nm.

Procedure 3: Synthesis of Examples 54 and 55



[0209] Preparation of ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate: To a solution of 2-(pyridin-2-yl)acetonitrile (2 g, 16.9 mmol, 1 *eq*) and ethyl prop-2-enoate (3.79 mL, 35.6 mmol, 2.1 *eq*) in anhydrous THF (5 mL) at 0 °C was added KO^{t}Bu (2.28 g, 20.3 mmol, 1.2 *eq*) and stirred at 0 °C for 5 min, then the reaction was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and distilled under reduced pressure to afford ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate (3.3 g, 71.59%) which was carried to the next step without any purification. LCMS (ES) m/z = 273.1

[0210] Preparation of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile: To a solution of ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate (0.3 g, 1.1 mmol, 1 eq) in conc. HCl (8 mL) at 0 °C was slowly added acetic acid (25 mL). The reaction mixture was heated to 100 °C. for 16 h. All volatiles were evaporated under reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (20 mL) . The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude which was taken to the next step without any purification. LCMS (ES) m/z = 201.1 $[M+H]^+$.

[0211] Preparation of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile: To a stirred solution of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile (1.5 g, 7.49 mmol, 1 *eq*) in toluene (3 mL) were added ethane-1,2-diol (418 µL, 7.49 mmol, 1 eq) and 4-methylbenzene-1-sulfonic acid (129 mg, 749 µmol, 0.1 eq) portionwise under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 120 °C for 6 h, and the reaction progress was checked by TLC monitoring. After completion of the reaction, the reaction mass was concentrated under reduced pressure to yield a residue, which was quenched with saturated aqueous sodium bicarbonate solution (10 mL), extracted with ethyl acetate (2 x 30 mL), and the combined organic layers were concentrated under reduced pressure to yield 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile(1.6 g, 87.43%). LCMS (ES) m/z: 245.2 $[M+H]^+$.

[0212] Preparation of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carboxamide: To a stirred solution of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (0.8 g, 3.27 mmol, 1 *eq*) in DMSO were added K_2CO_3 (905 mg, 6.55 mmol, 2 *eq*) and H_2O_2 (3.84 mL, 49.1 mmol, 15 *eq*) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 14 h, and reaction progress was checked by TLC monitoring. The reaction mixture was diluted with excess water and stirred for l h. The resulting mixture was extracted with DCM, and the organic layer was concentrated under reduced pressure to get 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carboxamide (1.2 g, crude). LCMS (ES) m/z = 263.1 $[M+H]^+$.

[0213] Preparation of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-amine: To a stirred solution of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carboxamide (0.8 g, 3.05 mmol, 1 eq) in 1,4-dioxane (10 mL) were added 9-10% sodium hypochlorite (0.5 mL, 3.05 mmol) and sodium hydroxide (244 mg, 6.1 mmol, 2 eq) dissolved in water, portionwise at 0 °C. The reaction mixture was stirred at 80 °C for 10 h, and reaction progress was checked by TLC monitoring. After completion of the reaction, the reaction mass was concentrated under reduced pressure to yield a residue, which was diluted with water, extracted with 10% MeOH/DCM (2 x 30 mL), and the combined organic layers were concentrated under reduced pressure to yield the crude, which was purified by combiflash using MeOH/DCM to afford 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-amine (150 mg, 20.36%). LCMS (ES) m/z = 235 $[M+H]^+$.

[0214] Preparation of 4-amino-4-(pyridin-2-yl)cyclohexan-1-one: To a stirred solution of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-amine (150 mg, 640 mmol, 1 *eq*) in THF (10 mL) was added 4 N HCl in water (1.7 mL in 5 mL water) and allowed to stir at room temperature for 3 h. After completion of the reaction, the reaction mass was concentrated under reduced pressure to yield the crude residue. The obtained residue was basified with saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate (2 x 15 mL), the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. (0.05 g, crude). LCMS (m/z) = 191.1$[M+1]^+$.

[0215] Preparation of *tert*-butyl N-[4-oxo-1-(pyridin-2-yl)cyclohexyl]carbamate: To a stirred solution of 4-amino-4-(pyridin-2-yl)cyclohexan-1-one (50 mg, 0.263 mmol, 1 *eq*) in THF (0.213 mL, 2.62 mmol, 9.96 *eq*) were added triethylamine (0.11 mL, 0.788 mmol, 3 *eq*), BOC (0.90 mL, 0.394 mmol, 1.5 *eq*) and DMAP (0.640 µg, 0.0526 mmol, 0.002 *eq*) portionwise, and the reaction was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate, and concentrated under reduced pressure to yield the crude, which was purified by combiflash using 5% MeOH/DCM to afford *tert*-butyl N-[4-oxo-1-(pyridin-2-yl)cyclohexyl]carbamate (45 mg, 58.97%). LC-MS (ES) m/z = 291.2 $[M+H]^+$.

[0216] Preparation of *tert*-butyl ((1r,4r)-1-(pyridin-2-yl)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)carbamate and *tert*-butyl ((1s,4s)-1-(pyridin-2-yl)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)carbamate: To a solution of chirally pure (i.e., as single unknown enantiomer) N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (82.3 mg, 241 µmol) in THF (6.58 mL, 80.9 mmol) was added triethylamine (0.203 mL, 6 eq, 1.45 mmol) and the solution was stirred for 5 min. Then *tert*-butyl N-[4-oxo-1-(pyridin-2-yl)cyclohexyl]carbamate (70 mg, 0.241 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then sodium bis(acetyloxy)boranuidyl acetate (102 mg, 2 eq., 482 µmol) was added and stirred at room temperature for 2h. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude product where both non-polar and polar isomers were separated by prep-TLC using 6% methanolic ammonia in DCM to afford the non-polar isomer (30mg, 10.11%) and the polar isomer (35 mg, 11.79%). LCMS (ES) m/z: 616.3 $[M+H]^+$.

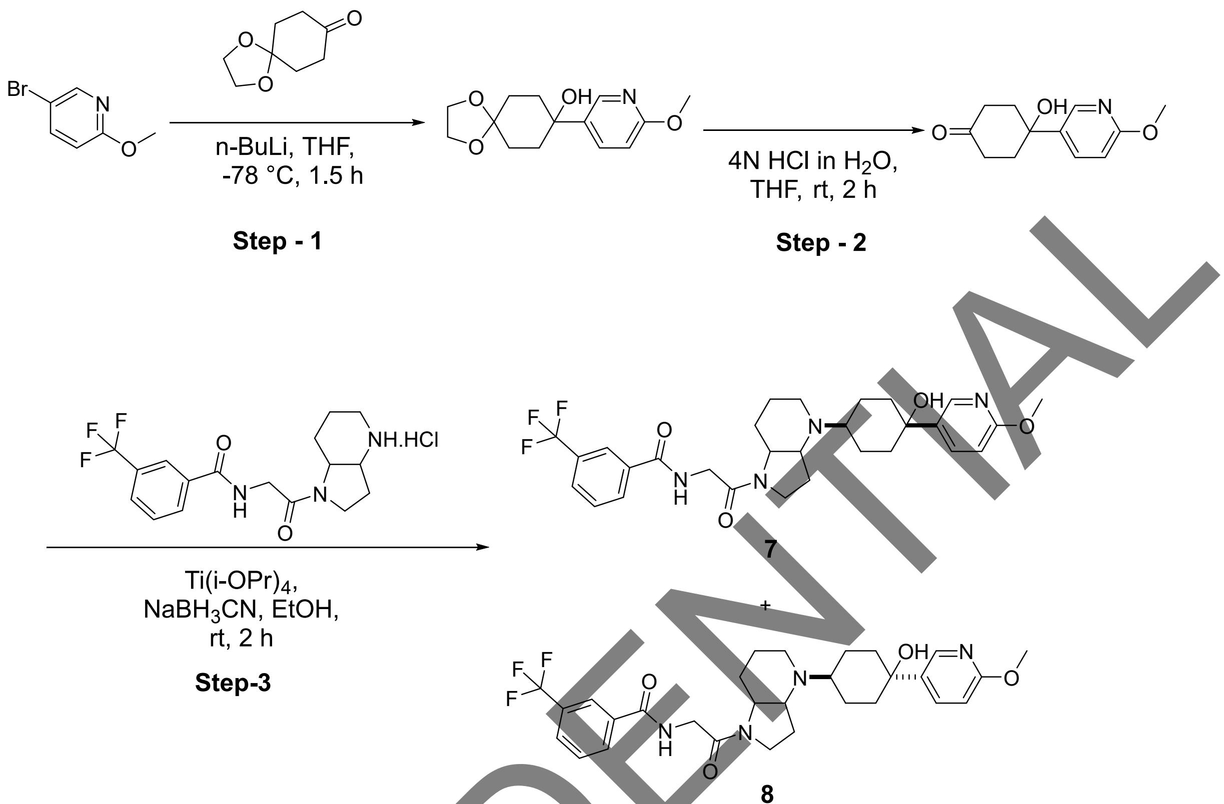
[0217] Preparation of Example 54: To a solution *tert*-butyl N-[1-(pyridin-2-yl)-4-[4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]cyclohexyl]carbamate (25 mg, 0.040 mmol) in dichloromethane (2 mL) was added 4 N HCl in 1,4- dioxane (3 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was evaporated to yield the crude, which was washed with the diethyl ether and *n*-pentane, then purified by prep-TLC using 4% methanolic ammonia in DCM to afford N-(2-{4-[4-amino-4-(pyridin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (9 mg, 40.15%).

[0218] Example 54 (by TLC, non-polar). LC-MS (ES) m/z: 516.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO d6) δ ppm : 8.96-8.95 (m,1 H), 8.64 (7.79 (d, J = 8 Hz, 1 H), 8.15 (m, 2 H), 7.91 (m, 3 H), 7.72 (t, J = 8 Hz,1 H), 7.63 (d, J = 8 Hz, 1 H), 7.36 (m, 1 H), 4.41 (m, 1 H), 4.08 (m, 2 H), 3.52 (m, 3 H), 3.20 (m, 1 H), 2.80 (m, 1 H), 2.35 (m, 1 H), 2.05 (m, 1 H), 1.80 (m, 4 H), 1.66 (m, 4 H), 1.41 (m, 4 H). HPLC purity: 98.39% at 230 nm.

[0219] Preparation of Example 55: To a solution *tert*-butyl N-[1-(pyridin-2-yl)-4-[4-(2-{[3(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]cyclohexyl]carbamate (30 mg, 0.048 mmol) in dichloromethane (2 mL) was added 4 N HCl in 1,4-dioxane (3 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was evaporated to yield the crude and washed with the diethyl ether and *n*-pentane, which was then purified by prep-TLC using 4% methanolic ammonia in DCM to afford N-(2-{4-[4-amino-4-(pyridin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (9 mg, 33.46%).

[0220] Example 55 (by TLC, polar): LC-MS (ES) m/z : 516.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO d6) δ ppm : 8.96-8.89 (m, 1 H), 8.64 (d, J = 8 Hz, 1 H), 8.15 (m, 2 H), 7.89 (m, 2 H), 7.74 (t, J = 8 Hz,1 H), 7.63 (d, J = 8 Hz, 1 H), 7.36 (m, 1 H), 4.49 (m, 1 H), 4.10 (m, 2 H), 3.67-3.40 (m, 2 H), 3.52 (m, 2 H), 3.20 (m, 1 H), 2.70 (m, 2 H), 2.65 (m, 1 H), 2.34 (m, 1 H), 2.12-1.82 (m, 3 H), 1.57 (m, 6 H), 1.31 (m, 1 H). HPLC purity: 84.21% at 230 nm.

Procedure 4: Synthesis of Examples 7 and 8



[0221] Preparation of 8-(6-methoxypyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol: To a solution of 5-bromo-2-methoxy-pyridine (1.0 g, 5.32 mmol, 1 eq) in THF (10 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 3.99 mL, 6.38 mmol, 1.2 eq) dropwise over 10 mins. The reaction was stirred for an additional 30 mins. at -78 °C. A solution of 1,4-dioxa-spiro[4.5]decan-8-one (0.831 g, 5.32 mmol, 1 eq) in THF (10 mL) was added dropwise into the reaction, and the reaction was stirred for an additional 1.5 hours at -78 °C. The reaction was then quenched with water, warmed to room temperature, and extracted using ethyl acetate (100 mL x 2) and water (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude product, which was then purified by silica gel column on a combiflash system using 13% ethyl acetate in hexane to afford 8-(6-methoxypyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.2 g, 96%). LCMS (m/z) = 266.1 $[M+H]^+$.

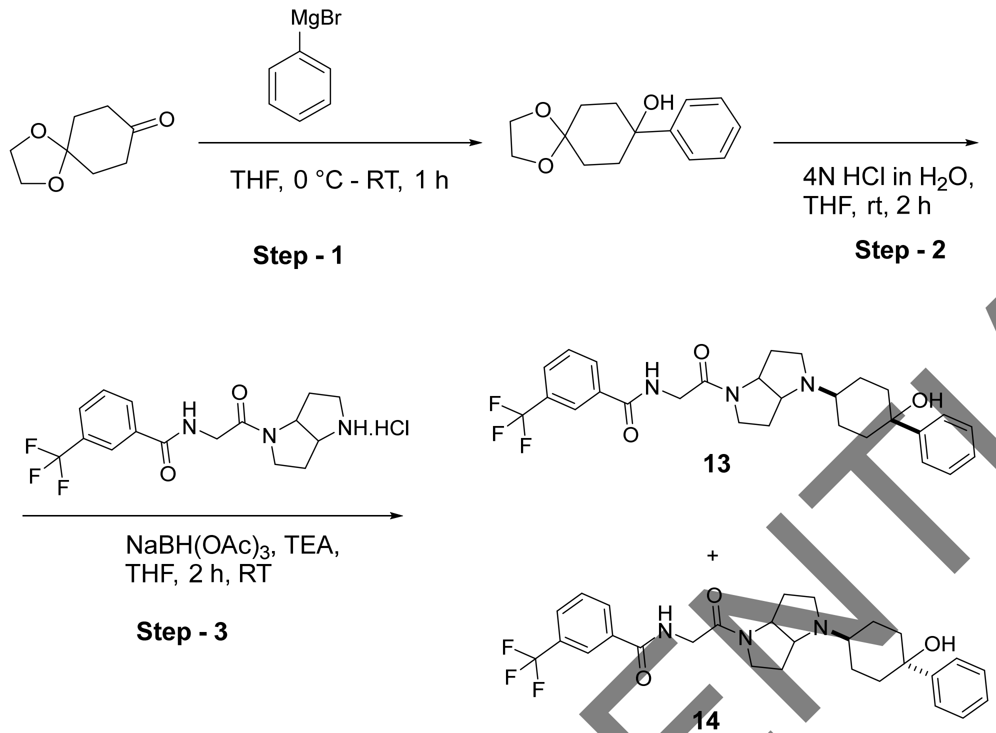
[0222] Preparation of 4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexan-1-one: To a stirred solution of 8-(6-methoxypyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.0 g, 3.77 mmol, 1 eq) in THF (10 mL) was added 4 N HCl in water (10 mL) at 0 °C. The reaction mixture was stirred for 2h at room temperature. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum and triturated with *n*-pentane and diethyl ether to afford 4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexan-1-one (0.65 g, 77.94%). LC-MS (m/z) = 222.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (m, 1 H), 2.22 - 2.30 (m, 4 H), 2.35 - 2.39 (m, 2 H), 2.86 - 2.95 (m, 2 H), 3.94 (s, 3 H), 6.76 (d, *J* = 8.4 Hz, 1H), 7.73 - 7.76 (m, 1 H), 8.31 (s, 1 H).

[0223] Preparation of N-(2-(4-((1r,4r)-4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide and N-(2-(4-((1s,4s)-4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.15 g, 0.422 mmol, 1 eq) in titanium (IV) isopropoxide (4.5 mL) at room temperature was added 4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexan-1-one (0.112 g, 0.507 mmol, 1.2 eq) and the reaction mixture was stirred for 1 h. Then sodium cyanoborohydride (0.032 g, 0.51 mmol, 1.2 eq) was added and stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (20 mL) and extracted using ethyl acetate (20 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using combiflash with 10% MeOH in DCM as eluent, followed by preparative TLC using 5% methanolic ammonia in ethyl acetate to afford two isomers of N-(2-(4-((1r,4r)-4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (7.8 mg, 3.3%) and N-(2-(4-((1s,4s)-4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (12 mg, 5.07%).

[0224] Example 7: non-polar on TLC: LC-MS (ES) m/z: 561.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6): 1.18 - 1.24 (m, 2 H), 1.32 - 1.36 (m 1 H), 1.45 - 1.51 (m, 2 H), 1.51 - 1.64 (m, 4 H), 1.82 - 1.85 (m, 2 H), 1.96 - 1.95 (m, 2 H), 2.05 - 2.20 (m, 4 H), 3.37 - 3.39 (m, 1 H), 3.47 - 3.51 (m, 1 H), 3.57 - 3.60 (m, 1 H), 3.83 - 3.84 (m, 3 H), 3.87 - 3.95 (m, 1 H), 3.98 - 4.07 (m, 2 H), 4.84 (s, 1 H), 6.76 - 6.78 (m, 1 H), 7.72 - 7.76 (m, 2 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.24 (m, 3 H), 8.88 - 8.95 (m, 1 H). HPLC purity: 99.74% at 230 nm.

[0225] Example 8: polar on TLC: LC-MS (ES) m/z: 561.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6): 1.17 - 1.44 (m, 3 H), 1.54 - 1.80 (m, 10 H), 1.98 - 2.06 (m, 2 H), 2.06 - 2.22 (m, 2 H), 3.38 - 3.41 (m, 1 H), 3.43 - 3.51 (m, 1 H), 3.60 - 3.66 (m, 1 H), 3.89 - 3.95 (m, 4 H), 3.95 - 4.19 (m, 2 H), 4.83 (s, 1 H), 6.73 - 6.75 (m, 1 H), 7.73 - 7.79 (m, 2 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.24 (m, 3 H), 8.89 - 8.97 (m, 1 H). HPLC purity: 99.88% at 230 nm.

Procedure 5: Synthesis of Examples 13 and 14



[0226] Preparation of 8-phenyl-1,4-dioxaspiro[4.5]decan-8-ol: To a stirred solution of 1,4-dioxaspiro[4.5]decan-8-one (2 g, 12.8 mmol, 1 eq) in THF (20 mL), was added phenylmagnesium bromide (4.27 mL, 3M, 12.8 mmol, 1 eq) dropwise at 0 °C. The reaction mixture was stirred for 2 h at room temperature and the progress of the reaction mixture was monitored by TLC and LCMS. The reaction was then quenched with aqueous ammonium chloride (20 mL), warmed to room temperature, and extracted with ethyl acetate (100 mL x 2) and water (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude product, which was then purified by silica gel column on a combiflash system using 34% ethyl acetate in hexane to afford the compound 8-phenyl-1,4-dioxaspiro[4.5]decan-8-ol (1.1 g, 36.66%). LC-MS (m/z): 217.1 $[M+H]^+$ (-OH cleaved mass). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.67 (m, 5 H), 1.87 - 1.97 (m, 5 H), 3.83 - 3.86 (m, 4 H), 7.15 - 7.19 (m, 1 H), 7.23 (m, 2 H), 7.43 - 7.44 (m, 2 H).

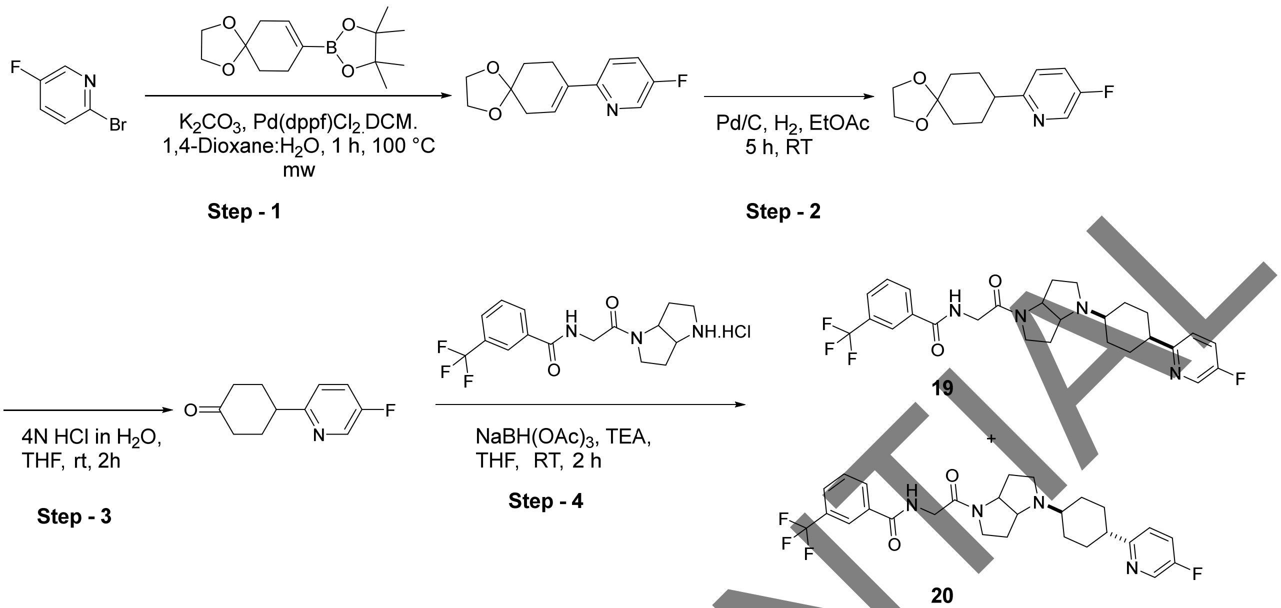
[0227] Preparation of 4-hydroxy-4-phenylcyclohexan-1-one: To a stirred solution of 8-phenyl-1,4-dioxaspiro[4.5]decan-8-ol (1.1 g, 4.69 mmol, 1 eq) in THF (10 mL) was added 4 N aqueous HCl (10 mL) and the reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated and neutralized with saturated aqueous sodium bicarbonate solution (100 mL) then extracted with ethyl acetate (100 mL x 2). The organic layer was dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude compound. The crude material was purified by flash column chromatography with using 30% ethyl acetate in hexane as a eluent to obtain 4-hydroxy-4-phenylcyclohexan-1-one (0.35 g, 39.19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 - 1.96 (m, 2 H), 2.11 - 2.27 (m, 4 H), 2.74 - 2.82 (m, 2 H), 5.37 (s, 1 H), 7.21 - 7.25 (m, 1 H), 7.31 - 7.35 (m, 2 H), 7.54 - 7.56 (m, 2 H).

[0228] Preparation of N-(2-(4-((1r,4r)-4-hydroxy-4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide and N-(2-(4-((1s,4s)-4-hydroxy-4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.15 g, 0.439 mmol, 1 eq) in THF (5 mL) at room temperature were added 4-hydroxy-4-phenylcyclohexan-1-one (0.092 g, 0.483 mmol, 1.1 eq) and triethylamine (0.298 mL, 2.2 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 0.5 h then sodium bis(acetyloxy)boranuidyl acetate (0.185 g, 0.879 mmol, 2 eq) was added and stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, diluted with water (20 mL), and extracted using ethyl acetate (2 x 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using combiflash with 10% MeOH in DCM as eluent, followed by preparative TLC using 5% methanolic ammonia in ethyl acetate to afford two isomers of N-(2-(4-((1r,4r)-4-hydroxy-4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (10.2 mg, 4.5%). and N-(2-(4-((1s,4s)-4-hydroxy-4-phenylcyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (48 mg, 21.19%).

[0229] Example 13: non-polar on TLC: LC-MS (ES) m/z: 516.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm : 1.24 (m, 1 H), 1.45 - 1.65 (m, 5 H), 1.69 - 2.09 (m, 5 H), 2.09 - 2.29 (m, 3 H), 2.77 - 2.86 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.51 - 3.61 (m, 2 H), 3.98 - 4.30 (m, 2 H), 4.30 - 4.72 (m, 1 H), 4.72 (s, 1 H), 7.18 - 7.22 (m, 1 H), 7.30 - 7.34 (m, 2 H), 7.46 - 7.48 (m, 2 H), 7.73 - 7.76 (m, 1 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.19 (m, 1 H), 8.22 (s, 1 H), 8.88 - 8.98 (m, 1 H). HPLC purity: 98.2% at 230 nm.

[0230] Example 14: polar on TLC: LC-MS (ES) m/z: 516.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm : 1.47 - 1.77 (m, 8 H), 1.79 - 1.85 (m, 2 H), 1.88 - 2.10 (m, 1 H), 2.07 - 2.16 (m, 1 H), 2.34 - 2.48 (m, 1 H), 2.88 - 2.99 (m, 1 H), 3.17 - 3.30 (m, 1 H), 3.39 - 3.45 (m,1 H), 3.60 - 3.65 (m, 2 H), 3.93 - 3.99 (m, 1 H), 4.11 - 4.17 (m, 1 H), 4.24 - 4.52 (m ,1 H), 4.70 (m, 1 H), 7.14 - 7.29 (m, 3 H), 7.46 - 7.48 (m, 2 H), 7.71 - 7.74 (m, 1 H), 7.90 - 7.923 (m, 1 H), 8.15 - 8.17 (m, 1 H), 8.20 (s, 1 H), 8.89 - 8.98 (m, 1 H). HPLC purity: 99.3% at 230 nm.

Procedure 6: Synthesis of Examples 19 and 20



[0231] Preparation of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-5-fluoropyridine: To a stirred solution of 2-bromo-5-fluoropyridine (1.0 g, 5.68 mmol, 1 eq) in 1,4-dioxane (5 mL) and water (2.5 mL) were added 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.66 g, 6.25 mmol, 1.1 eq) and potassium carbonate (2.36 g, 17.0 mmol, 3 equiv). The reaction mixture was purged under N_2 atmosphere for 10 mins, then Pd(dppf)Cl_2.DCM (0.232 g, 0.284 mmol, 0.05 eq) was added. The reaction mixture was irradiated 100 °C in a microwave for 1 h . The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by flash column chromatography by using 0-30% ethyl acetate in *n*-hexane as eluent to obtain 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-5-fluoropyridine (0.75 g, 56%). LC-MS (m/z) = 236.0 $[M+H]^+$.

[0232] Preparation of 2-{1,4-dioxaspiro[4.5]decan-8-yl}-5-fluoropyridine: To a stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-5-fluoropyridine (0.75 g, 3.19 mmol, 1 eq) in ethyl acetate (10 mL) was added 10% palladium on carbon (50% moisture, 0.339 g, 3.19 mmol, 1 eq) and the reaction mixture was stirred for 5 h at room temperature under hydrogen atmosphere. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was filtered through a sintered funnel with a celite bed. The filtrate was concentrated under reduced pressure to yield 2-{1,4-dioxaspiro[4.5]decan-8-yl}-5-fluoropyridine (0.65 g, 85.93%). LC-MS (m/z) = 238.2 $[M+H]^+$.

[0233] Preparation of 4-(5-fluoropyridin-2-yl)cyclohexan-1-one: To a stirred solution of 2-{1,4-dioxaspiro[4.5]decan-8-yl}-5-fluoropyridine (0.7 g, 2.95 mmol, 1 eq) in THF (10 mL) was added 4N HCl in water (10 mL). The reaction mixture was stirred for 3 h at room temperature. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to remove the solvent. The reaction mixture was neutralized by adding sodium bicarbonate and extracted using ethyl acetate (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to yield 4-(5-fluoropyridin-2-yl)cyclohexan-1-one (0.45 g, 78.94%). LC-MS (m/z) = 194.1 $[M+H]^+$.

[0234] Preparation of N-(2-(4-((1s,4s)-4-(5-fluoropyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide and N-(2-(4-((1r,4r)-4-(5-fluoropyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (0.1 g, 0.293 mmol, 1 eq) in THF (5 mL) at room temperature were added 4-(5-fluoropyridin-2-yl)cyclohexan-1-one (0.0623 g, 0.322 mmol, 1.1 eq) and triethylamine (0.204 mL, 1.46 mmol, 5 eq). The reaction mixture was stirred at room temperature for 0.5 h then sodium bis(acetyloxy)boranuidyl acetate (0.124 g, 0.586 mmol, 2 eq) was added and stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (20 mL), and extracted using ethyl acetate (20 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using combiflash with 10% MeOH in DCM as eluent, followed by preparative TLC using 5% methanolic ammonia in ethyl acetate to afford two isomers of N-(2-oxo-2-{4-[(1r,4r)-4-(5-fluoropyridin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (11.5 mg, 7.57%) and N-(2-oxo-2-{4-[(1s,4s)-4-(5-fluoropyridin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (13 mg, 8.56%).

[0235] Example 19: non-polar spot on TLC: LC-MS (ES) m/z: 519.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 8.91 - 9.0 (m, 1 H), 8.48 (s, 1 H), 8.22 (s, 1 H), 8.17 - 8.19 (m, 1 H), 7.92 - 9.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.33 - 7.37 (m, 1 H), 4.27 - 4.49 (m, 1 H), 3.98 - 4.18 (m, 2 H), 3.40 - 3.52 (m, 3 H), 2.67 - 2.83 (m, 2 H), 1.71 - 2.16 (m, 8 H), 1.14 - 1.68 (m, 6 H). HPLC purity: 98.4% at 230 nm.

[0236] Example 20: polar spot on TLC: LC-MS (ES) m/z: 519.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 8.91 - 9.0 (m, 1 H), 8.46 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.33 - 7.36 (m, 1 H), 4.20 - 4.46 (m, 1 H), 3.95 - 4.18 (m, 2 H), 3.40 - 3.53 (m, 3 H), 3.22 - 3.32 (m, 1 H), 2.87 - 3.0 (m, 2 H), 1.73 - 2.14 (m, 7 H), 1.39 - 1.74 (m, 6 H). HPLC purity: 99.7% at 230 nm.

[0237] The following compounds were synthesized according to Procedure 6 (racemic with respect to the 5,5-fused bicyclic core).

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
27	N-(2-oxo-2-(4-((1s,4s)-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.99-8.89 (m,1 H), 8.47 (d, J = 4.4 Hz, 1 H), 8.17 (t, J = 12.4 Hz, 2 H), 7.91 (d, J = 8 Hz, 1 H), 7.74-7.66 (m, 2 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.17-7.14 (m, 1 H), 4.48-4.25 (m, 1 H), 4.12-3.91 (m, 2 H), 3.60-3.38 (m, 3 H), 2.80-2.73 (m, 3 H), 2.65-2.54 (m, 1 H), 2.31-2.11 (m, 2 H), 2.05-1.92 (m, 3 H), 1.88-1.56 (m, 3 H), 1.52-1.32 (m, 5 H).	501.1
28	N-(2-oxo-2-(4-((1r,4r)-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.97-8.91(m,1H), 8.45(d, J= 4.4 Hz, 1H), 8.17(t, J=12 Hz, 2H), 7.91(d, J=7.6 Hz, 1H) , 7.75-7.65(m, 2H), 7.23(d, J= 7.6 Hz, 1H), 7.18-7.15(m, 1H), 4.48-4.25(s, 1H), 4.12-3.91(m, 2H), 3.60-3.38(m, 3H), 2.80-2.73(m, 3H), 2.65-2.54(m, 1H), 2.31-2.11(m, 2H), 2.05-1.92(m, 3H), 1.88-1.56(m, 3H), 1.52-1.32(m, 5H)	501.1

Procedure 7: Synthesis of Examples 29 and 30

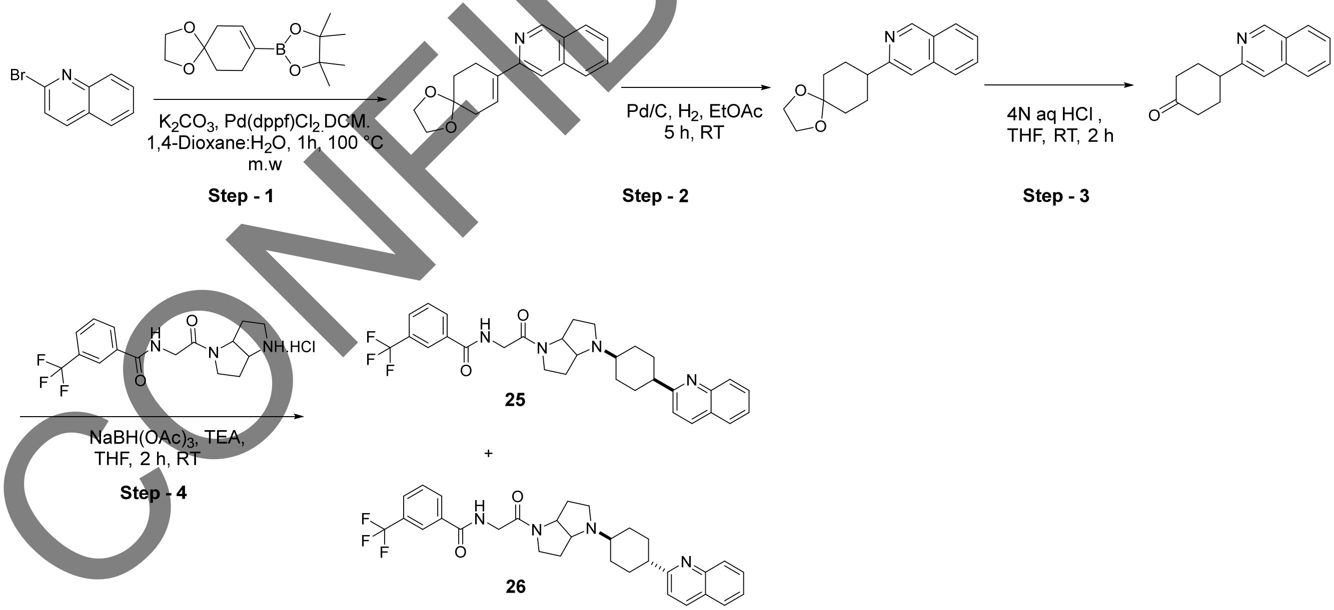
[0238] Example 27 was further purified to separate the isomers with respect to the 5,5-fused-bicyclic core using the below mentioned chiral HPLC condition to afford Enantiomer-1 (Example 29) eluting first (RT: 3.49 min) and Enantiomer 2 (Example 30) eluting later (RT: 4.00 min); HPLC column: CHIRALPAK IC (100 mm X 4.6 mm X 3 µm); Mobile phase: n-hexane: Ethanol with 0.1% DEA (50:50; Flow rate: 1.0 mL/min.

[0239] Examples 29 and 30 are both assigned as cis-isomers with respect to 1,4-cyclohexane disubstitution. However, with respect to 5,5-fused-bicyclic core both Example 29 and Example 30 are enantiomerically pure isomers, but the absolute stereochemistry with respect to the 5,5-fused-bicyclic core is not assigned.

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
29	N-(2-oxo-2-(4-((1s,4s)-4-(pyridin-2-	8.97-8.90 (m, 1 H), 8.49 (d, J = 4.4 Hz, 1 H), 8.22 (s, 2 H), 8.18 (d, J = 7.6 Hz, 1 H) , 7.30	501.1

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
	yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	(m, 2 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.17-7.14 (m, 1 H), 4.48-4.25 (s, 1 H), 4.12-3.91(m, 2 H), 3.60-3.38 (m, 3 H), 2.80-2.73 (m, 3 H), 2.65-2.54 (m, 1 H), 2.31-2.11 (m, 2 H), 2.05-1.92 (m, 3 H), 1.88-1.56 (m, 3 H), 1.52-1.32 (m, 5 H)	
30	N-(2-oxo-2-(4-((1r,4r)-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.96-8.89 (m,1 H), 8.47(d, *J*= 4.4 Hz, 1 H), 8.17(t, *J* =11.6 2 H), 7.9 1 (d, *J* =8 Hz, 1 H) , 7.74-7.66 (m, 2 H), 7.25 (d, *J*= 7.6 Hz, 1 H), 7.16 (t, *J*=5.2 Hz, 1 H), 4.45 (s, 1 H), 4.29 (s, 1 H), 4.12-3.9 7 (m, 2 H), 3.56-3.43 (m, 3 H), 2.77-2.48 (m, 3H),2.31-1.96 (m, 6 H),1.58-1.22 (m, 4 H)	501.1

Procedure 8: Synthesis of Examples 25 and 26



[0240] Preparation of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}quinoline: To a stirred solution of 2-bromoquinoline (0.5 g, 2.40 mmol, 1 eq) in 1,4-dioxane (5 mL) and water (2.5 mL) were added 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.644 g, 2.4 mmol, 1.0 eq) and potassium carbonate (0.996 g, 7.21 mmol, 3 eq). The reaction mixture was purged under N_2 atmosphere for

10 mins, then Pd(dppf)Cl_2.DCM (0.098 g, 0.120 mmol, 0.05 eq) was added. The reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. The progress of the reaction was checked by TLC and LCMS. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by flash column chromatography using 0-30% ethyl acetate in *n*-hexane as eluent to obtain 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}quinoline (0.45 g, 70%). LC-MS (m/z) = 268.2 $[M+H]^+$.

[0241] Preparation of 2-{1,4-dioxaspiro[4.5]decan-8-yl}quinoline: The stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}quinoline (0.45 g, 1.68 mmol, 1 eq) in ethyl acetate (10 mL) was added 10% palladium on carbon (50% moisture, 0.179 g, 1.68 mmol, 1 eq) and the reaction mixture was stirred for 5 h at room temperature under hydrogen atmosphere. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was filtered by using a sintered funnel with a celite bed. The filtrate was concentrated under vacuum to yield 2-{1,4-dioxaspiro[4.5]decan-8-yl}quinoline (0.25 g, 55%). LC-MS (m/z) = 270.1 $[M+H]^+$.

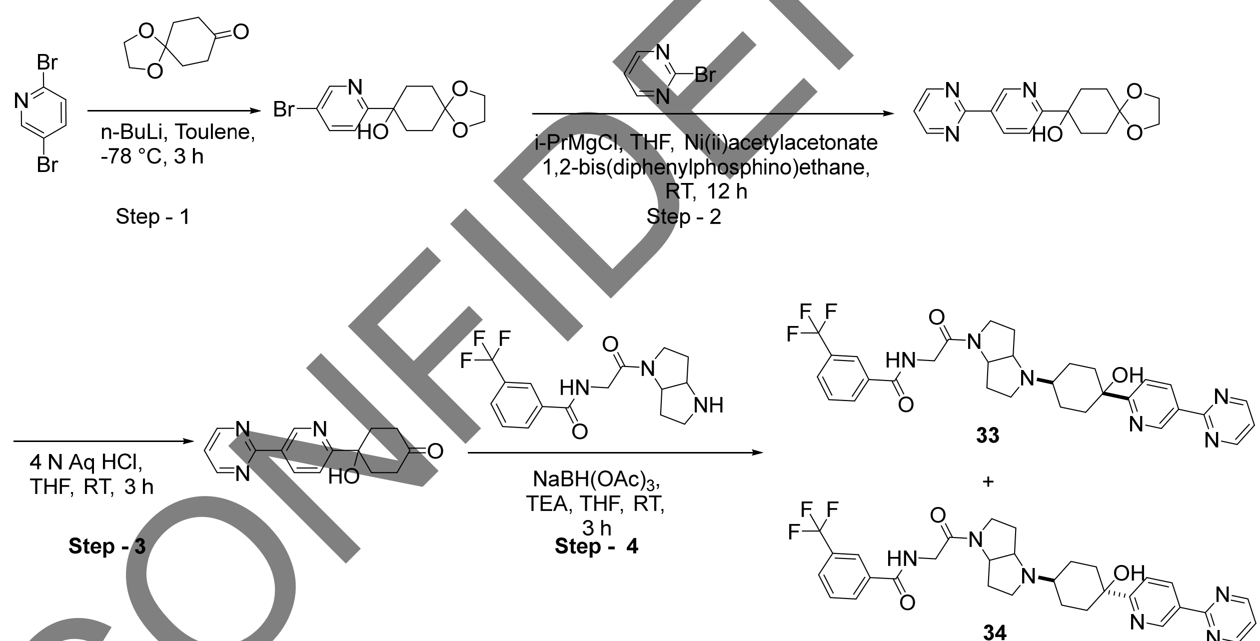
[0242] Preparation of 4-(quinolin-2-yl)cyclohexan-1-one: To a stirred solution of 2-{1,4-dioxaspiro[4.5]decan-8-yl}quinoline (0.25 g, 0.928 mmol, 1 eq) in THF (5 mL) was added 4N aqueous HCl (5 mL). The reaction mixture was stirred for 3 h at room temperature. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to remove the solvent, neutralized by adding sodium bicarbonate, and extracted by using ethyl acetate (50 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to yield 4-(quinolin-2-yl)cyclohexan-1-one (0.15 g, 71.73%). LC-MS (m/z) = 226.0 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.15 - 2.26 (m, 2 H), 2.36 - 2.4 (m, 2 H), 2.52 - 2.62 (m, 4 H), 3.5 (m, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 7.52 (m, 1 H), 7.71 (m, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 8.06 - 8.08 (m, 1 H), 8.14 (d, J = 8.4 Hz, 1 H).

[0243] Preparation of N-(2-oxo-2-(4-(4-(quinolin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide and N-(2-oxo-2-(4-(4-(quinolin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (0.1 g, 0.293 mmol, 1 eq) in THF (5 mL) at room temperature were added 4-(quinolin-2-yl)cyclohexan-1-one (0.066 g, 0.293 mmol, 1 eq) and triethylamine (0.204 mL, 1.46 mmol, 5 eq). The reaction mixture was stirred at room temperature for 0.5 h, then sodium bis(acetyloxy)boranuidyl acetate (0.124 g, 0.586 mmol, 2 eq) was added and stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (20 mL), and extracted using ethyl acetate (20 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using combiflash with 10% MeOH in DCM as eluent, followed by preparative TLC using 5% methanolic ammonia in ethyl acetate to afford two isomers, Example 25 and Example 26 (23.4 mg, 14.51%) and (26.1 mg, 16.18%), respectively.

[0244] Example 25: by TLC, non-polar spot: LC-MS (ES) m/z : 551.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm: 8.88 - 8.98 (m, 1 H), 8.26 - 8.28 (m, 1 H), 8.22 (s, 1 H), 8.17 - 8.19 (m, 1 H), 7.91 - 7.96 (m, 3 H), 7.70 - 7.76 (m , 2 H), 7.52 - 7.56 (m, 1 H), 7.47 - 7.49 (m, 1 H), 4.29 - 4.50 (m, 1 H), 3.99 - 4.19 (m, 2 H), 3.45 - 352 (m, .3 H), 3.0 - 3.05 (m, 1 H), 2.68 - 2.88 (m, 1 H), 2.55 - 2.56 (m, 1 H), 2.33 - 2.34 (m, 1 H), 2.08 - 2.18 (m, 3 H), 1.81 - 2.08 (m, 4 H), 1.55 - 1.80 (m, 5 H). HPLC purity: 99.4% at 230 nm.

[0245] Example 26: by TLC, polar spot: LC-MS (ES) m/z : 551.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm: 8.90 - 8.99 (m, 1 H), 8.24 - 8.26 (m, 1 H), 8.21 (s, 1 H), 8.16 - 8.18 (m, 1 H), 7.89 - 7.92 (m, 3 H), 7.67 - 7.73 (m , 2 H), 7.50 - 7.54 (m, 1 H), 7.45 - 7.47 (m, 1 H), 4.28 - 4.48 (m, 1 H), 3.96 - 4.25 (m, 2 H), 3.42 - 3.68 (m, 3 H), 3.24 - 3.31 (m, 1 H), 2.80 - 3.0 (m, 2 H), 2.31 - 2.48 (m, 1 H), 1.81 - 2.16 (m, 6 H), 1.63 - 1.1.77 (m, 3 H), 1.40 - 1.52 (m, 3 H). HPLC purity: 99.5% at 230 nm.

Procedure 9: Synthesis of Examples 33 and 34



[0246] Preparation of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol: To a solution of 2,5-dibromopyridine (5.0 g, 21.1 mmol, 1 eq) in toluene (150 mL) at -78 °C, *n*-BuLi (1.6 M, 15.8 mL, 25.3 mmol, 1.2 eq) was added dropwise. After being stirred at -78 °C for 2.5 h, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (3.30 g, 21.1 mmol, 1 eq) in dichloromethane (10 mL) was added into the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous $NaHCO_3$ (200 mL) and extracted with EtOAc (200 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum.

The resulting solid purified by using combiflash with 0-15 % ethyl acetate/*n*-hexane as eluent to afford 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (4.2 g, 64%). LC-MS (m/z) = 316.0$[M+H]^+$.

[0247] Preparation of 8-[5-(pyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol. A solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (3 g, 9.55 mmol, 1 eq) in THF (40 mL) was degassed with nitrogen for 30 min, then a 2.0 M solution of isopropyl magnesium bromide in THF (19.5 mL, 38.2 mmol, 4 eq) was added dropwise over 15 min at room temperature. The reaction mixture was stirred for 3 h at 25 ºC. Another flask was charged with THF (15 mL) degassed with nitrogen for 10 min, and nickel(II) acetylacetonate (0.247 g, 0.955 mmol, 0.1 eq) and 1,2-bis(diphenylphosphino)ethane (0.38 g, 0.955 mmol, 0.1 eq) were added under nitrogen flush. After stirring for 10 min, 2-bromopyrimidine (2.58 g, 16.2 mmol,1.7 eq) was added. After being stirred for 30 min at 25 ºC, the resulting suspension was transferred to the first solution and the reaction mixture was stirred at room temperature 2.5 h. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mass was quenched with saturated aqueous NH_4Cl solution (100 mL), extracted with ethyl acetate (2 x 200 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by silica gel column chromatography using 40% ethyl acetate in heptane as eluent to obtain the 8-[5-(pyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (1 g, 33%). LC-MS (ES) m/z: 314.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 - 1.65 (m, 4 H), 1.91 - 1.98 (m, 2 H), 2.22 - 2.29 (m, 2 H), 3.82 - 3.84 (m, 1 H), 3.88 - 3.90 (m, 4 H), 7.49 - 7.51 (m, 1 H), 7.83 - 7.85 (m, 1 H), 8.64 - 8.67 (m, 1 H), 8.94 - 8.96 (m, 2 H), 9.42 - 9.43 (m, 1 H).

[0248] Preparation of 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one: To a stirred solution of 8-[5-(pyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (2.0 g, 6.38 mmol, 1 eq) in THF (15 mL), 4N HCl in water (15 mL) was added dropwise while cooling, and the reaction mixture was stirred at room temperature for 2 h. The reaction progress was monitored by TLC (50% EA in heptane). The reaction mixture was concentrated under reduced pressure to yield an aqueous residue, which was basified with saturated aq. Na_2CO_3 to pH 8~9. Then the aqueous layer was extracted with ethyl acetate (2 x 100 mL), and the combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (1.5 g, 44.75%). LC-MS (ES) m/z **:** 270.0 $[M+H]^+$: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 – 1.98 (m, 2 H), 2.17 – 2.20 (m, 2 H), 2.30 – 2.48 (m, 2 H), 2.71 – 2.79 (m, 2 H), 5.74 (s, 1 H), 7.48 – 7.50 (m, 1 H), 7.90 (d, 8.4 Hz, 1 H), 8.67 – 8.69 (m, 1 H), 8.92 - 8.93 (m , 2 H), 9.41 – 9.15 (m, 1 H).

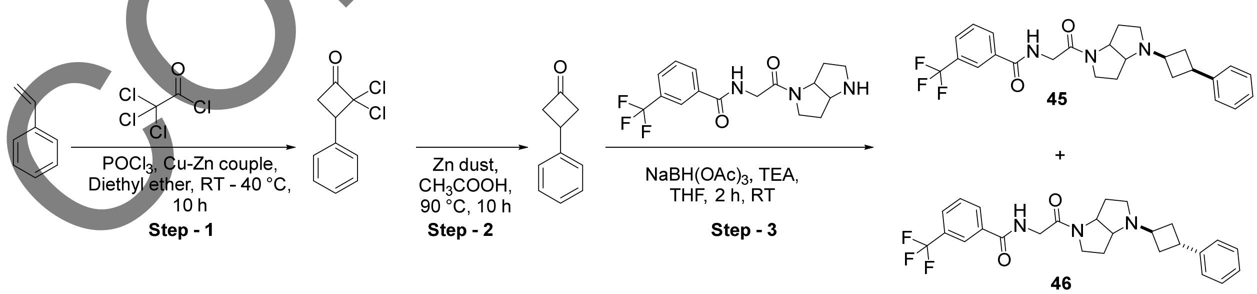
[0249] Preparation of N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide and N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-

{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (0.05 g, 0.146 mmol, 1 eq) in THF (2 mL) at 0 °C were added 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (0.043 g, 0.161 mmol, 1.1 eq) and triethylamine (0.1 mL, 0.732 mmol, 5 eq). The reaction mixture was stirred at room temperature for 0.5 h, then sodium bis(acetyloxy)boranuidyl acetate (0.062 g, 0.293 mmol, 2 eq) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (10 mL), and extracted using ethyl acetate (10 mL x 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using combiflash with 10% MeOH in DCM as eluent, then preparative TLC using 5% methanolic ammonia in ethyl acetate to afford 2 isomers N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (5.0 mg, 6.08%) and N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (35.0 mg, 40%).

[0250] Example 33: non- polar spot on TLC: LC-MS (ES) m/z : 595.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6): 9.44 (m, 1 H), 8.90 - 9.01 (m, 3 H), 8.65 - 8.67 (m, 1 H), 8.14 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.80 - 7.82 (m, 1 H), 7.73 - 7.76 (m, 1 H), 7.51 (t, J = 5.4 Hz, 1 H), 5.12 (s, 1 H), 4.31 - 4.54 (m, 1 H), 3.98 - 4.29 (m, 2 H), 3.48 - 3.63 (m, 3 H), 2.72 - 2.86 (m ,1 H), 2.33 - 2.40 (m, 1 H), 1.76 - 1.83 (m, 7 H), 1.39 - 1.63 (m, 6 H). HPLC purity: 99.9% at 230 nm.

[0251] Example 34: polar spot on TLC: LC-MS (ES) m/z : 595.3 [M+H]+. ^{1}HNMR (400 MHz, DMSO-d_6): 9.42 - 9.43 (m, 1 H), 8.89 - 8.99 (m, 3 H), 8.65 - 8.67 (m, 1 H), 8.18 - 8.23 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.84 - 7.86 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.50 (t, J = 5.4 Hz, 1 H), 5.12 (s, 1 H), 4.21 - 4.32 (m, 1 H), 3.98 - 4.19 (m, 2 H), 3.44 - 3.68 (m, 3 H), 2.91 - 3.03 (m ,1 H), 1.97 - 2.25 (m, 4 H), 1.49 - 1.91 (m, 10 H). HPLC purity: 99.84% at 230 nm.

Procedure 10: Synthesis of Examples 45 and 46



[0252] Preparation of 2,2-dichloro-3-phenylcyclobutan-1-one: To a stirred solution of 1-chloro-4-ethenylbenzene (1.0 g, 9.6 mmol, 1 eq) and zinc-copper couple (3.09 g, 24 mmol, 2.5 eq) in diethyl ether (25 mL) were added a solution of trichloroacetyl chloride (2.16 mL, 19.2 mmol, 2 eq) and phosphorus oxychloride (1.26 mL, 1.4 mmol, 1.4 eq) in ether (20 mL) dropwise via addition funnel over 15 min. The resulting solution was heated at 40 °C for 10 h. After cooling to room temperature the mixture was filtered over a celite bed and washed with diethyl ether (20 mL). The filtrate was then quenched with saturated aqueous $NaHCO_3$ and the layers separated. The aqueous layer was extracted with ether (25 mL) and the combined organic layers were washed with brine (15 mL), dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude material was purified by using flash column chromatography using 0-25% ethyl acetate in hexane as eluent to obtain 2,2-dichloro-3-phenylcyclobutan-1-one (0.5 g, 24.21%).

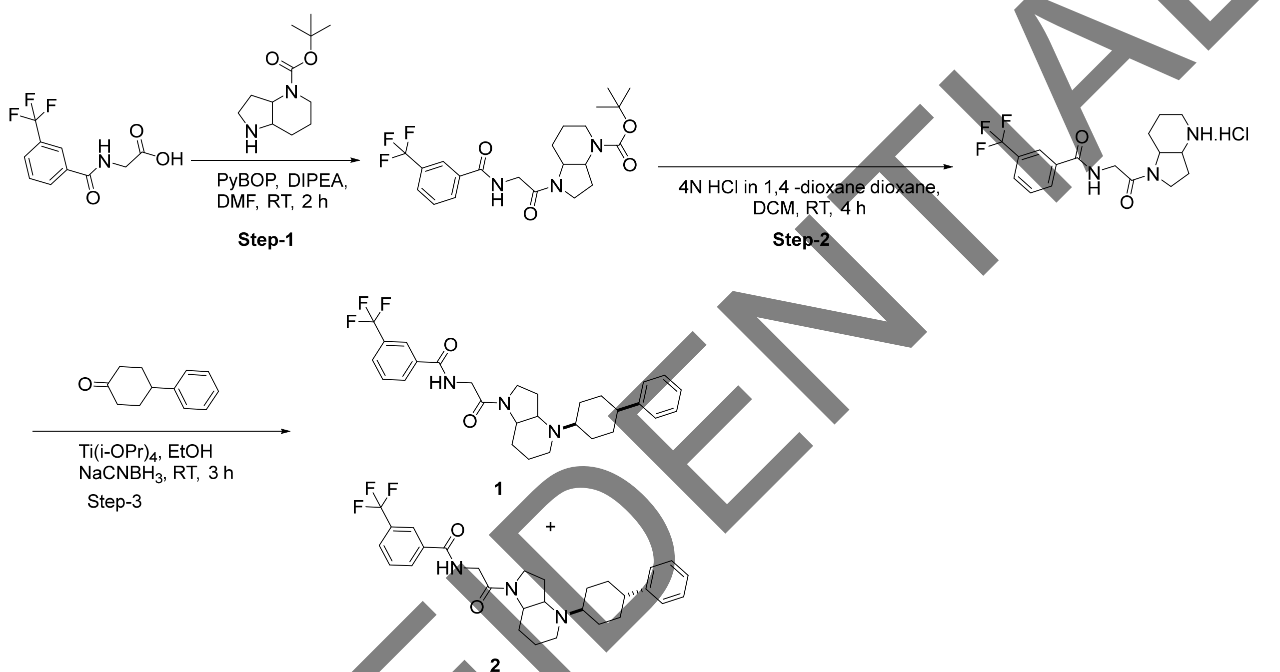
[0253] Preparation of 3-phenylcyclobutan-1-one: To a stirred solution of 2,2-dichloro-3-phenylcyclobutan-1-one (0.2 g, 0.930 mmol, 1 eq) in acetic acid (2.5 mL) was added zinc dust (0.243 g, 3.72 mmol, 4 eq) portionwise at 0 °C. The reaction mixture was stirred for 10 h at 100 °C. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water and neutralized with saturated aqueous $NaHCO_3$ solution, then extracted using ethyl acetate (20 mL x 2) and dried over Na_2SO_4, filtered, and concentrated under vacuum to yield the crude material. The crude material was purified by flash column chromatography by using 0-10 % ethyl acetate in *n*-hexane as eluent to afford 3-phenylcyclobutan-1-one (0.15 g, 100%).

[0254] Preparation of N-(2-oxo-2-(4-((1s,3s)-3-phenylcyclobutyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl) and N-(2-oxo-2-(4-((1r,3r)-3-phenylcyclobutyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.06 g, 0.176 mmol, 1 eq) in THF (5 mL) at 0 °C were added 3-phenylcyclobutan-1-one (0.039 g, 0.264 mmol, 1.2 eq) and triethylamine (0.185 mL, 1.32 mmol, 6 eq). The reaction mixture was stirred at room temperature for 0.5 h, then sodium bis(acetyloxy)boranuidyl acetate (0.093 g, 0.439 mmol, 2 eq) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (10 mL), and extracted using ethyl acetate (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by using preparative TLC using 2% methanol in DCM to afford 2 isomers N-(2-oxo-2-(4-((1s,3s)-3-phenylcyclobutyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (4.0 mg, 3.86 %) and N-(2-oxo-2-(4-((1r,3r)-3-phenylcyclobutyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (4.0 mg, 3.86%).

[0255] Example 45: non-polar on TLC: LC-MS (ES) m/z : 472.3 $[M+H]^+$. ^{1}HNMR (400 MHz, DMSO-d_6): 8.89 - 8.97 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.76 (m, 1 H), 7.16 - 7.32 (m, 5 H), 4.27 - 4.51 (m, 1 H), 3.93 - 4.17 (m, 2 H), 3.48 - 3.85 (m, 3 H), 3.06 - 3.22 (m, 3 H), 2.87 - 3.06 (m, 1 H), 2.33 - 2.45 (m, 1 H), 2.07 - 2.30 (m, 2 H), 1.95 - 2.04 (m, 2 H), 1.63 - 1.97 (m, 1 H), 1.45 - 1.63 (m, 2 H). HPLC purity: 99.3% at 230 nm.

[0256] Example 46: polar on TLC: LC-MS (ES) m/z : 472.3 $[M+H]^+$. ^{1}HNMR (400 MHz, DMSO-d_6): 8.91 - 8.95 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.16 - 7.33 (m, 5 H), 4.27 - 4.51 (m, 1 H), 3.97 - 4.17 (m, 2 H), 3.48 - 3.75 (m, 3 H), 2.87 - 3.22 (m, 4 H), 2.38 - 2.46 (m, 1 H), 2.08 - 2.33 (m, 2 H), 1.66 - 2.06 (m, 3 H). HPLC purity: 99.5% at 230 nm.

Procedure 11: Synthesis of Examples 1 and 2



[0257] Preparation of *tert*-butyl 1-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate): To a stirred solution of 2-{[3-(trifluoromethyl)phenyl]formamido}acetic acid (300 mg, 1.21 mmol, 3 eq) in DMF (8.00 mL) were added (1H-1,2,3-benzotriazol-1-yloxy)tris(pyrrolidin-1-yl)phosphanium; hexafluoro-λ⁵-phosphanuide (632 mg, 1.21 mmol, 3 eq), *tert*-butyl octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (275 mg, 1.21 mmol) and triethylamine (512 μL, 3 eq, 3.64 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by LCMS. After completion of the reaction, the reaction mixture was poured into cold water (2 x 30 mL), extracted with ethyl acetate (50 mL) and dried with anhydrous Na_2SO_4, filtered, and concentrated to yield *tert*-butyl 1-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (0.6 g, 95%). LC-MS (ES) m/z = 456.2 $[M + H]^+$.

[0258] Preparation of N-(2-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamidehydrochloride: To a solution of of *tert*-butyl 1-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (600 mg, 1.32 mmol, 1 *eq*) in DCM (10 mL), 4M HCl in dioxane (3.00 mL) was added at 0 °C and resultant mixture was stirred at room temperature for 4 h. progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the mixture was concentrated in vacuo to yield the crude N-(2-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (0.43 g, 1.1 mmol, 83.3% yield). LC-MS (ES) m/z = 356.2 $[M+H]^+$.

[0259] Preparation of N-(2-oxo-2-(4-((1s,4s)-4-phenylcyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)ethyl)-3-(trifluoromethyl)benzamide and N-(2-oxo-2-(4-((1r,4r)-4-phenylcyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)ethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of N-(2-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (140 mg, 357 µmol, 1 *eq*) in anhydrous THF (1.5 mL), 4-phenylcyclohexan-1-one (62.3 mg, 357 µmol) and tetrakis(propan-2-yloxy)titanium (0.5 mL, 1.66 mmol, 2 *eq*) were added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethanol (2 mL) and boron(3+) sodium iminomethanide trihydride (33.7 mg, 536 µmol, 1.5 *eq*) was added and stirred at room temperature for 2 h. The reaction mixture was quenched with 2 mL water and stirred for 5 mins, then the inorganic solid was filtered and washed with 10% MeOH/DCM (10 mL). The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by prep TLC using 5% MeOH/DCM afford racemic product N-(2-oxo-2-(4-((1s,4s)-4-phenylcyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)ethyl)-3-(trifluoromethyl)benzamide (0.010 g, 8.17%) and N-(2-oxo-2-(4-((1r,4r)-4-phenylcyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)ethyl)-3-(trifluoromethyl)benzamide (0.005 g, 7.1%).

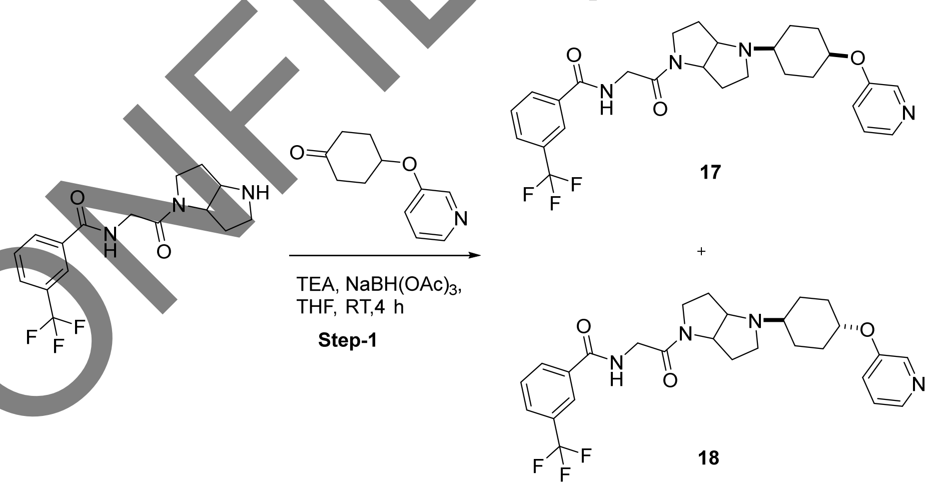
[0260] Example 1: non-polar on TLC: LC-MS (ES) m/z = 514.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96-8.87 (m,1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.92 (t, *J*=7.6 Hz, 1 H), 7.74 (t, *J*= 7.6Hz, 1 H), 7.31-7.23 (m, 4 H), 7.19-7.14 (m, 1 H), 4.23-4.17 (m, 1 H), 4.08-4.03 (m, 1 H), 4.00-3.91 (m, 1 H), 3.69-3.58 (m, 1 H), 3.53-3.49 (m, 1 H), 3.18-2.95 (m, 1 H), 2.80 (t, *J* = 11.6, 2 H), 2.18-1.99 (m, 6 H), 1.86-1.77 (m, 3 H), 1.67 (d, *J* = 12 Hz, 1 H), 1.52 (s, 5 H), 1.40-1.30 (m, 1 H), 1.24-1.13 (m, 1 H). HPLC Purity: 99.39% at 230 nm.

[0261] Example 2: polar on TLC: LC-MS (ES) m/z = 514.2 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96-8.87 (m, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.92 (t, *J* = 7.6 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.31-7.23 (m, 4 H), 7.19-7.14 (m, 1 H), 4.23-4.17 (m, 1 H), 4.08-4.03 (m, 1 H), 4.00-3.91 (m, 1 H), 3.69-3.58 (m, 1 H), 3.53-3.49 (m, 1 H), 3.18-2.95 (m, 1 H), 2.80 (t, *J* =1 1.6 Hz, 2 H), 2.18-1.99 (m, 6 H), 1.86-1.77 (m, 3 H), 1.67 (d, *J* = 12 Hz, 1 H), 1.52 (s, 5 H), 1.40-1.30 (m, 1 H), 1.24-1.13 (m, 1 H). HPLC Purity: 99.35% at 230 nm.

[0262] The following compounds were synthesized according to Procedure 11.

Example No.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
4	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.96 (d, *J* = 4.8 Hz, 2 H), 8.71 (d, *J*=6.8Hz, 2 H), 8.21-8.16 (m, 2 H), 7.93 (d, *J* =7.6, 1 H), 7.86-7.74 (m, 2 H) , 7.57-7.49 (m, 2H), 7.17-7.08 (m, 1 H), 4.07-4.00 (m, 3 H), 3.51-3.48 (m, 2 H), 2.22-2.16 (m, 5 H), 2.07-1.98 (m, 3 H), 1.72-1.49 (m, 10 H)	609.2
3	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.41 (s, 1 H), 8.93-8.92 (m, 2 H), 8.66(m, 1 H), 8.19-8.15 (m, 2 H), 7.91 (s, 1 H), 7.91-7.73 (m, 3 H), 7.49-7.48 (m, 1 H), 4.06-3.42 (m, 9 H), 2.99-2.74 (m, 4 H), 2.15-1.96 (m, 10 H)	609.2

Procedure 12: Synthesis of Examples 17 and 18

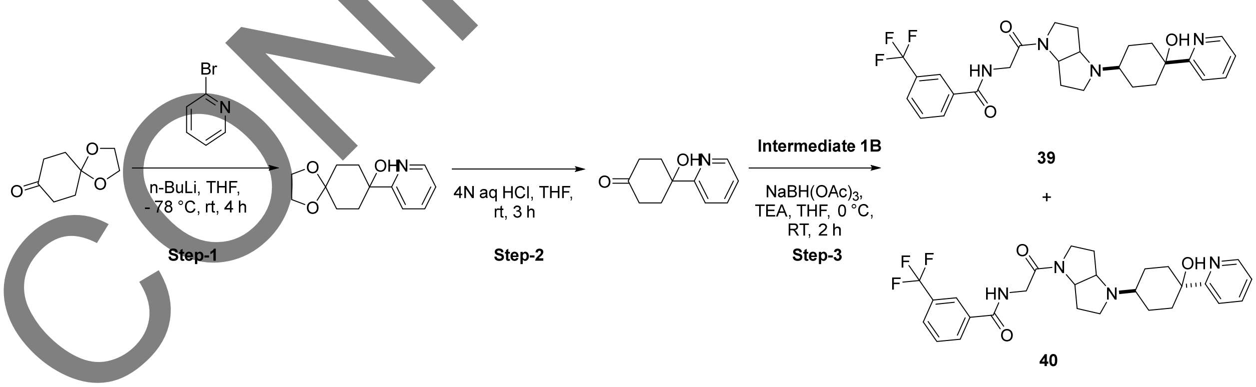


[0263] Preparation of N-(2-oxo-2-(4-((1s,4s)-4-(pyridin-3-yloxy)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (17) and N-(2-oxo-2-(4-((1r,4r)-4-(pyridin-3-yloxy)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (18): To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.11 g, 0.58 mmol, 2 eq) in THF (5 mL) at 0 °C were added triethylamine (0.2 mL, 1.76 mmol, 6 eq) and 4-(pyridin-2-yloxy)cyclohexan-1-one (0.1 g, 0.29 mmol, 1 eq). The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, then sodium bis(acetyloxy)boranuidyl acetate (0.1 g, 0.58 mmol, 2 eq) was added and stirred at room temperature for 1 h. Progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the mixture was evaporated under reduced pressure, extracted with DCM (2 x 50 mL), and combined organic layer were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude product was purified by preparative TLC plate using 5% methanolic ammonia in ethyl acetate to afford both geometrical isomers N-(2-oxo-2-(4-((1s,4s)-4-(pyridin-3-yloxy)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (17, non polar isomer - 10 mg, 6% yield) and N-(2-oxo-2-(4-((1r,4r)-4-(pyridin-3-yloxy)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (18, polar isomer - 10 mg, 6% yield).

[0264] Analytical Data for Example 17: (Non- polar spot on TLC): LC-MS (m/z) = 517.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.99 - 8.91 (m, 1 H), 8.29 (s, 1 H), 8.22 - 8.14 (m, 3 H), 7.93 (d, J = 8 Hz, 1 H), 7.76 (t, J = 8 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.33 - 7.29 (m, 1 H), 4.62 (s, 1 H), 4.46 (d, J = 6.8 Hz, 1 H), 4.29 - 3.96 (m, 2 H), 3.64 - 3.59 (m, 3 H), 2.93 - 2.85 (m, 1 H), 2.13 (d, J = 6.8 Hz, 1 H), 1.93 - 1.74 (m, 4 H), 1.67 - 1.64 (m, 8 H). HPLC purity: 99.90% (230nm).

[0265] Analytical Data for Example 18: (Polar spot on TLC): LC-MS (m/z): 517.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.99 - 8.27 (m, 1 H), 8.26 (d, J = 2.4 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, J = 8 Hz, 1 H), 8.13 (d, J = 4.4 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.32 - 7.29 (m, 1 H), 4.62 (s, 1 H), 4.46 - 4.42 (m, 1 H), 4.38 - 4.25 (m, 1 H), 4.19 - 4.10 (m, 4 H), 4.03 - 3.95 (m, 1 H), 3.65 - 3.42 (m, 2 H), 2.94 - 2.86 (m, 1H), 2.09 (d, J = 7.6 Hz, 3H), 1.94 - 1.86 (m, 5H), 1.80 - 1.64 (m, 2H), 1.53 - 1.24 (m, 4H). HPLC Purity: 92.04% (230 nm).

Procedure 13: Synthesis of Examples 39 and 40



[0266] Preparation of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol: To a solution of 2-bromopyridine (1 g, 6.33 mmol, 1 eq) in THF (5 mL) at -78 °C, *n*-BuLi (4.75 mL, 7.60 mmol, 1.2 eq) was added dropwise. After being stirred at -78 °C for 2.5 h, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (0.98 g, 6.33 mmol, 1 eq) in THF (5 mL) was added into the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (10 mL) and extracted with EtOAc (100 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated yield the crude product, which was purified by combiflash column chromatography using 40% EtOAc–heptane as eluent, to afford 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-oll (0.7 g, 47% yield). LC-MS (m/z) : 236.1 $[M+H]^+$

[0267] Preparation of 4-hydroxy-4-(pyridin-2-yl)cyclohexan-1-one: To a stirred solution of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.25 g, 1.06 mmol, 1 equiv.) in THF (4 mL) was added 4N HCl in water dropwise while cooling, then the reaction mixture was stirred at room temperature for 2 h and reaction progress was checked by TLC monitoring. After completion of the reaction, the mixture was concentrated under reduced pressure to yield the aqueous residue, which was basified with solid $NaHCO_3$ to pH 8~9. The aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 4-hydroxy-4-(pyridin-2-yl)cyclohexan-1-one (0.2 g, 98%). LC-MS (m/z) : 192.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.57 (d, J = 4.8 Hz, 1 H), 8.77 (t, J = 6.4 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.30 (s, 1 H), 5.29 (s, 1 H), 2.39 (d, J = 14.4 Hz, 2 H), 2.28 – 2.20 (m, 4 H), 2.09 – 1.92 (m, 2 H).

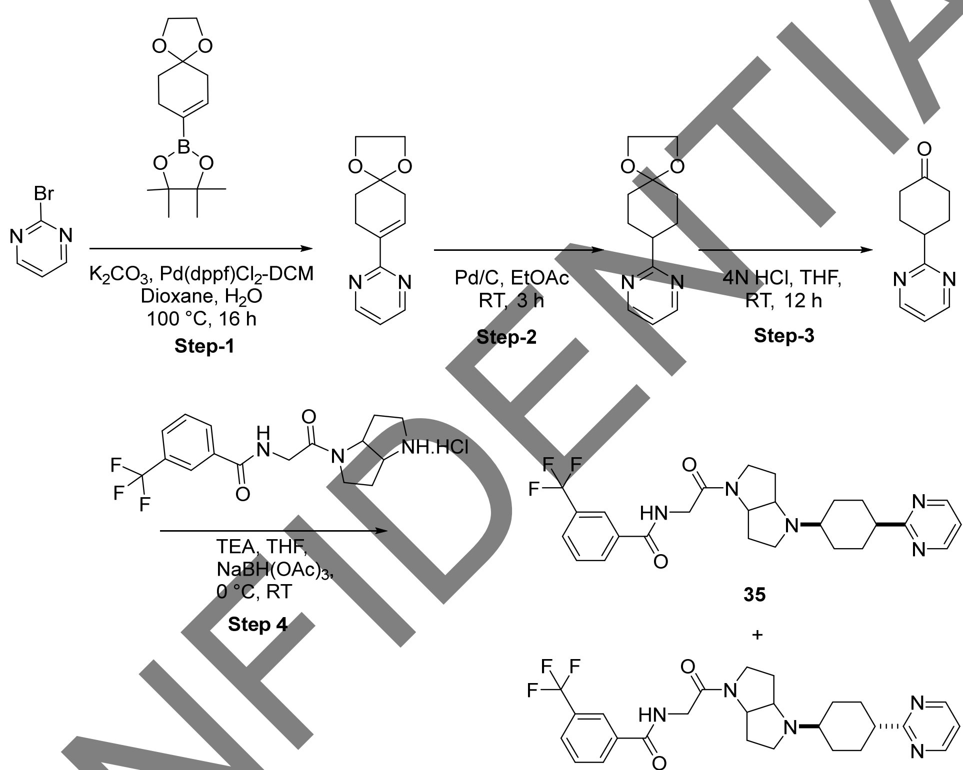
[0268] Preparation of N-(2-(4-((1r,4r)-4-hydroxy-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (39) and N-(2-(4-((1s,4s)-4-hydroxy-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (40): To a stirred solution of 4-hydroxy-4-(pyridin-2-yl)cyclohexan-1-one (0.03 g, 0.17 mmol, 1.2 eq) in THF (3 mL) were added N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (Intermediate 1B, 0.05 g, 0.14 mmol, 1 eq) and triethylamine (0.01 mL, 0.87 mmol, 6 eq) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, then sodium bis(acetyloxy)boranuidyl acetate (0.06 g, 0.29 mmol, 2 eq) was added and stirred at room temperature for 1 h. Progress of the reaction mixture was checked by TLC monitoring, and after completion of the reaction, the mixture was evaporated under reduced pressure and extracted with DCM (2 x 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by preparative TLC plate using 5 % methanolic ammonia in ethyl acetate. Non-polar and polar bands were separated and isolated to afford both geometrical isomers N-(2-(4-((1r,4r)-4-hydroxy-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (39, non-polar isomer - 5mg, 6% yield) and N-(2-(4-((1s,4s)-4-hydroxy-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (40, polar isomer - 15 mg, 20% yield) as single enantiomers.

[0269] Analytical Data of Example 39: (Non-polar by TLC): LC-MS (m/z) : 517.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 - 8.90 (m, 1 H), 8.51 (d, J = 4.4 Hz, 1 H), 8.20 (t, J = 12 Hz, 2 H), 7.93 (d, J = 8 Hz, 1 H), 7.79 - 7.73 (m, 2 H), 7.63 (d, J = 8 Hz, 1 H), 7.23 (t, J = 5.2 Hz, 1 H), 4.97 (s, 1 H), 4.48 -

4.44 (m, 1 H), 4.30 - 3.94 (m, 2 H), 3.59 - 3.41 (m, 3 H), 2.98 - 2.78 (m, 1 H), 2.20 - 2.07 (m, 2 H), 1.91 - 1.70 (m, 5 H), 1.60 - 1.51 (m, 4 H), 1.37 - 1.24 (m, 3 H). HPLC Purity: 86.65% (230nm).

[0270] Analytical Data of Example 40: (Polar by TLC): LC-MS (ES) m/z : 517.3 $[M+H]^{+.}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 - 8.89 (m, 1 H), 8.47 (d, J = 4.4 Hz, 1 H), 8.19 (t, J = 12 Hz, 2 H), 7.91 (d, J = 8 Hz, 1 H), 7.77 - 7.64 (m, 3 H), 7.20 (t, J = 6 Hz, 1 H), 7.23 (t, J = 5.2 Hz, 1 H), 4.99 (s, 1 H), 4.27 - 4.26 (m, 1 H), 4.15 - 3.95 (m, 3 H), 3.62 - 3.40 (m, 3 H), 3.30 - 3.23 (m, 1 H), 2.89 (m, 1 H), 2.13 - 1.92 (m, 4 H), 1.82 - 1.56 (m, 7 H). HPLC Purity: 98.09% (230 nm).

Procedure 14: Synthesis of Examples 35 and 36



35

36

[0271] Preparation of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}pyrimidine: To a stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (837 mg, 3.14 mmol) in 1,4-dioxane (7.00 mL) and water (3.00 mL) were added 2-bromopyrimidine (0.4 g, 0.8 eq., 2.52 mmol) and potassium carbonate (1.3 g, 3 eq., 9.43 mmol). The reaction mixture was purged with Ar for 5 mins, to which Pd(dppf)Cl_2.DCM (257 mg, 0.1 eq.,0.314 mmol) was added portionwise and the reaction mixture was stirred at 100 °C for 16 h. After completion of the reaction, the mixture was quenched with water (3 mL), extracted with ethyl acetate (2 x 10 mL), and the combined organic layer were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude was purified by flash column chromatography using 30% of EtOAc/heptane to afford 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}pyrimidine

(510 mg, 74.3%). LC-MS (m/z) = 219.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.70 (d, *J*=4.8 Hz, 2H), 7.27 (m, 1H), 7.11 (t, 1H), 4.05 (s, 4H), 2.88 (m, 2H), 2.59 (s, 2H), 1.96 (t, *J*=6.4Hz, 3H)

[0272] Preparation of 2-{1,4-dioxaspiro[4.5]decan-8-yl}pyrimidine: To a stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}pyrimidine (0.5 g, 2.29 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (488 mg, 2 eq., 4.58 mmol) and the reaction mixture was allowed to stir at room temperature for 3 h under hydrogen atmosphere. After the completion of the reaction, the reaction mixture was filtered through a celite bed and washed further with methanol (20 mL). The organic layer was concentrated *in vacuo* to afford 2-{1,4-dioxaspiro[4.5]decan-8-yl}pyrimidine (440 mg, 87.19%). LC-MS (m/z) = 221.1 $[M+H]^+$

[0273] Preparation of 4-(pyrimidin-2-yl)cyclohexan-1-one: To a stirred solution of 2-{1,4-dioxaspiro[4.5]decan-8-yl}pyrimidine (425 mg, 1.93 mmol) in oxolane (10 mL), 4N HCl in 1,4-dioxane (6 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 12 h. After the completion of the reaction, the reaction mixture was evaporated to yield the crude product and neutralized with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 4-(pyrimidin-2-yl)cyclohexan-1-one(260 mg, 76.47%). LC-MS (m/z) = 177.1 $[M+H]^+$

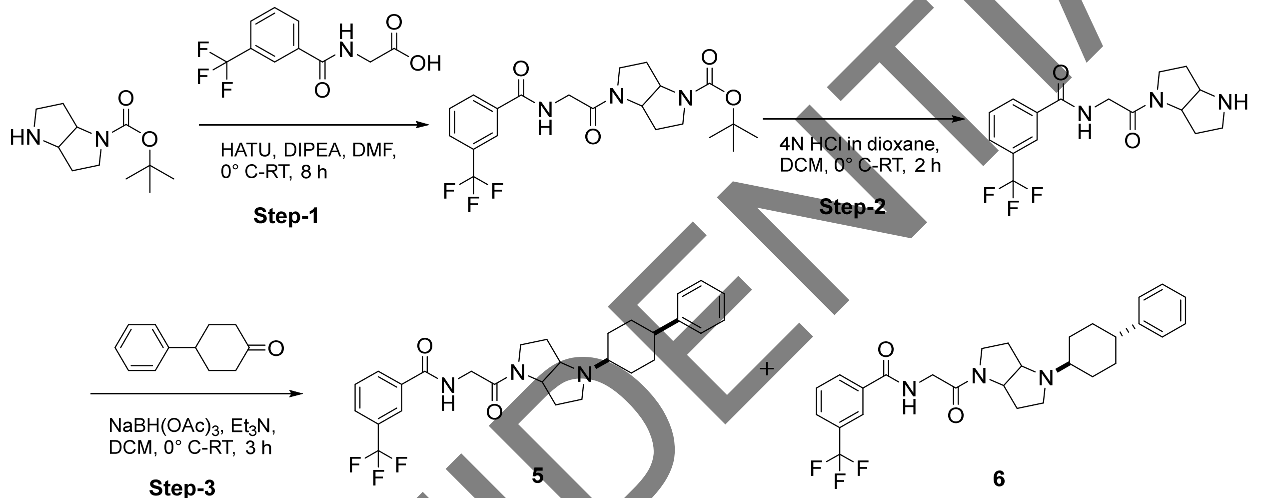
[0274] Preparation of N-(2-oxo-2-{4-[(1s,4s)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (35) & N-(2-oxo-2-{4-[(1r,4r)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (36): To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (50 mg, 0.146 mmol) in THF (1.5 mL, 18.4 mmol) 0 °C to were added 4-(pyrimidin-2-yl)cyclohexan-1-one (31 mg, 1.2 eq, 176 µmol) and triethylamine (124 µL, 6 eq, 0.879 mmol). The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, then sodium bis(acetyloxy)boranuidyl acetate (62.1 mg, 2 eq, 0.293 mmol) was added and stirred at room temperature for 12 h. Progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, extracted with DCM (2 x 50 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude product was purified by Prep-TLC plate using 2.5% of methanolic ammonia in EtOAc as eluent to afford N-(2-oxo-2-{4-[(1s,4s)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (**35**, 8 mg, 10.89%) and N-(2-oxo-2-{4-[(1r,4r)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (**36**, 5 mg, 6.81%).

[0275] Analytical Data for Example 35: (Non-polar spot on TLC): N-(2-oxo-2-{4-[(1s,4s)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (8 mg). LC-MS (ES) m/z: 502.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.96-8.90 (m, 1H), 8.73 (d, *J*=4.8 Hz, 2H), 8.19 (s, 1H), 8.16 (d, *J*=4 Hz, 1H), 7.91 (d, *J*=8 Hz, 1H), 7.73 (t, *J*=7.6 Hz, 1H), 7.31-7.29 (m, 1H), 4.45-4.43

(m, 2H), 4.15-3.97 (m, 3H), 3.55-3.49 (m, 3H), 2.95-2.74 (m, 3H). 2.31-2.06 (m, 2H), 1.89 (s, 1H), 1.73-1.49 (m, 6H), 1.28-1.22 (m, 2H). HPLC Purity: 99.91% (230 nm)

[0276] Analytical Data for Example 36: (Polar spot on TLC): N-(2-oxo-2-{4-[(1r,4r)-4-(pyrimidin-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (5 mg). LC-MS (ES) m/z: 502.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.97-8.91 (m, 1H), 8.75 (d, *J*=4.8 Hz, 2H), 8.22 (s, 1H), 8.18 (d, *J*=4 Hz, 1H), 7.93 (d, *J*=8 Hz, 1H), 7.75 (t, *J*=7.6 Hz, 1H), 7.33-7.31 (m, 1H), 4.48-4.28 (m, 1H), 4.18-3.99 (m, 2H), 3.57-3.41 (m, 3H), 2.98 (m, 1H), 2.84-2.72 (m, 1H) 2.33-2.17 (m, 3H), 1.91 (s, 2H), 1.88-1.40 (m, 9H), 1.34-1.27 (m, 3H). HPLC purity : 97.44% (230 nm).

Procedure 15: Synthesis of Examples 5 and 6



[0277] Preparation of *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate: To a stirred solution of *tert*-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (300 mg, 1.41 mmol, 1 eq) in DMF (6 mL) were added 2-{[3-(trifluoromethyl)phenyl]formamido}acetic acid (419 mg, 1.7 mmol, 1.2 eq), [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (1.07 g, 2.83 mmol, 2 eq), and ethylbis(propan-2-yl)amine (0.8 mL, 4.24 mmol, 3 eq) at 0°C. The reaction mixture was stirred at room temperature for 3 h and the progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was poured into cold water (30 mL) and extracted with EtOAC (2 x 100 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude, which was purified by combiflash (70% EtOAc in hexane) to afford *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (460 mg, 73.7%). LC-MS (m/z) = 422.2 $[M + H]^+$

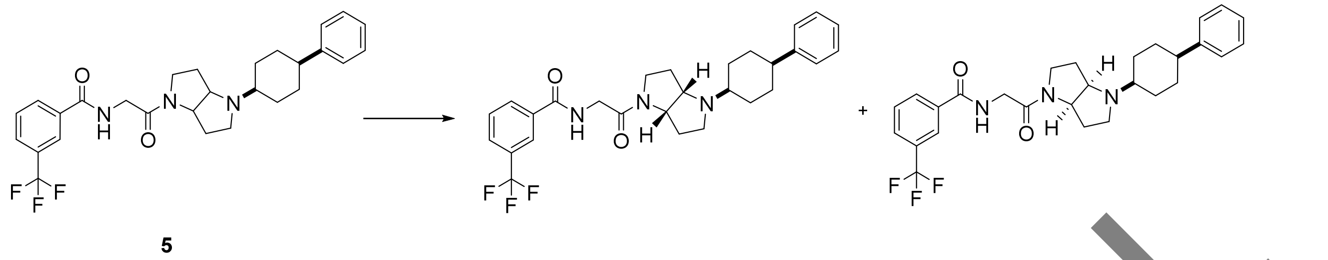
[0278] Preparation of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (520 mg, 1.18mmol, 1eq) in DCM (8 mL) was added 4N HCl in 1,4-dioxane (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was evaporated to yield the crude and washed with the diethyl ether and *n*-pentane to afford N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (380 mg, 94.5%). LC-MS (m/z) = 342.2 $[M + H]^+$

[0279] Preparation of N-{2-oxo-2-[4-(4-phenylcyclohexyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]ethyl}-3-(trifluoromethyl)benzamide (5) and N-{2-oxo-2-[4-(4-phenylcyclohexyl)-octahydropyrrolo[3,2-b]pyrrol-1-yl]ethyl}-3-(trifluoromethyl)benzamide (6): To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (280 mg, 0.820 mmol, 1eq) in THF (5 mL) was added trimethylamine (0.668 mL, 4.92 mmol, 6 eq). After stirring for 5 min, 4-phenylcyclohexan-1-one (143 mg, 0.820mmol, 1eq) was added. The resulting mixture was stirred at room temperature for 30 min, then sodium bis(acetyloxy)boranuidyl acetate (344 mg, 1.64 mmol, 2 eq) was added. The reaction was maintained at room temperature for 3 h. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 30 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude which was purified by prep TLC using 7% MeOH in DCM to afford N-(2-oxo-2-(4-((1s,4s)-4-phenylcyclohexyl)octahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (60 mg, 7.32%) and N-(2-oxo-2-(4-((1r,4r)-4-phenylcyclohexyl)octahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (30 mg, 14.64%).

[0280] Analytical Data for Example 5: (Non-Polar by TLC): LC-MS (m/z) = 500.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.569 - 1.675 (m, 6 H), 1.831 - 1.934 (m, 6 H), 2.050 - 2.196 (m, 2 H), 2.529 - 2.587 (m, 2 H), 2.963 - 3.610 (m, 3 H), 4.086 - 4.475 (m, 3 H), 7.148 - 7.313 (m, 5 H), 7.731 (t, *J* = 15.6 Hz, 1H), 7.886 (d, *J* = 8 Hz, 1 H), 8.173 (d, *J* = 7.6 Hz, 1 H), 8.202 (s, 1 H), 8.602 (s, 1 H). HPLC Purity: 99.66% (230 nm).

[0281] Analytical Data for Example 6: (Polar by TLC): LC-MS (m/z) = 500.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.278 - 1.417 (m, 4 H), 1.461 - 1.599 (m, 4 H), 1.890 - 1.99 (m, 4 H), 2.034 - 2.175 (m, 4 H), 3.145 - 3.658 (m, 3 H), 4.058 - 4.44 (m, 3 H), 7.152 - 7.304 (m, 5 H), 7.732 (t, *J* = 15.6 Hz, 1H), 7.886 (d, *J* = 7.6 Hz, 1 H), 8.173 (d, *J* = 8 Hz, 1 H), 8.202 (s, 1 H), 8.599 (s, 1 H). HPLC Purity: 99.89% (230 nm).

Procedure 16: Synthesis of Examples 9 and 10

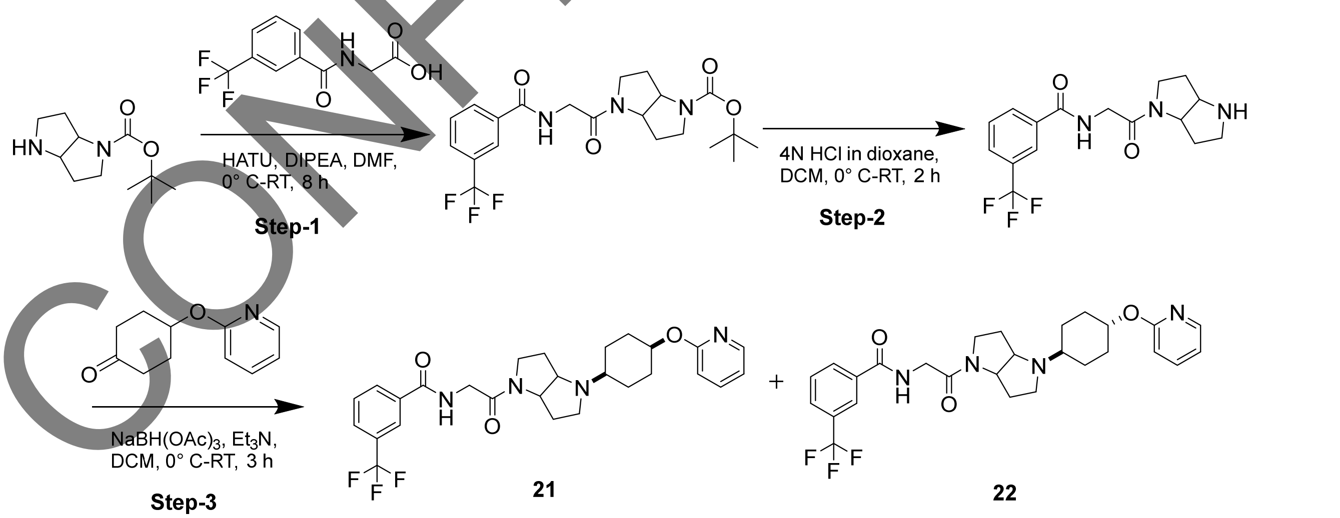


[0282] Separation of Example 5 by chiral prep. HPLC afforded Examples 9 and 10 as single enantiomers. Prep Conditions: Column: Chiral cell OJ-RH (20 X 150) mm; 5 µm; Mobile phase(A): 5 mM Ammonium acetate in water; Mobile phase(B): Acetonitrile; Flow rate: 10 mL/min.

[0283] Analytical Data for Example 9: Non-Polar fraction: Yield: 9.9 mg, 2.42%. LC-MS (m/z) = 500.3[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.563 - 1.636 (m, 5 H), 1.785 - 1.99 (m, 8 H), 2.553 - 2.562 (m, 2 H), 2.607 - 2.681 (m, 1 H), 3.37 - 3.63 (m, 3 H), 4.013 - 4.091 (m, 2 H), 4.106 - 4.331 (m, 1 H), 7.152 - 7.311 (m, 5H), 7.753 (t, *J* = 15.6 Hz, 1 H), 7.947 - 7.928 (d, *J* = 7.6 Hz, 1 H), 8.189 (d, *J* = 7.6 Hz, 1 H), 8.23 (s, 1 H), 8.928 - 9.00 (m, 1 H). HPLC Purity: 99.9% (230 nm).

[0284] Analytical Data for Example 10: Polar fraction: Yield: 15.9 mg, 2.42%. LC-MS (ES) m/z = 500.3 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.536 - 1.627 (m, 5 H), 1.697 - 2.133 (m, 8 H), 2.541 - 2.554 (m, 2 H), 2.673 - 2.2.863 (m, 1 H), 3.408 - 3.658 (m, 2 H), 3.989 - 4.184 (m, 1 H), 4.309 - 4.323 (m, 1 H), 7.144 - 7.303 (m, 5 H), 7.745 (t, J = 17.6 Hz,1 H), 7.921 (d, *J* = 8 Hz, 1 H), 8.171 - 8.221 (m, 2 H), 8.904 - 9.004 (m, 1 H). HPLC Purity: 99.9% (230 nm).

Procedure 17: Synthesis of Examples 21 and 22



[0285] Preparation of *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate: To a stirred solution of *tert*-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (300 mg, 1.41 mmol, 1 eq) in DMF (6 mL) were added 2-{[3-

(trifluoromethyl)phenyl]formamido}acetic acid (419 mg, 1.7 mmol, 1.2 eq), [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (1.07 g, 2.83 mmol, 2 eq), and ethylbis(propan-2-yl)amine (0.8 mL, 4.24 mmol, 3 eq) at 0°C. The reaction mixture was stirred at room temperature for 3 h and progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was poured into cold water (30 mL) and extracted with EtOAc (2 x 100 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield the crude, which was purified by combiflash (70% EtOAc in hexane) to afford *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (460 mg, 73.7%). LC-MS (m/z) = 442.2 $[M + H]^+$.

[0286] Preparation of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a solution *tert*-butyl 4-(2-{[3-(trifluoromethyl)phenyl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (520 mg, 1.18 mmol, 1eq) in DCM (8 mL) was added 4N HCl in 1,4-dioxane (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was evaporated to yield the crude and washed with the diethyl ether and *n*-pentane to afford N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (380 mg, 94.5%). LC-MS (m/z) = 342.2 $[M + H]^+$.

[0287] Preparation of N-(2-oxo-2-{4-[4-(pyridin-2-yloxy)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (21) and N-(2-oxo-2-{4-[4-(pyridin-2-yloxy)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (22): To a solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (280 mg, 0.820 mmol, 1 eq) in THF (5 mL) was added triethylamine (0.668 mL, 4.92 mmol, 6 eq). After stirring for 5 min, 4-phenylcyclohexan-1-one (143 mg, 0.820 mmol, 1eq) was added and the resulting mixture was stirred at room temperature for 30 min. Then sodium bis(acetyloxy)boranuidyl acetate (344 mg, 1.64 mmol, 2eq) was added. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to yield the crude which was purified with prep HPLC to afford N-(2-oxo-2-{4-[4-(pyridin-2-yloxy)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (11 mg, 7.27%) and N-(2-oxo-2-{4-[4-(pyridin-2-yloxy)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (12.8 mg, 7.93%).

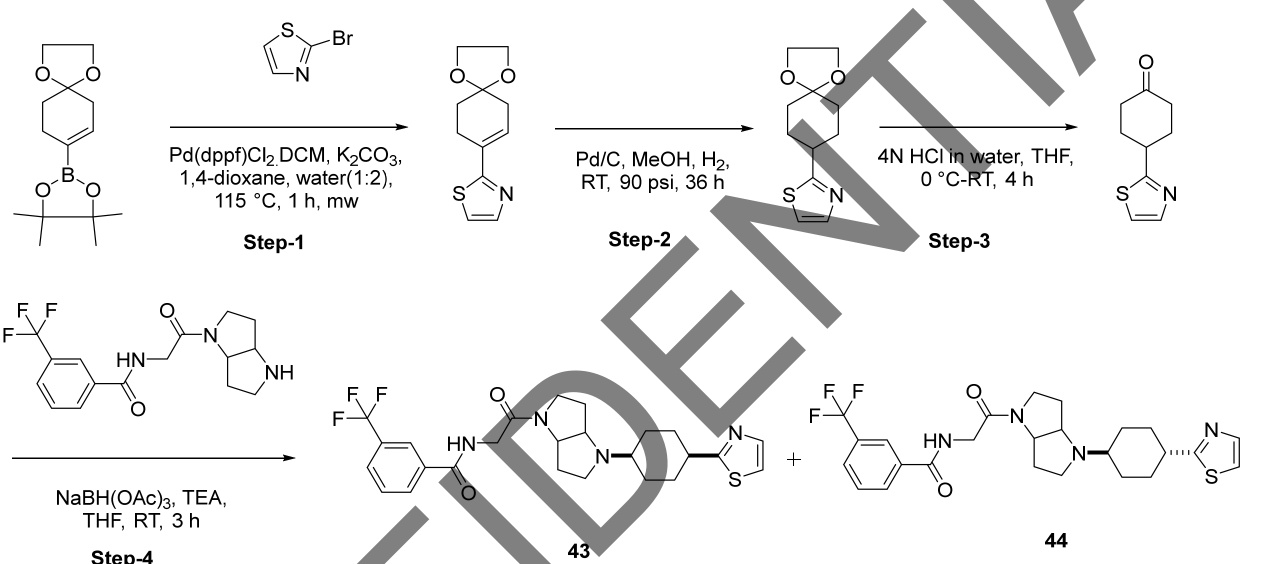
[0288] Prep HPLC Conditions: Column: Sunfire C18 (250 mm X 19 mm X 5 µm); Mobile phase(A):5 mM ammonium acetate in water; Mobile phase(B): Acetonitrile; Flow rate: 19 mL/min.

[0289] Analytical Data for Example 21: Non-Polar fraction: LC-MS (m/z) = 517.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.221 (s, 1 H), 1.630 (m, 6 H), 1.871 - 1.919 (m, 5 H), 2.122 (m, 1 H), 2.836 (m, 1 H), 3.400 (m, 1 H), 3.517 - 3.598 (m, 2 H), 3.959 - 4.00 (m, 1 H), 4.015 - 4.095 (m, 2 H), 4.121 - 4.132 (m, 1 H), 4.261 - 4.276 (m, 1 H), 5.134 (s, 1 H), 6.761 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 12 Hz, 1 H), 7.642 -

7.749 (m, 3 H), 7.915 (d, J = 8 Hz, 2 H), 8.115 - 8.204 (m, 3 H), 8.904 - 8.965 (m, 1 H). HPLC Purity: 99.6% (230 nm).

[0290] Analytical Data for Example 22: Polar fraction: LC-MS (m/z) = 517.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.316 - 1.627 (m, 6 H), 1.734 - 1.842 (m, 2 H), 1.864 - 1.954 (m, 3 H), 2.119 (m, 3 H), 2.854 - 2.973 (m, 1 H), 3.464 - 3.685 (m, 3 H), 3.951 - 4.163 (m, 2 H), 4.182 - 4.462 (m, 1 H), 4.916 - 4.925 (m, 1 H), 6.742 (d, J = 8.4 Hz, 1 H), 6.933 (t, J = 12 Hz, 1 H), 7.652 - 7.695 (m, 1 H), 7.750 (t, J = 15.6 Hz, 1 H), 7.935 (d, J = 7.6 Hz, 1 H), 8.14 - 8.226 (m, 3 H), 8.914 - 9.002 (m, 1 H). HPLC Purity: 99.7% (230 nm).

Procedure 18: Synthesis of Examples 43 and 44



[0291] Preparation of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-1,3-thiazole: To a stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 1.88 mmol, 1 eq) in 1,4-dioxane (10 mL) and water (3 mL) were added 2-bromo-1,3-thiazole (308 mg, 1.88 mmol, 1 eq) and potassium carbonate (779 mg, 5.64 mmol, 3 eq), and the reaction mixture was purging under N_2 atmosphere for 10 mins. Then Pd(dppf)Cl_2.DCM (153 mg, 0.188 mmol, 0.1 eq) was added portionwise, and reaction mixture was stirred at 115 °C for 1h under microwave irradiation. Progress of the reaction checked by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (3 mL), extracted with ethyl acetate (2 x 10 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified with flash column chromatography (50% EtOAc in hexane) to afford 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-1,3-thiazole (275 mg, 65.5%). LC-MS (m/z) = 224.1 [M + H]$^+$.

[0292] Preparation of 2-{1,4-dioxaspiro[4.5]decan-8-yl}-1,3-thiazole: To a stirred solution of 2-{1,4-dioxaspiro[4.5]dec-7-en-8-yl}-1,3-thiazole (200 mg, 0.896 mmol, 1 equiv) in MeOH (4 mL) was added Pd/C (50 mg) and the reaction mixture was stirred at room temperature for 36 h in H_2 atmosphere at 90 psi. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under vacuum to afford 2-{1,4-dioxaspiro[4.5]decan-8-yl}-1,3-thiazole (160 mg, 79.28%). LC-MS (m/z) = 226.1 $[M + H]^+$

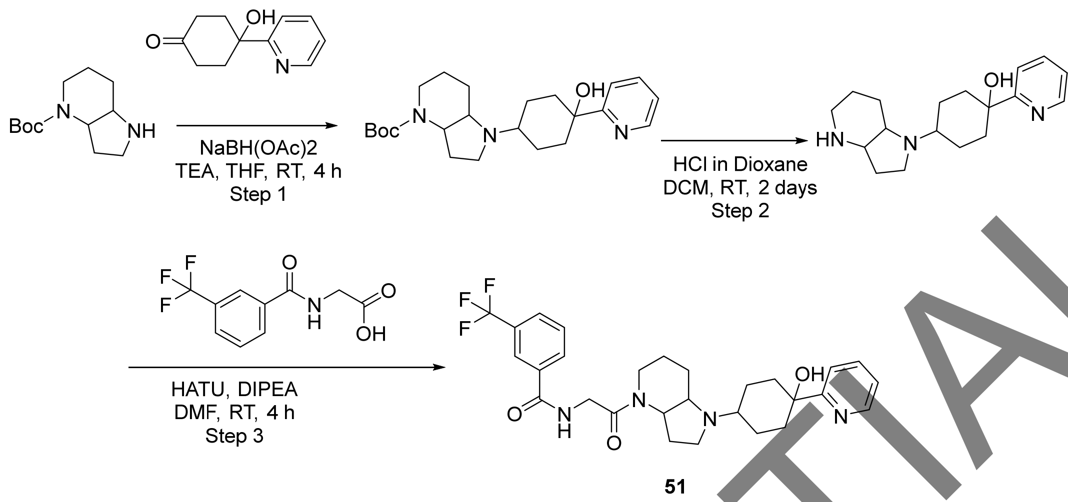
[0293] Preparation of 4-(1,3-thiazol-2-yl)cyclohexan-1-one: To a stirred solution of 2-{1,4-dioxaspiro[4.5]decan-8-yl}-1,3-thiazole (160 mg, 0.71 mmol, 1 eq) in THF (3 mL) was added 4N HCl in 1,4-dioxane (2.5 mL), and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was concentrated and neutralized with aqueous sodium bicarbonate and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude and purified with flash column chromatography (40% EtOAc in hexane) to afford 4-(1,3-thiazol-2-yl)cyclohexan-1-one (60 mg, 46.62%). LC-MS (m/z) = 182.1 $[M + H]^+$

[0294] Preparation of N-(2-oxo-2-{4-[4-(1,3-thiazol-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (43) and N-(2-oxo-2-{4-[4-(1,3-thiazol-2-yl)cyclohexyl]-octahydropyrrolo[3,2-b]pyrrol-1-yl}ethyl)-3-(trifluoromethyl)benzamide (44): To a solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (50 mg, 0.146 mmol, 1 eq) in THF (2 mL) was added triethylamine(0.119 mL, 0.879 mmol, 6 eq). After stirring for 5 min, 4-(1,3-thiazol-2-yl)cyclohexan-1-one (26.6 mg, 0.146 mmol, 1 eq) was added and the resulting mixture was stirred at room temperature for 30 min. Then sodium bis(acetyloxy)boranuidyl acetate (61.5 mg, 0.293 mmol, 2 eq) was added and the reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude which was purified with flash column chromatography (3% MeOH in EtOAc) to afford N-(2-oxo-2-(4-((1s,4s)-4-(thiazol-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (14 mg, 18.8%) and N-(2-oxo-2-(4-((1r,4r)-4-(thiazol-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide (7 mg, 12.13%).

[0295] Analytical Data for Example 43: (Non-Polar by TLC): LC-MS (m/z) = 507.3$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.974 - 8.918 (m, 1 H), 8.215 - 8.168 (m, 2 H), 7.932 (d, *J* = 7.6 Hz, 1 H), 7.767 - 7.728 (m, 2 H), 7.605 (s, 1 H), 4.31 (m, 1 H), 4.179 - 3.973 (m, 2 H), 3.585 (m, 3 H), 2.9 (m, 3 H), 2.076 (m, 4 H), 1.915 - 1.716 (m, 9 H). HPLC Purity: 99.6% (230 nm).

[0296] Analytical Data for Example 44: (Polar by TLC): LC-MS (ES) m/z = 507.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 8.963 - 8.906 (m, 1 H), 8.224 - 8.176 (m, 2 H), 7.936 (d, *J* = 7.6 Hz, 1 H), 7.772 - 7.707 (m, 2 H), 7.575 (s, 1 H), 4.465 - 4.282 (m, 1 H), 4.2 - 4.109 (m, 3 H), 3.642 - 3.407 (m, 2 H), 2.968 - 2.889 (m, 3 H), 2.339 - 2.33 (m, 4 H), 2.289 - 1.735 (m, 4 H), 1.591 - 1.184 (m, 5 H). HPLC Purity: 99.7% (230 nm).

Procedure 19: Synthesis of Example 51



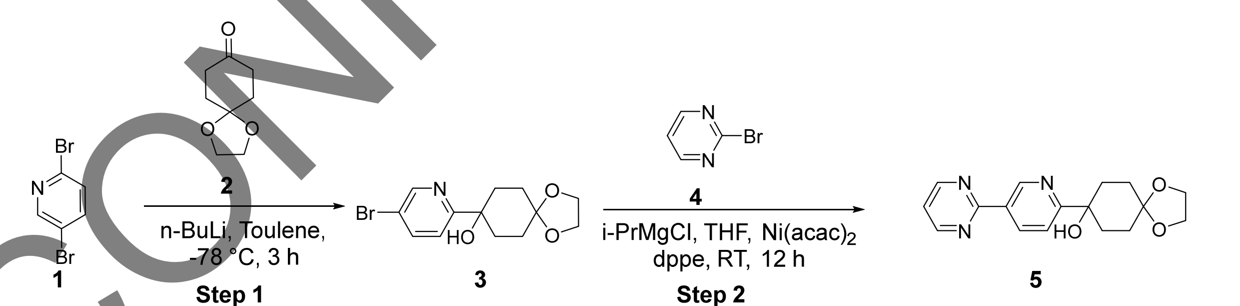
[0297] Preparation of *tert*-butyl 1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate: To a stirred solution of 4-hydroxy-4-(pyridin-2-yl)cyclohexan-1-one (127 mg, 0.663 mmol) in THF (10 mL, 123 mmol), *tert*-butyl octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (150 mg, 0.663 mmol) and triethylamine (0.559 mL, 6 eq, 3.98 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, then sodium bis(acetyloxy)boranuidyl acetate (281 mg, 2 eq, 1.33 mmol) was added and stirred at room temperature for 12 h. Progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, quenched with aqueous $NaHCO_3$ (10 mL), extracted with DCM (2 x 20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude *tert*-butyl 1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (210 mg) which was used in the next step without any further purification. LC-MS (m/z) = 402.6 $[M+H]^+$

[0298] Preparation of 4-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-1-(pyridin-2-yl)cyclohexan-1-ol: To a cooled, stirred solution of *tert*-butyl 1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridine-4-carboxylate (210 mg, 523 µmol) in DCM (10 mL, 156 mmol), 4N HCl in 1,4-dioxane (2 mL) was added and the reaction mixture was stirred at room temperature for 20 h. At 50% conversion, the reaction mixture was evaporated to yield the crude to which HCl in dioxane (2 mL) was added and the reaction mixture was stirred at room temperature for another 20 h. Progress of the reaction mixture was checked by TLC monitoring, and after completion of the reaction, the mixture was evaporated under reduced pressure and extracted with DCM (2 x 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, 4-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-1-(pyridin-2-yl)cyclohexan-1-ol (150 mg, 95.15%). LC-MS (m/z) = 302.3 $[M+H]^+$

[0299] Preparation of N-(2-{1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridin-4-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide: To a stirred solution of 2-{[3-(trifluoromethyl)phenyl]formamido}acetic acid (99.2 mg, 1.1 eq, 0.401 mmol) in DMF (2 mL) were added [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium;hexafluoro-λ^5-phosphanuide (278 mg, 2 eq., 0.730 mmol), ethylbis(propan-2-yl)amine (195 µL, 3 eq., 1.09 mmol), and 4-{octahydro-1H-pyrrolo[3,2-b]pyridin-1-yl}-1-(pyridin-2-yl)cyclohexan-1-ol (110 mg, 0.365 mmol) at 0°C. The reaction mixture was stirred at room temperature for 3 h and the progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was poured into cold water (10 mL) and extracted with EtOAC (2 x 20 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude, which was purified by flash column chromatography using 12% methanolic ammonia in DCM as eluent to afford the diastereomeric mixture of compound (50 mg) with a polar impurity. The compound was repurified by prep TLC using 5% methanolic ammonia in DCM to afford N-(2-{1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridin-4-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (5 mg) as a mixture of diastereomers.

[0300] N-(2-{1-[4-hydroxy-4-(pyridin-2-yl)cyclohexyl]-octahydro-1H-pyrrolo[3,2-b]pyridin-4-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (51): Yield: 5 mg, 2.84%. LC-MS (m/z) = 531.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm : 8.88 (m, 1H), 8.49-8.48 (m, 1H), 8.22 (s, 1H), 8.19-8.17 (m, 1H), 7.94-7.92(m, 1H), 7.77-7.73 (m, 2H), 7.68-7.66 (m, 1H), 7.23-7.21 (m, 1H), 4.97 (s, 1H), 4.34-4.05 (m, 3H), 3.70 (m, 1H), 3.35-2.68 (m, 6H), 2.18-1.91(m, 3H), 1.80-1.59 (m, 7H), 1.41-1.24 (m, 7H). HPLC Purity: 99.59% (230 nm).

Procedure 20: Synthetic of 4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexan-1-one



Step-1: 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0301] To a solution of 2,5-dibromopyridine (40 g, 168.8 mmol, 1 *eq*) in anhydrous toluene (300 mL) at -78 °C, *n*-BuLi (1.6 M, 126.4 mL, 202.8 mmol, 1.2 *eq*) was added dropwise. After being stirred at -78 °C for 2.5 h, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (26.4 g, 168.8 mmol, 1 *eq*) in toluene (40 mL) was added to the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. After completion of the reaction, the reaction mixture was poured into aqueous $NaHCO_3$ (400 mL) and extracted with EtOAc (600 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum at rotavapor. The resulting solid was purified by using combiflash using eluent of 0-15 % ethyl acetate/*n*-hexane to afford 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (34.3 g, 64%).

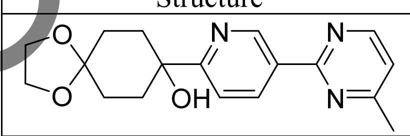
[0302] LCMS (ES) m/z: 316.1 $[M+H]^+$

Step-2: 8-(5-(pyrimidin-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

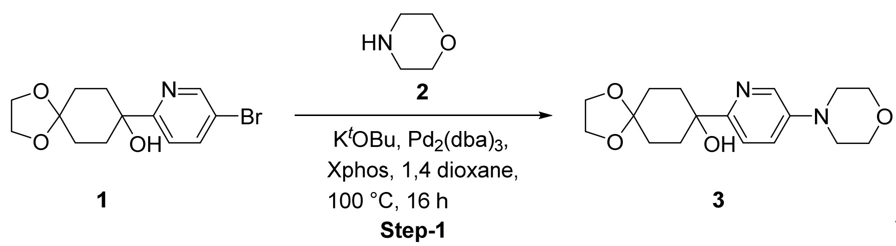
[0303] To a degassed (with Ar) solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (3) (34.3 g, 109 mmol , 1 *eq*) in THF (300 mL), 2.0 M isopropylmagnesium bromide in THF (218 mL, 437 mmol , 4 eq) was added dropwise over 15 min. Reaction mixture was allowed to stir for 3 h at room temperature. In another flask (RBF 2) was charged THF (60 mL) and to it nickel(II) acetylacetonate (1.98 g, 7.64 mmol, 0.07 *eq*) and 1,2-bis(diphenylphosphino)ethane (3.04 g, 7.64 mmol, 0.07 eq) were added and stirred for 15 min. To this mixture (RBF 2), 2-bromopyrimidine (24.3 g, 153 mmol, 1.4 eq) was added and stirred for 30 min. The above suspension (in RBF 2) was transferred to the solution in RBF1 at room temperature and the reaction mixture was stirred for another 12 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (600 mL), extracted with ethyl acetate (2 x 400 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated at rotavapor under reduced pressure to yield the crude product. The crude was further purified using flash HPLC using (4: 6) EA:hexane as mobile phase to afford the title compound (10 g, 29%). LCMS (ES) m/z: 314.2 $[M+H]^+$

[0304] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 - 1.65 (m, 4 H), 1.91 - 1.98 (m, 2 H), 2.22 - 2.29 (m, 2 H), 3.82 - 3.84 (m, 1 H), 3.88 - 3.90 (m, 4 H), 7.49 - 7.51 (m, 1 H), 7.83 - 7.85 (m, 1 H), 8.64 - 8.67 (m, 1 H), 8.94 - 8.96 (m, 2 H), 9.42 - 9.43 (m, 1 H).

[0305] The following compound was synthesized using general procedure of Step-2 of Procedure 20.

Structure	LCMS (ES) m/z
	328.2 $[M+H]^+$

Procedure 21: Synthesis of 8-(5-morpholinopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



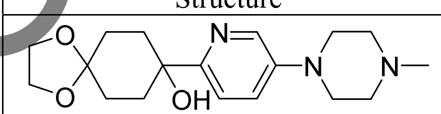
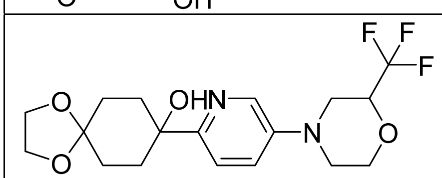
Step-1: 8-(5-morpholinopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0306] To a solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 1.59 mmol), morpholine (180 mg, 1.3 eq, 2.07 mmol) in 1,4-dioxane (8 mL) was added potassium 2-methylpropan-2-olate (357 mg, 2 eq, 3.18 mmol) and purged with Ar for 10 min, followed by the addition of (2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl) (152 mg, 0.2 eq, 318 µmol) and tris(dibenzylideneacetone)dipalladium(0) (146 mg, 0.1 eq, 159 µmol). The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (15 mL), extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. The crude material was purified by ethyl acetate in *n*-heptane as an eluent to afford 8-(5-morpholinopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.2 g, 39%).

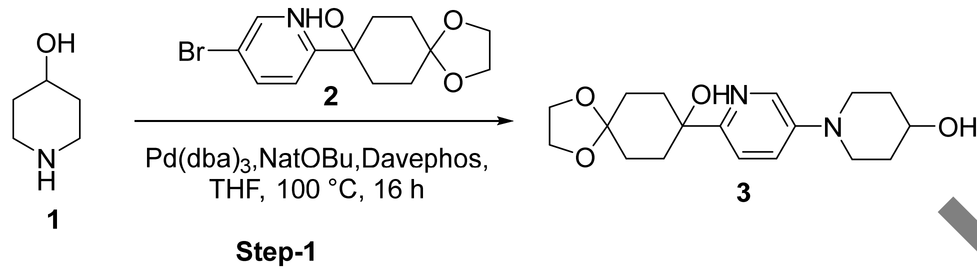
[0307] LCMS (ES) m/z: 321.2 $[M+H]^+$

[0308] 1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.8 Hz, 1H), 7.29-7.27 (m, 1H), 7.21 (dd, *J* = 2.4 Hz, *J* = 2.4 Hz, 1H), 4.96 (s, 1H), 4.00-3.98 (m, 4H), 3.88-3.81 (m, 4H), 3.18-3.16 (m, 4H), 2.21-2.0 (m, 4H), 1.70 (t, *J* = 11.2 Hz, 4H).

[0309] The following compounds were synthesized using Procedure 21.

Structure	LCMS (ES) m/z
	334.3 $[M+H]^+$
	389.2 $[M+H]^+$

Procedure 22: Synthesis of 8-(5-morpholinopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

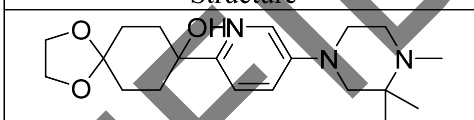
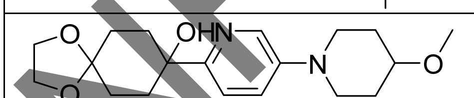


Step 1: Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidin-4-ol

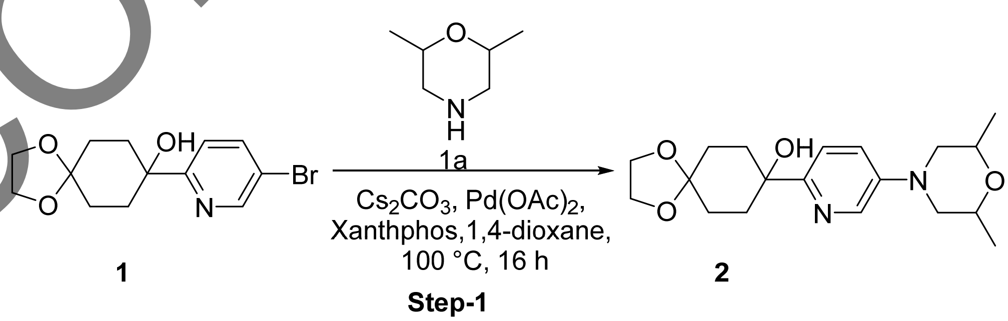
[0310] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.1 g, 3.46 mmol, 1 eq) in THF (12 mL) were added sodium 2-methylpropan-2-olate (665 mg, 6.92 mmol, 3 eq) and piperidin-4-ol (350 mg, 3.46 mmol, 1 eq). The reaction mixture was purged with N_2 for 15 min, then Davephos (410 mg, 1.04 mmol, 0.2 eq) and $Pd_2(dba)_3$ (634 mg, 0.692 mmol, 0.1 eq) were added and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (2 x 5 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude (210 mg, 14%).

[0311] LCMS (ES) m/z: 335.1

[0312] Following compounds were synthesized using Procedure 22.

Structure	LCMS (ES) m/z
	362.1 $[M+H]^+$
	349.1 $[M+H]^+$

Procedure 23: Synthesis of 8-(5-(2,6-dimethylmorpholino)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

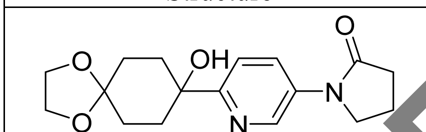
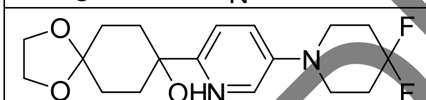
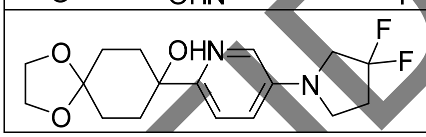


Step 1: Preparation of 8-[5-(2,6-dimethylmorpholin-4-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

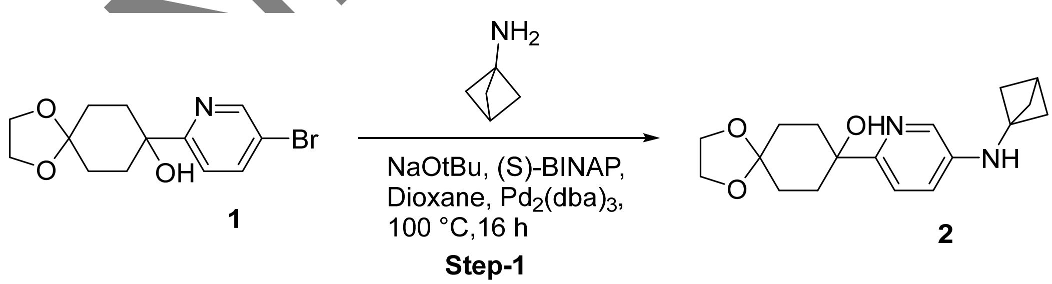
[0313] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 1.59 mmol, 1 eq) in 1,4- dioxane (10 mL) were added 2,6-dimethylmorpholine (0.275 g, 2.39 mmol, 1.5 eq) and cesium carbonate (1.56 g, 4.77 mmol, 3 eq). The reaction mixture was purged with Ar for 5 minutes, then [5-(diphenylphosphanyl)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphane (0.138 g, 0.239 mmol, 0.15 eq) and palladium(2+) diacetate (0.036 g, 0.159 mmol, 0.1 eq) were added portionwise under Ar atmosphere. The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was diluted with water (25 mL) and extracted by using ethyl acetate (25 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to yield the crude compound, which was purified by flash column chromatography by using 0-30 % ethyl acetate in hexane as eluent to afford 8-[5-(2,6-dimethylmorpholin-4-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.2 g, 36%).

[0314] LCMS (ES) m/z: 349.3 $[M+H]^+$

[0315] Following compounds were synthesized using Procedure 23.

Structure	LCMS (ESI) m/z
	319.1 $[M+H]^+$
	355.2 $[M+H]^+$
	341.4 $[M+H]^+$

Procedure 24: Synthesis of 8-(5-(bicyclo[1.1.1]pentan-1-ylamino)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



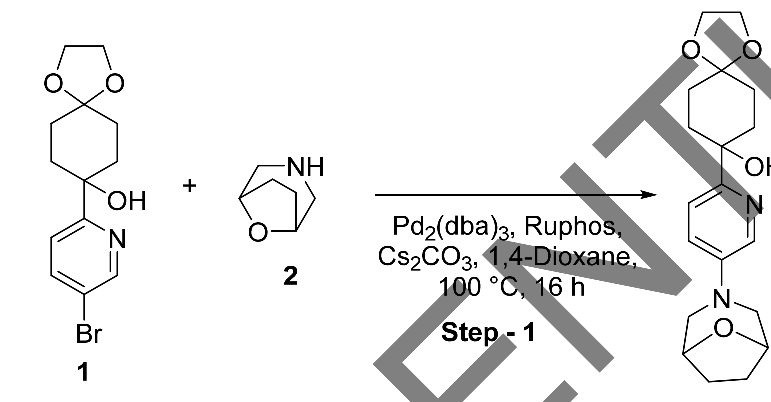
Step 1: 8-[5-({bicyclo[1.1.1]pentan-1-yl}amino)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0316] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2 g, 6.37 mmol) and bicyclo[1.1.1]pentan-1-amine (635 mg, 6.37 mmol) in dioxane (15 mL), NaOtBu (1.84 g, 6.37 mmol) and (S)-BINAP (793 mg, 6.37 mmol) were added. The reaction mixture was purged with Ar for 10 min, followed by the addition of tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (583 mg, 6.37 mmol). The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC and

LCMS. After completion of the reaction, the reaction mixture was quenched with water (25 mL), extracted with ethyl acetate (2 x 100 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude. The crude material was purified by flash column chromatography using 40% EtOAc:hexane to afford the title compound (620 mg, 31%).

[0317] LCMS (ES) m/z: 317.2 $[M+H]^+$

Procedure 25: Synthesis of 8-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

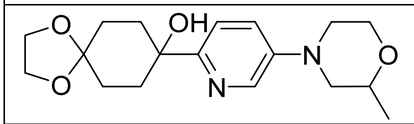


Step 1: Preparation of 8-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

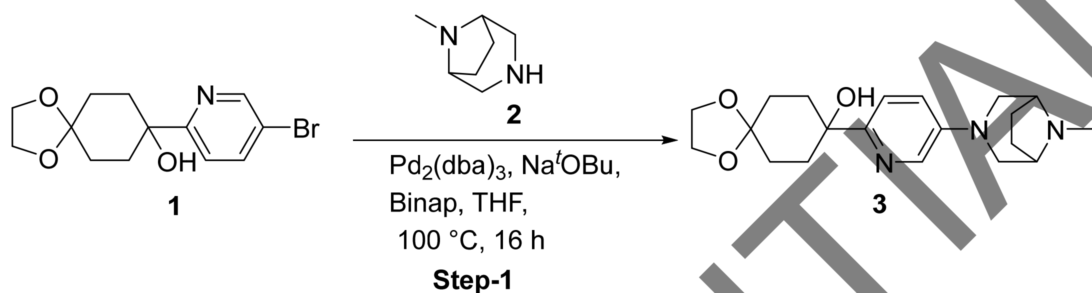
[0318] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (150 mg, 0.8 eq, 477 µmol) and 8-oxa-3-azabicyclo[3.2.1]octane (81 mg, 1.2 eq, 716 µmol) in 1,4-dioxane (15.1 mL, 178 mmol) were added Ruphos (27.8 mg, 0.1 eq, 59.7 µmol) and cesium carbonate (583 mg, 3 eq, 1.79 mmol) portionwise and the reaction mixture was purged with Ar for 5 minutes. Then tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one palladium (24.1 mg, 0.05 eq., 29.8 µmol) was added portionwise under N_2 atmosphere, and the reaction mixture was stirred at 100 °C for 16 h. The reaction progress was checked by TLC monitoring. After completion of the reaction, the mixture was quenched with water (5 mL), extracted with ethyl acetate (2 x 15 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude. The crude was purified by flash column chromatography using 60% EA/heptane to afford 8-(5-{8-oxa-3-azabicyclo[3.2.1]octan-3-yl}pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (120 mg, 58%).

[0319] LCMS (ES) m/z: 347.2 $[M+H]^+$

[0320] The following compound was synthesized using Procedure 25.

Structure	LCMS (ES) m/z
	335.2 [M+H]$^+$

Procedure 26: Synthesis of 8-(5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

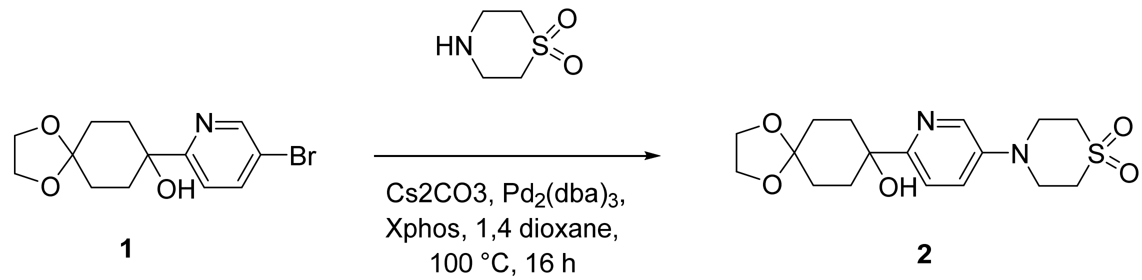


Step-1: 8-(5-{8-methyl-3,8-diazabicyclo [3.2.1] octan-3-yl}pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0321] To a solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.1 g, 0.8 eq., 318 µmol) in THF (5 mL, 61.4 mmol), sodium 2-methylpropan-2-olate (115 mg, 3 eq., 1.19 mmol), 8-methyl-3,8-diazabicyclo[3.2.1]octane (55.2 mg, 1.1 eq., 438 µmol), and [2'-(diphenylphosphanyl)-[1,1'-binaphthalen]-2-yl]diphenylphosphane (124 mg, 0.5 eq., 199 µmol) were added. The reaction mixture was purged with Ar for 10 min, then tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (36.4 mg, 0.1 eq., 39.8 µmol) was added to mixture and purged with Ar for 5 min. The reaction mixture was stirred at 100 °C for 1 h. After completion of the reaction, the mixture was cooled and quenched with water (15 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by MPLC using methanol in DCM (0% - 20%) as eluent which effort 8-(5-{8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl}pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (20 mg, 14% yield).

[0322] LCMS (ES) m/z: 360.3 [M+H]$^+$

Procedure 27: Synthesis of 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)thiomorpholine 1,1-dioxide



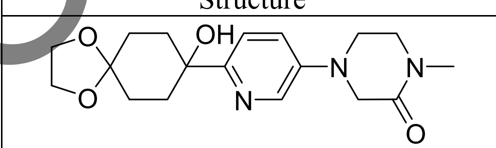
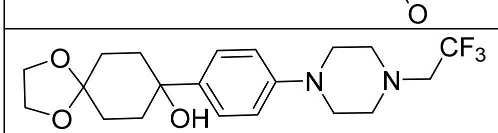
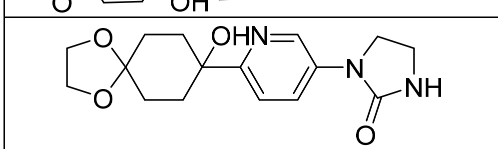
Step-1

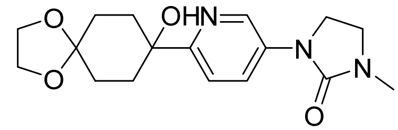
Step-1: Synthesis of 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)thiomorpholine 1,1-dioxide

[0323] To a solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1 g, 3.18 mmol), 1λ⁶-thiomorpholine-1,1-dione (559 mg, 1.3 eq., 4.14 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate (3.11 g, 3 eq., 9.55 mmol). The reaction mixture was purged with Ar for 10 min, followed by the addition of dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (303 mg, 0.2 eq., 637 μmol) and tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (291 mg, 0.1 eq., 318 μmol). The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (30 mL), extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude compound. The crude was purified by flash column MPLC using 5% MeOH in DCM as eluent to afford 4-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-1λ⁶-thiomorpholine-1,1-dione (0.85 g, Yield: 72%).

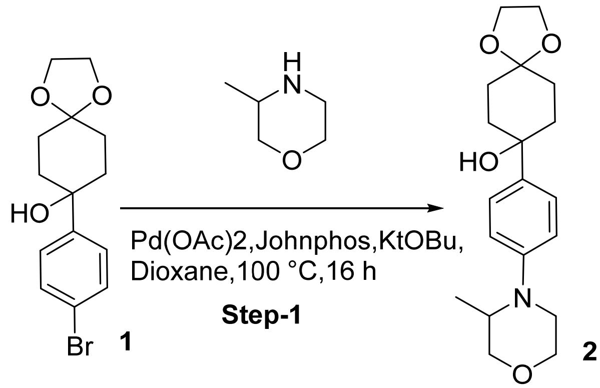
[0324] LCMS (ES) m/z: 369.2 $[M+H]^+$

[0325] The following compounds were synthesized using Procedure 27.

Structure	LCMS (ES) m/z
	348.2 $[M+H]^+$
	402.1 $[M+H]^+$
	320.1 $[M+H]^+$

Structure	LCMS (ES) m/z
	334.1 $[M+H]^+$

Procedure 28: Synthesis of 8-(4-(3-methylmorpholino)phenyl)-1,4-dioxaspiro[4.5]decan-8-ol

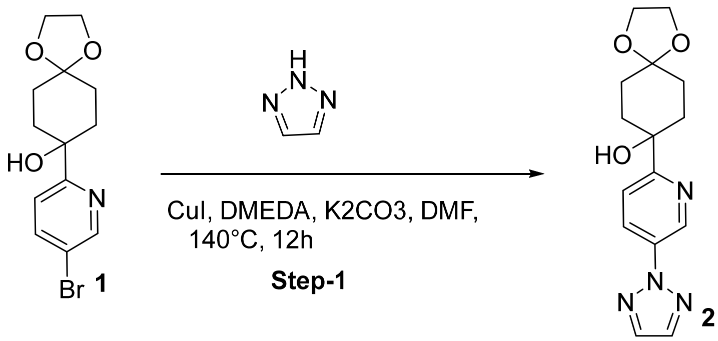


Step-1: Preparation of 8-(4-(3-methylmorpholino)phenyl)-1,4-dioxaspiro[4.5]decan-8-ol

[0326] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.9 g, 2.86 mmol) were added 3-methylmorpholine (7.08 mg, 1.1 eq., 70 µmol, 1,4-dioxane (10 mL) in 1,4-dioxane (10 mL) and Johnphos (85.5 mg, 0.1 eq., 286 µmol) was added KtOBu (964 mg, 3 eq., 8.59 mmol) portion wise under nitrogen condition, reaction mixture was purged with argon for 5 minutes, after that Pd(OAc)2 (64.3 mg, 0.1 eq., 286 µmol) added portion wise under nitrogen atmosphere, reaction mixture was stirred at 100 °C for 16 h, reaction progress was checked by TLC monitoring, after completion of the reaction, reaction mixture was quenched with water (5 mL) extracted with ethyl acetate (2 x 50 mL), combined organic layer were dried with anhydrous Na2SO4, filtered and concentrated under reduced pressure to get the crude which was purified by combiflash using 80% EA/Heptane to afford 8-[5-(3-methylmorpholin-4-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.1 g, 10 %).

[0327] LCMS (ES) m/z: 335.2 $[M+H]^+$

Procedure 29: Synthesis of 8-[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

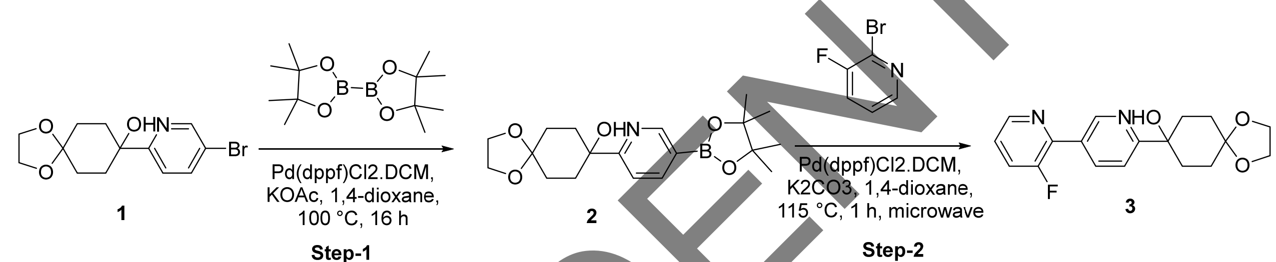


Step-1: 8-[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0328] To a stirred solution of 2H-1,2,3-triazole (87.9 mg, 1.27 mmol) in DMF (10 mL) were added CuI (24.2 mg, 0.1 eq., 127 µmol), DMEDA (554 µL, 4 eq., 5.09 mmol), K_2CO_3 (352 mg, 2 eq., 2.55 mmol), and 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.4 g, 1.27 mmol). The reaction mixture was stirred at 140 °C for 12 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (2 x 100 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to yield the crude which was purified using 30% EA/heptane to afford 8-[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (360 mg, 88%).

[0329] LCMS (ES) m/z: 303.1[M+H]$^+$

Procedure 30: Synthesis of 8-(3-fluoro-[2,3'-bipyridin]-6'-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step-1: Synthesis of 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0330] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.6 g, 1.91 mmol) in 1,4-dioxane (6 mL) were added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (582 mg, 1.2 eq., 2.29 mmol) and potassium acetate (562 mg, 3 eq., 5.73 mmol). The reaction mixture was purged with N_2 atmosphere for 10 mins, then 1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (156 mg, 0.1 eq., 191 µmol) was added and the reaction mixture was stirred at 100 °C for 16 h. After completion of the reaction, reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol as a crude product (0.5 g, crude).

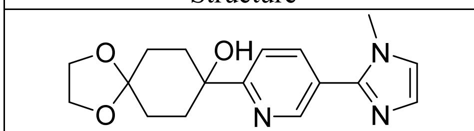
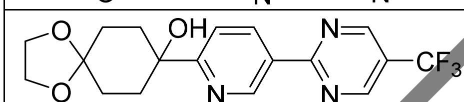
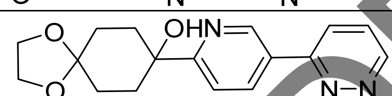
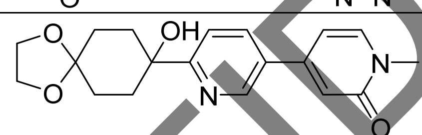
[0331] LCMS (ES) m/z: 280.1 [M+H]$^+$ (boronic acid mass)

Step-2: Synthesis of 8-{3-fluoro-[2,3'-bipyridin]-6'-yl}-1,4-dioxaspiro[4.5]decan-8-ol

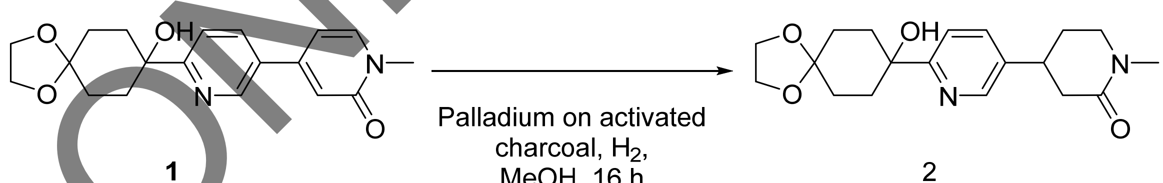
[0332] To a stirred solution of 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.6 g, 1.66 mmol, 1 eq) in 1,4-dioxane(6 mL) and water (3 mL) were added 2-bromo-3-fluoropyridine (292 mg, 1.66 mmol, 1 eq) and potassium carbonate (689 mg, 4.98 mmol, 3 eq). The reaction mixture was purged under N_2 atmosphere for 10 mins, then Pd(dppf)Cl_2.DCM (68 mg, 0.083 mmol, 0.05 eq) was added portionwise, and the reaction mixture was stirred at 115 °C for 1 h under microwave irradiation. After completion of the reaction, the reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (2 x 30 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude which was purified by flash column chromatography (50% EtOAc in hexane) to afford 8-{3-fluoro-[2,3'-bipyridin]-6'-yl}-1,4-dioxaspiro[4.5]decan-8-ol (350 mg, 20% yield).

[0333] LCMS (ES) m/z: 331.1 $[M+H]^+$

[0334] The following compounds were synthesized using Procedure 30.

Structure	LCMS (ES) m/z
	316.2 $[M+H]^+$
	382.0 $[M+H]^+$
	314.2 $[M+H]^+$
	343.1 $[M+H]^+$

Procedure 31: Synthesis of 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methylpiperidin-2-one



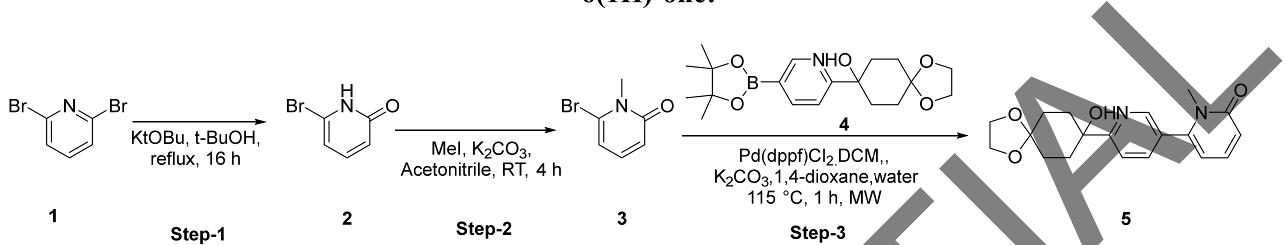
Step-1

Step-1: Preparation of 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-1-methylpiperidin-2-one

[0335] To a stirred solution of 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1'-methyl-1',2'-dihydro-[3,4'-bipyridin]-2'-one (0.3 g, 0.87 mmol, 1 eq) in methanol (4 mL) was added palladium on carbon (0.18 g, 1.75 mmol, 2 eq) and allowed to stir at room temperature for 16 h under hydrogen atmosphere. The reaction mixture was filtered through a celite bed and washed with methanol. The methanol was concentrated *in* *vacuo* to yield the crude 4-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-1-methylpiperidin-2-one (0.25 g, 82% yield).

[0336] LCMS (ES) m/z: 347.2 $[M+H]^+$

Procedure 32: Synthesis of 6'-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-1-methyl-[2,3'-bipyridin]-6(1H)-one:



Step-1: Synthesis of 6-bromo-1,2-dihydropyridin-2-one

[0337] To a stirred solution of 2,6-dibromopyridine (2 g, 8.44 mmol, 1 eq) were added potassium *t*-butoxide (7.6 g, 67.5 mol, 8 eq) and *t*-butyl alcohol (30 mL) and the reaction mixture was refluxed overnight. After cooling, the solvent was removed in vacuo, ice/water was carefully added, and the aqueous layer was extracted with chloroform (50 mL×2) to remove the unreacted staring material. The aqueous layer was acidified with 3 N HCl, extracted with chloroform (50 mL×2), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford crude 6-bromo-2-pyridone (110 mg, 4% yield).

[0338] LCMS (ES) m/z: 176.0 $[M+H]^+$

Step-2: Synthesis of 6-bromo-1-methyl-1,2-dihydropyridin-2-one

[0339] To a mixture of 6-bromo-1H-pyridin-2-one (1.8 g, 10.3 mmol, 1 eq) and K_2CO_3 (2.86 g, 20.7 mmol, 2 eq) in acetonitrile (25 mL) was added iodomethane (1.3 mL, 20.7 mmol, 2 eq). The mixture was stirred overnight. The mixture was then filtered. The filtrate was concentrated and purified by flash column chromatography (50% ethyl acetate in hexane) to afford 6-bromo-1-methyl-pyridin-2-one (1.4 mg, 70% yield).

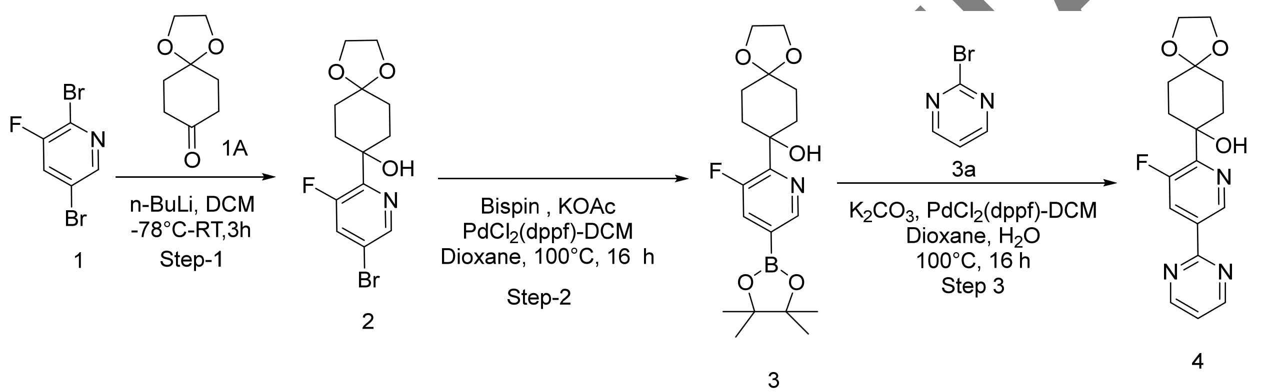
[0340] LCMS (ES) m/z: 190.2 $[M+H]^+$

Step-3: Synthesis of 6'-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1-methyl-1,6-dihydro-[2,3'-bipyridin]-6-one

[0341] To a stirred solution of 6'-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1-methyl-1,6-dihydro-[2,3'-bipyridin]-6-one (0.7 g, 1.94 mmol, 1 eq) in 1,4-dioxane (8 mL) and water (4 mL) were added 6-bromo-1-methyl-1,2-dihydropyridin-2-one (364 mg, 1.94 mmol, 1 eq) and potassium carbonate (803 mg, 5.81 mmol, 3 eq). The reaction mixture was purged under N_2 atmosphere for 10 mins, then Pd(dppf)Cl_2.DCM (80 mg, 0.096 mmol, 0.05 eq) was added portionwise, and the reaction mixture was stirred at 115 °C for 1h under microwave irradiation. After completion of the reaction, the reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (2 x 5 mL), and the combined organic layer were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude which was purified by column chromatography (0-5% MeOH in DCM) to afford 6'-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1-methyl-1,6-dihydro-[2,3'-bipyridin]-6-one (0.6 g, 76% yield).

[0342] LCMS (ES) m/z: 343.2 $[M+H]^+$

Procedure 33: Synthesis of 8-(3-fluoro-5-(pyrimidin-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step-1: 8-(5-bromo-3-fluoropyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0343] To a solution of 2,5-dibromo-3-fluoropyridine (0.6 g, 2.35 mmol) in DCM (15 mL) at -78 °C, 1.6 M *n*-butyl lithium (2.94 mL) in hexane was added dropwise. After being stirred at -78 °C for 15 min, 1,4-dioxaspiro[4.5]decan-8-one (368 mg, 2.35 mmol) in DCM (5 mL) was added to the reaction mixture. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was poured into aqueous NH_4Cl (15 mL) and extracted with DCM (30 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuum at high pressure to yield the crude, which was purified by flash column chromatography using 60% EA/heptane as eluent to afford 8-(5-bromo-3-fluoropyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (410 mg, 52%).

[0344] LCMS (ES) m/z: 333.4 $[M+H]^+$

Step-2: 8-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0345] To a stirred solution of 8-(5-bromo-3-fluoropyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.1 g, 301 µmol) in 1,4-dioxane (5 mL, 58.6 mmol) was added Bispin (115 mg, 1.5 eq., 452 µmol) followed by potassium acetate (88.6 mg, 3 eq., 903 µmol). The reaction mixture was purged with Ar atmosphere for 10 mins, then 1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium I) (22.0 mg, 0.1 eq., 30.1 µmol) was added and the reaction mixture was stirred at 100 °C for 16 h. After completion of the reaction, the reaction mixture was filtered through a celite pad and washed with ethyl acetate (10 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude 8-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (550 mg, crude).

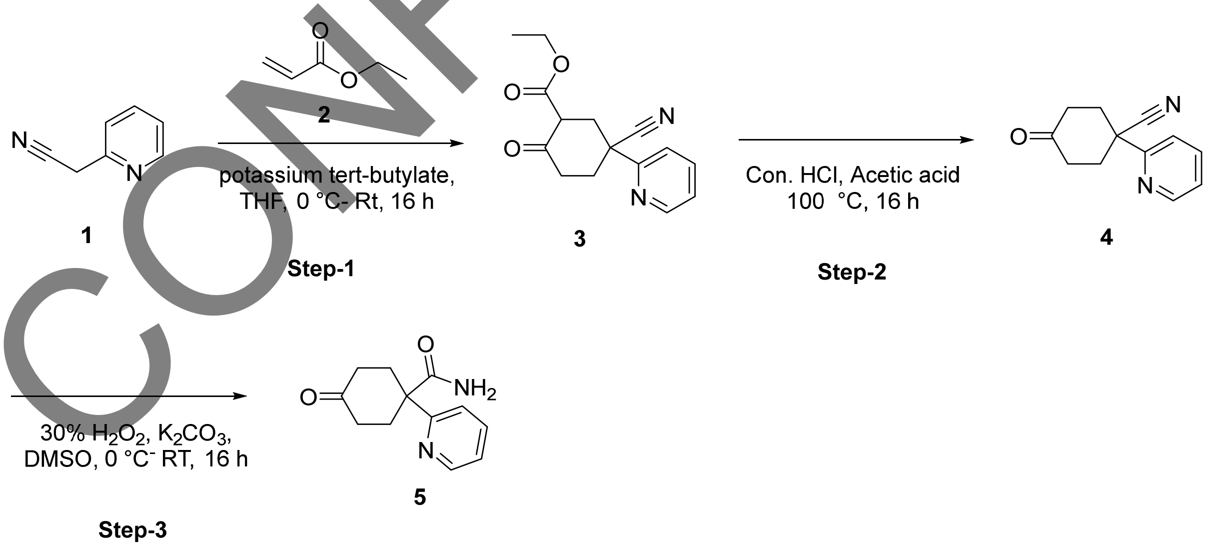
[0346] LCMS (ES) m/z: 298.1 $[M+H]^+$

Step-3: 8-[3-fluoro-5-(pyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0347] To a stirred solution of 8-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 1.32 mmol) and 2-bromopyrimidine (252 mg, 1.2 eq., 1.58 mmol) in 1,4-dioxane (10 mL) and water (5 mL) was added potassium carbonate (547 mg, 3 eq., 3.96 mmol). The reaction mixture was purged under Ar atmosphere for 10 mins, then $Pd(dppf)Cl_2$.DCM (53.8 mg, 0.05 eq., 65.9 µmol) was added portionwise, and the reaction mixture was stirred at 110 °C for 16 h in a sealed tube. After completion of the reaction, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (2 x 30 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude. The crude was purified by flash column chromatography using 60% EA/heptane as eluent to afford 8-[3-fluoro-5-(pyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.35 g, 80%)

[0348] LCMS (ES) m/z: 332.2 $[M+H]^+$

Procedure 34: Synthesis of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxamide:



Step-1: ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate

[0349] Potassium *tert*-butoxide (3.42 g, 1.2 eq., 30.5 mmol) was added to a solution of 2-(pyridin-2-yl)acetonitrile (3 g, 25.4 mmol) and ethyl prop-2-enoate (5.34 g, 2.1 eq., 53.3 mmol) in THF (30.0mL) at 0 °C, and stirred at room temperature for 16 h. Progress of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (2 x 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and distilled under reduced pressure to afford ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate (5.0 g, Yield: 72%).

[0350] LCMS (ES) m/z: 273.1 $[M+H]^+$

Step 2: 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile

[0351] A solution of ethyl 5-cyano-2-oxo-5-(pyridin-2-yl)cyclohexane-1-carboxylate (5 g, 0.97 eq., 18.4 mmol) was added to a mixture of HCl (17 mL) and acetic acid (50 mL) at 0 °C. The reaction mixture was heated at 100 °C for 16 h. Progress of the reaction was monitored by TLC. Once the reaction was complete, the volatiles were evaporated, and the residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and distilled under reduced pressure to afford 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile (2.0 g, 53%).

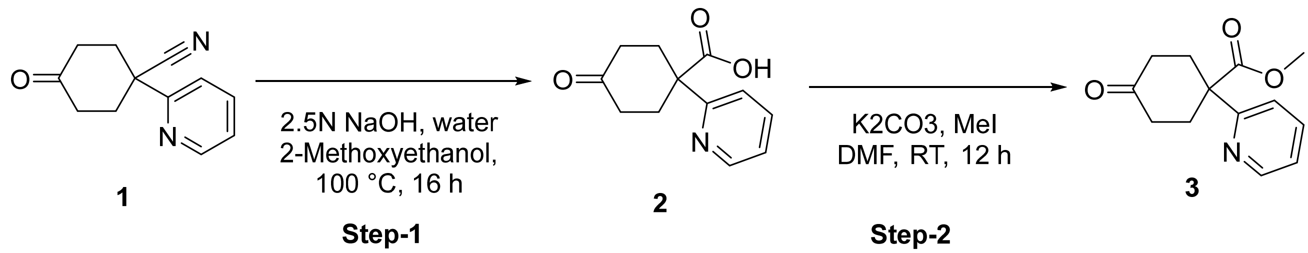
[0352] LCMS (ES) m/z: 201.1 $[M+H]^+$

Step 3: 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxamide

[0353] Potassium carbonate (2.48 g, 2 eq., 18 mmol) and 30% aqueous hydrogen peroxide (7.03 mL, 10 eq., 89.9 mmol) were added to a solution of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile (1.8 g, 8.99 mmol) in DMSO (15 mL) at 0 °C and stirred at room temperature for 16 h. Progress of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude compound which was further purified by flash column MPLC using 5% MeOH in DCM as eluent to afford 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxamide (250 mg, Yield: 13%).

[0354] LCMS (ES) m/z: 219.1 $[M+H]^+$

Procedure 35: Synthesis of methyl 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylate



Step 1: Synthesis of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylic acid

[0355] A mixture of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carbonitrile (480 mg, 2.4 mmol) in 2-methoxyethan-1-ol (7 mL) and sodium hydroxide (7 mL, 17.5 mmol) was heated at 100 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was acidified with concentrated HCl to pH = 2.0 and evaporated to dryness under vacuum to afford 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylic acid (2.5 g, crude).

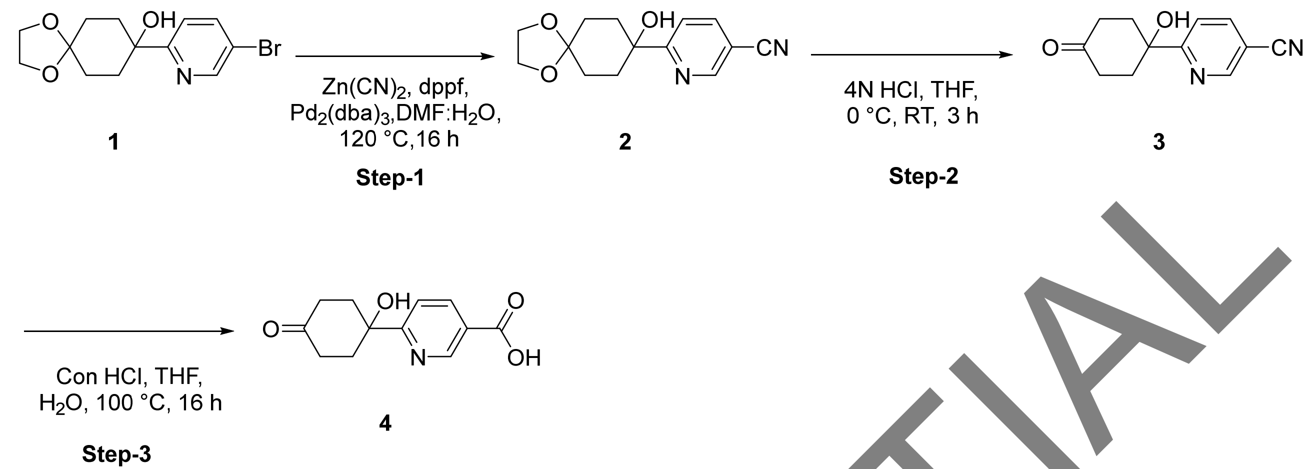
[0356] LCMS (ES) m/z: 220.0 $[M+H]^+$

Step 2: Synthesis of methyl 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylate

[0357] To a solution of 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylic acid (2.5 g, 11.4 mmol) in DMF (25 mL, 323 mmol) was added iodomethane (1.42 mL, 2 eq., 22.8 mmol) at room temperature followed by the addition of potassium carbonate (7.88 g, 5 eq., 57 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h and progress of the reaction was monitored by TLC and LCMS. Once the reaction was completed, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude compound, which was further purified by flash column MPLC chromatography using 5 % MeOH in DCM as eluent to afford methyl 4-oxo-1-(pyridin-2-yl)cyclohexane-1-carboxylate (230 mg, 9%).

[0358] LCMS (ES) m/z: 234.1 $[M+H]^+$

Procedure 36: Synthesis of 6-(1-hydroxy-4-oxocyclohexyl)nicotinic acid



Step1: Preparation of 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)nicotinonitrile

[0359] To a mixture of DMF:water (5:1, 6 mL) was added 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.2 g, mmol, 1 eq), zinc cyanide (0.04 g, 0.38 mmol, 0.6 eq), and I,Γ-bis(diphenylphosphino)ferrocene (0.03 g, 0.06 mmol, 0.1 eq), and the reaction mixture was degassed for 20 mins. To this was added tris(dibenzylideneacetone)dipalladium (0)(0.02 g, 0.03 mmol, 0.05 eq) and heated at 120 °C. After stirring for 16 h, the reaction mixture was cooled to room temperature. A saturated aqueous solution of ammonium chloride was added to the reaction mixture and extracted with EtOAc/heptane (2 x 50 mL). The combined organic layer was dried and concentrated to yield the crude, which was purified by flash column chromatography using 20% EtOAc/heptane as eluent to afford 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carbonitrile (0.13 g, 78% yield).

[0360] LCMS (ES) m/z: 261.1 $[M+H]^+$

Step-2: Preparation of 6-(1-hydroxy-4-oxocyclohexyl)nicotinonitrile

[0361] To a stirred solution of 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carbonitrile (0.13 g, 0.49 mmol, 1 eq) in THF (4 mL) was added 4N HCl in water dropwise while cooling, then the reaction mixture was stirred at room temperature for 2 h. The reaction progress was checked by TLC monitoring, and after completion of the reaction the reaction mixture was concentrated under reduced pressure to yield the aqueous residue. The obtained crude was basified with solid $NaHCO_3$ to pH 8~9, then the aqueous layer was extracted with ethyl acetate (2 x50 mL), and the combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 6-(1-hydroxy-4-oxocyclohexyl)pyridine-3-carbonitrile (0.09 g, 83% yield).

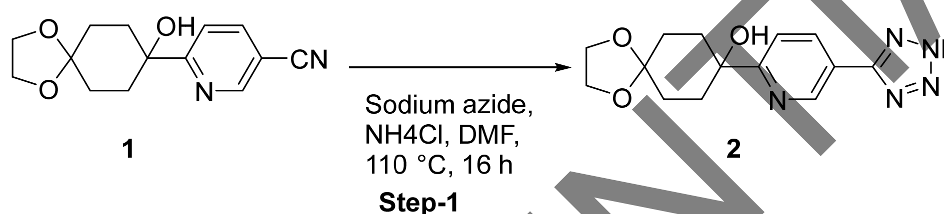
[0362] LCMS (ES) m/z: 217.1 $[M+H]^+$

Step 3: Preparation of 6-(1-hydroxy-4-oxocyclohexyl)pyridine-3-carboxylic acid

[0363] To a stirred solution of 6-(1-hydroxy-4-oxocyclohexyl)pyridine-3-carbonitrile (0.2 g, 0.92 mmol, 1 eq) in THF (5 mL) and water (6 mL) was added concentrated HCl (0.5 mL) dropwise while cooling, then the reaction mixture was stirred at 100 °C for 16 h. The reaction progress was checked by TLC monitoring, and after completion of the reaction, the reaction mass was concentrated under reduced pressure to afford 6-(1-hydroxy-4-oxocyclohexyl)pyridine-3-carboxylic acid (0.18 g, 82% yield).

[0364] LCMS (ES) m/z: **236.1** $[M+H]^+$

Procedure 37: Synthesis of 8-(5-(2H-tetrazol-5-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



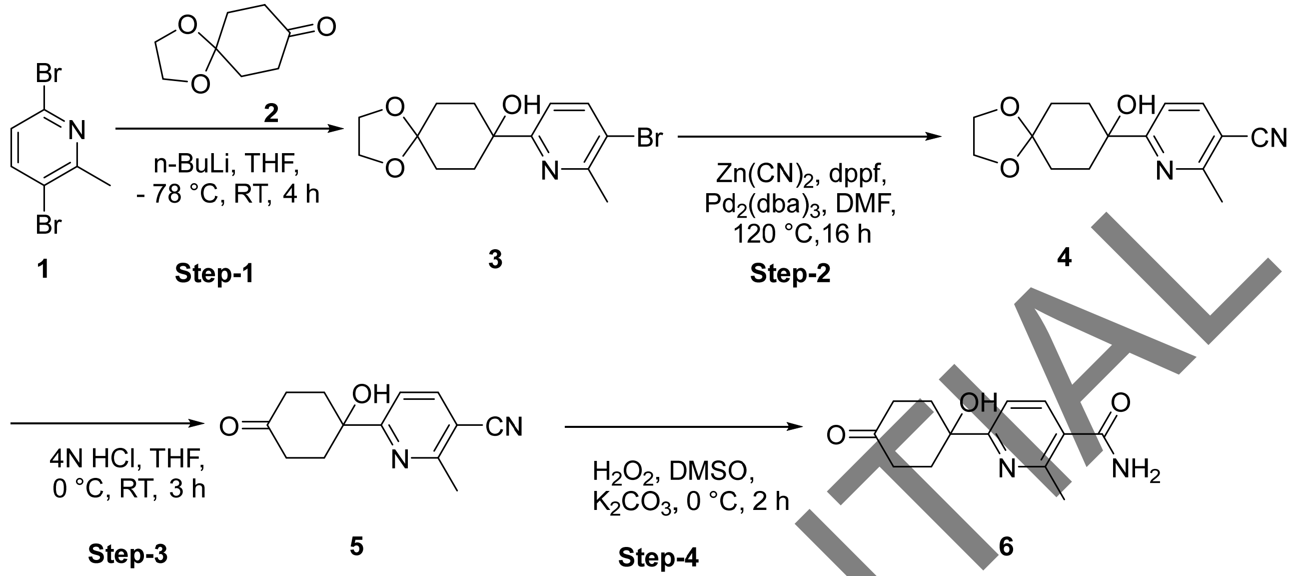
1 2

Step 1: Preparation of 8-(5-(2H-tetrazol-5-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0365] To a stirred solution of 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carbonitrile (0.13 g, 0.49 mmol, 1 eq) in DMF (5 mL) were added sodium azide (0.39 g, 5.99 mmol, 12 eq) and ammonium chloride (0.32 g, 5.99 mmol, 12 eq), and the reaction mixture was heated at 110 °C for 16 h. The reaction progress was checked by TLC monitoring, and after completion of the reaction, the mixture was quenched with water (5 mL), acidified with HCl, and extracted with 20% MeOH/DCM (2 x 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude 8-[5-(2H-1,2,3,4-tetrazol-5-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.2 g, 79% yield).

[0366] LCMS (ES) m/z: 304.0 $[M+H]^+$

Procedure 38: Synthesis of 6-(1-hydroxy-4-oxocyclohexyl)-2-methylnicotinamide



Step-1: Preparation of 8-(5-bromo-6-methylpyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0367] To a stirred solution of 3,6-dibromo-2-methylpyridine (1 g, 3.99 mmol, 1 eq) in 10 mL dry DCM at -40 °C, *n*-butyl lithium (10 mL, 16 mmol, 2 eq) was added. After stirring for 15 min, 1,4-dioxaspiro[4.5]decan-8-one (0.74 g, 4.78 mmol, 1.2 eq) in 2 mL DCM was added. The reaction was allowed to slowly warm to room temperature and stirred for 1 hour at room temperature. To quench the reaction, excess aqueous ammonium chloride was added. 5 mL ethyl acetate was added and the organic layer was washed with water, and the water layer was back extracted. The organic extractions were combined and dried with Na_2SO_4. The organics were concentrated to yield the crude product. The crude was purified by flash column chromatography using 25% EtOAc/heptane as eluent to afford 8-(5-bromo-6-methylpyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2 g, 91% yield).

[0368] LCMS (ES) m/z: 330.1 $[M+2]^+$

Step-2: Preparation of 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-2-methylnicotinonitrile

[0369] To a mixture of DMF:water (15:5 mL) was added 8-(5-bromo-6-methylpyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2 g, 6.09 mmol, 1 eq), zinc cyanide (0.42 g, 3.66 mmol, 0.6 eq), and I,Γ-bis(diphenylphosphino)ferrocene (0.33 g, 0.60 mmol, 0.1 eq) and degassed for 20 mins. To this was added tris(dibenzylideneacetone)dipalladium (0)(0.27 g, 0.30 mmol, 0.05 eq) and heated at 120 °C. After stirring for 16 h, reaction mixture was cooled to room temperature. To it was added mixture of saturated aqueous solution of ammonium chloride and extracted with EtOAc/heptane (2 x 100 mL), and the combined organic layer was dried and concentrated to yield the crude, which was purified by flash column chromatography using 35% EtOAc/heptane as eluent to afford 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-2-methylpyridine-3-carbonitrile (0.35 g, 20% yield).

[0370] LCMS (ES) m/z: 275.2 $[M+H]^+$

Step-3: Preparation 6-(1-hydroxy-4-oxocyclohexyl)-2-methylnicotinonitrile

[0371] To a stirred solution of 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-2-methylpyridine-3-carbonitrile (0.35 g, 1.28 mmol, 1 equiv) in THF (5 mL) was added 4N HCl in water (3 mL) dropwise while cooling, then the reaction mixture was stirred at room temperature for 3 h. The reaction progress was checked by TLC monitoring, and after completion of the reaction, the reaction mixture was concentrated under reduced pressure to yield an aqueous residue. The obtained residue was basified with solid $NaHCO_3$ to pH 8~9, then the aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 6-(1-hydroxy-4-oxocyclohexyl)-2-methylpyridine-3-carbonitrile (0.25 g, 85% yield).

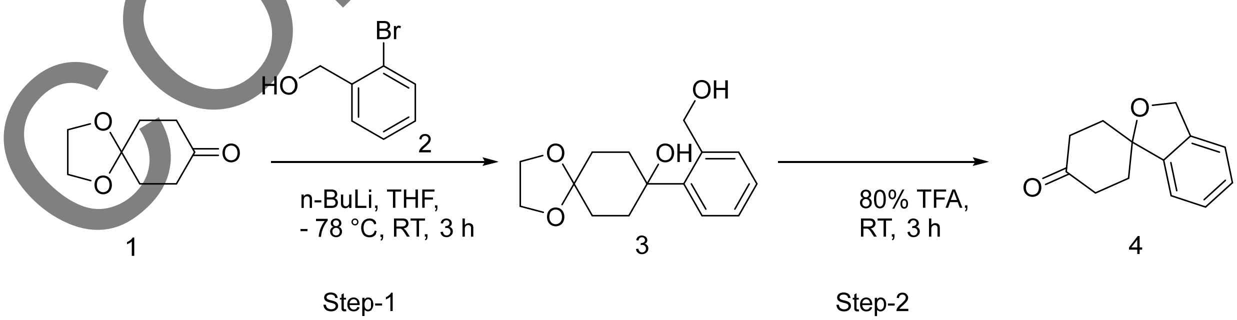
[0372] LCMS (ES) m/z: 231.2 $[M+H]^+$

Step-4: Preparation of 6-(1-hydroxy-4-oxocyclohexyl)-2-methylnicotinamide

[0373] To a stirred solution of 6-(1-hydroxy-4-oxocyclohexyl)-2-methylpyridine-3-carbonitrile (0.22 g, 0.95 mmol, 1 eq) in DMSO (8 mL) were added potassium carbonate (0.39 g, 2.87 mmol, 3 eq) and hydrogen peroxide (0.6 mL, 14.3 mmol, 15 eq) and stirred at 0 °C for 2 h. After stirring for 2 h, reaction mixture was warmed to room temperature. To it was added water and extracted with DCM (2 x 50 mL), and the combined organic layer was dried and concentrated to yield the crude 6-(1-hydroxy-4-oxocyclohexyl)-2-methylpyridine-3-carboxamide (0.13 g, 54% yield).

[0374] LCMS (ES) m/z: 249.1 $[M+H]^+$

Procedure 39: Synthesis of 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-one



Step 1: Preparation of 8-(2-(hydroxymethyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-ol

[0375] To a stirred solution of (2-bromophenyl)methanol (0.5 g, 2.67 mmol, 1 eq) in 10 mL dry THF at -78 °C, *n*-butyl lithium (3.34 mL, 5.35 mmol, 2 eq) was added over a period of 10 minutes. The dianion (lithium salt) began to precipitate after 15 min. The mixture was allowed to warm to 20 °C and after stirring for 1 h, 1,4-dioxaspiro[4.5]decan-8-one (0.5 g, 3.21 mol, 1.2 eq) in 10 mL THF was added and reaction was stirred for 18 h at room temperature. The reaction mixture was quenched with aqueous ammonium chloride. The reaction mass was further diluted with 100 mL of ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduce pressure to yield the crude product. The crude product was purified by combiflash column chromatography eluted on 40% EtOAc/heptane as eluent to afford 8-[2-(hydroxymethyl)phenyl]-1,4-dioxaspiro[4.5]decan-8-ol (0.4 g, 56% yield).

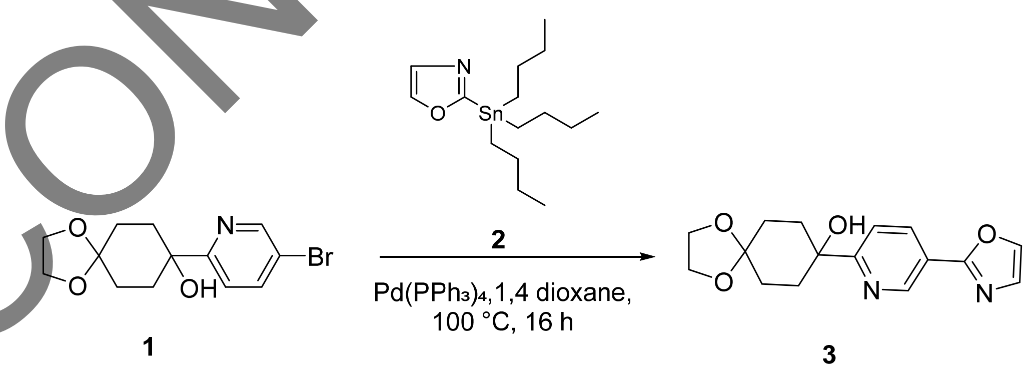
[0376] ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 7.54 (dd, *J* = 2 Hz, 1H), 7.38 (dd, *J* = 1.6 Hz, 1 H), 7.23 – 7.15 (m, 2 H), 5.04 (t, *J* = 5.6 Hz, 1 H), 4.98 (s, 1 H), 4.81 (d, *J* = 5.6 Hz, 2 H), 3.88 (s, 4 H), 2.03 – 1.94 (m, 4 H), 1.86 – 1.81 (m, 2H), 1.54 (d, *J* = 8.8 Hz, 2H).

Step 2: Preparation of 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-one

[0377] To a stirred solution of 8-(2-(hydroxymethyl)phenyl)-l,4-dioxaspiro[4.5]decan-8-ol (0.35 g, 1.32 mmol, 1 eq) was added 80% TFA (10 mL). The reaction was stirred overnight at room temperature. The reaction was cooled to -20 °C and THF (6 mL) was added. The pH was adjusted to ~11 with the careful addition of 25% NaOH, and water was added to induce precipitation. The solution was filtered and rinsed well with water. The resulting solid was dried in vacuo to yield the crude, which was purified by combiflash column chromatography eluted on 20% EtOAc/heptane as eluent to afford 3H-spiro[2-benzofuran-1,1'-cyclohexan]-4'-one (0.25 g, 93% yield).

[0378] LCMS (ES) m/z: 203.0 $[M+H]^+$

Procedure 40: Synthesis of 8-[5-(1,3-oxazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol



Step-1

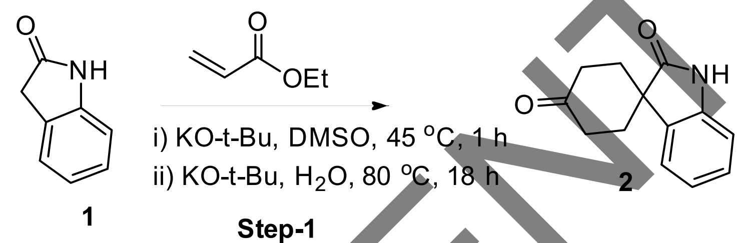
Step-1: Synthesis of 8-[5-(1,3-oxazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0379] A solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (250 mg, 796 µmol) and 2-(tributylstannyl)-1,3-oxazole (342 mg, 1.2 eq., 955 µmol) in 1,4-dioxane (5 mL, 58.6 mmol) was purged with

Ar for 10 min, followed by the addition of palladium(2+) bis(triphenylphosphane) dichloride (55.9 mg, 0.1 eq., 79.6 µmol). The reaction mixture was stirred at 100 °C for 8 h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (15 mL), extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by chromatography using 0-3% MeOH in DCM as eluent to afford 8-[5-(1,3-oxazol-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (120 mg, 50%).

[0380] LCMS (ES) m/z: 303.1 $[M+H]^+$

Procedure 41: Synthesis of 1',2'-dihydrospiro[cyclohexane-1,3'-indole]-2',4-dione

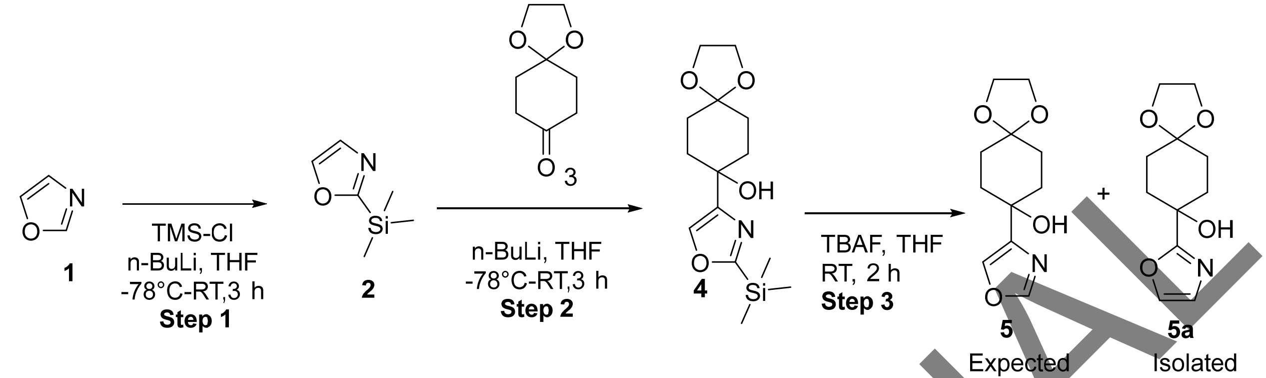


Step-1: 1',2'-dihydrospiro[cyclohexane-1,3'-indole]-2',4-dione

[0381] To a solution of 2,3-dihydro-1H-indol-2-one (2 g, 15 mmol) in DMSO (20 mL), KO-*t*-Bu (110 mg, 1.1 mmol) was added and the resultant solution was stirred for 15 min. Ethyl prop-2-enoate (4 mL, 37.6 mmol) was added slowly over a period of 30 min. The reaction mixture was heated at 45 °C for 1 h. KO-*t*-Bu (4.1 g, 36.5 mmol) was added slowly over a period of 20 min and heated at 60 °C for 1 h. The reaction mass was quenched with water (50 mL) and heated for 18 h at 80 °C. The reaction mass was extracted with ethyl acetate (2 x 100 mL) and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduce pressure to afford the crude compound. The crude was further purified using flash chromatography using EA:hexane (2:8) as mobile phase to afford the title compound (350 mg, 11%).

[0382] LCMS (ES) m/z: 216.1 $[M+H]^+$

Procedure 42: Synthesis of 4-hydroxy-4-(1,3-oxazol-4-yl)cyclohexan-1-one



Step 1: Preparation of 2-(trimethylsilyl)-1,3-oxazole

[0383] To a solution of 1,3-oxazole (47.6 µL, 724 µmol) in THF (616 µL, 7.57 mmol) at -78 °C, butyllithium (92.8 mg, 2 eq., 1.45 mmol) was added dropwise. After being stirred at -78 °C for 0.5 h, chlorotrimethylsilane (187 µL, 1.5 eq., 1.09 mmol) was added to the reaction mixture. After 1 hr, the progress of reaction was checked by TLC. The reaction mixture was used directly in the next step.

Step 2: Preparation of 8-[2-(trimethylsilyl)-1,3-oxazol-4-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0384] To a solution of 2-(trimethylsilyl)-1,3-oxazole (1 g, 7.08 mmol) in THF (616 µL, 7.57 mmol) at -78 °C, butyllithium (92.8 mg, 2 eq., 1.45 mmol) was added dropwise. After being stirred at -78 °C for 1.5 h, 1,4-dioxaspiro[4.5]decan-8-one (1.11 g, 7.08 mmol) was added to the reaction mixture. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into aqueous NH_4Cl (5 mL) and extracted with EtOAc (10 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum at high pressure to yield the crude. The crude was purified by flash column chromatography using 60% EtOAc/heptane as eluent to afford 8-[2-(trimethylsilyl)-1,3-oxazol-4-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 32%).

[0385] LCMS (ES) m/z: **298.2** $[M+H]^+$

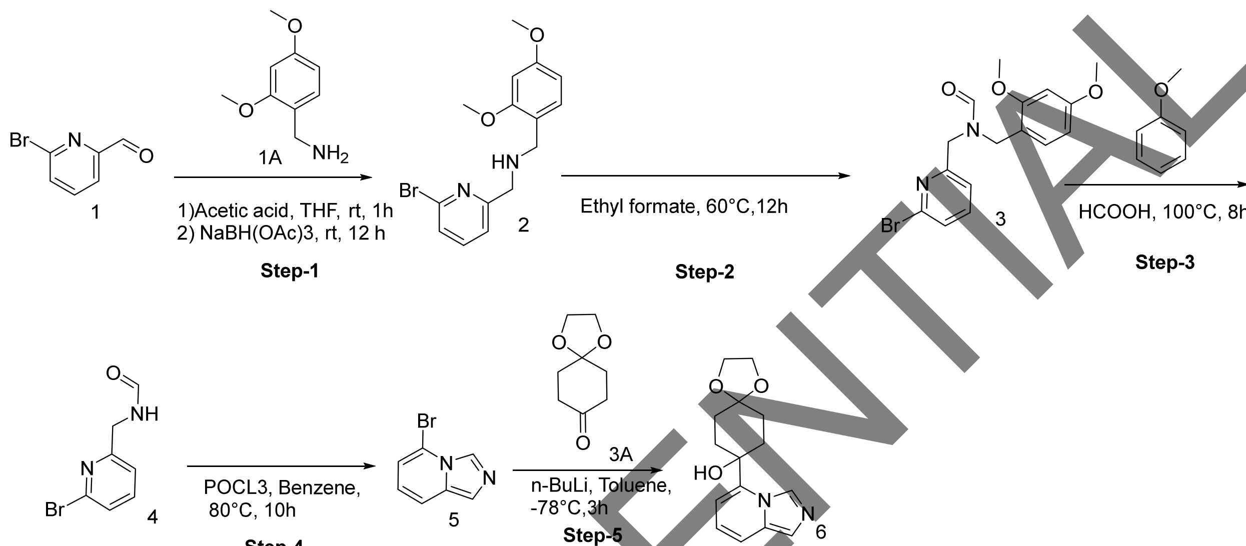
Step 3: Preparation of 4-hydroxy-4-(1,3-oxazol-4-yl)cyclohexan-1-one

[0386] To the stirred solution of 8-(1,3-oxazol-4-yl)-1,4-dioxaspiro[4.5]decan-8-ol (140 mg, 622 µmol) in THF (10 mL, 123 mmol) was added 4 N HCl (3 mL) and the reaction mixture was stirred at room temperature for 3 h . After completion of the reaction as evidenced from TLC, the reaction mixture was concentrated to remove solvent and extracted with EtOAc (20 mL) and water (5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude was purified by flash column chromatography using 70% EA/heptane as eluent to afford 4-hydroxy-4-(1,3-oxazol-4-yl)cyclohexan-1-one (80 mg, 71% yield).

[0387] LCMS (ES) m/z: **182.3** $[M+H]^+$

[0388] ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.01 (s, 1 H), 7.11 (s, 1 H), 5.49 (s, 1 H), 384-3.82 (m, 4 H), 2.01-1.45 (m, 8 H)

Procedure 43: Synthesis of 8-(imidazo[1,5-a]pyridin-5-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step-1: [(6-bromopyridin-2-yl)methyl][(2,4-dimethoxyphenyl)methyl]amine

[0389] To a solution of 6-bromopyridine-2-carbaldehyde (3 g, 16.1 mmol) and 1-(2,4-dimethoxyphenyl)methanamine (2.97 g, 1.1 eq., 17.7 mmol) in oxolane (5 mL), acetic acid was added and stirred for 1 h. Then sodium bis(acetyloxy)boranuidyl acetate (6.84 g, 2 eq., 32.3 mmol) was added and stirred at room temperature for 12 h. The reaction mixture was diluted with aqueous $NaHCO_3$ (2 x 20mL) and extracted with EtOAc (2 x 20mL), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the crude, which was purified by combiflash using 80% EA/heptane to afford [(6-bromopyridin-2-yl)methyl][(2,4-dimethoxyphenyl)methyl]amine (3.4 g, 60%).

[0390] LCMS (ES) m/z: 339 $[M+2]^+$

Step-2: N-[(6-bromopyridin-2-yl)methyl]-N-[(2,4-dimethoxyphenyl)methyl]formamide

[0391] To [(6-bromopyridin-2-yl)methyl][(2,4-dimethoxyphenyl)methyl]amine (3 g, 8.9 mmol) was added ethyl formate (7.19 mL, 10 eq., 89 mmol) and stirred at 60 °C for 12 h. The reaction mixture was evaporated under reduced pressure, and extracted with water (2 x 200 mL) and ethylacetate (2 x 200 mL). The combined organic layer were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product which was purified by combiflash using 30% EA/heptane to afford N-[(6-bromopyridin-2-yl)methyl]-N-[(2,4-dimethoxyphenyl)methyl]formamide (3 g, 93%).

[0392] LCMS (ES) m/z: 367.1[M+2]$^+$

Step-3: N-[(6-bromopyridin-2-yl)methyl]formamide

[0393] To a solution of N-[(6-bromopyridin-2-yl)methyl]-N-[(2,4-dimethoxyphenyl)methyl]formamide (4 g, 11 mmol) in anisole (5.95 mL, 5 eq., 54.8 mmol) was added formic acid (10 mL) and stirred at 100 °C for 12 h. The reaction mixture was evaporated under reduced pressure then extracted with $NaHCO_3$ (2 x 10 mL) and ethyl acetate (2 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified through MPLC using 40% EA/heptane to afford N-[(6-bromopyridin-2-yl)methyl]formamide (350 mg, 15%).

[0394] LCMS (ES) m/z: 217.1[M+2]$^+$

Step-4: 5-bromoimidazo[1,5-a]pyridine

[0395] To a solution of N-[(6-bromopyridin-2-yl)methyl]formamide (20 mg, 93 µmol) in benzene (1 mL) was added $POCl_3$ (43.5 µL, 5 eq., 465 µmol) and stirred at 120 °C for 10 h. The reaction mixture was quenched with 20% aqueous NaOH to pH = 8 and extracted with DCM (2 x 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude (0.3g, 94%).

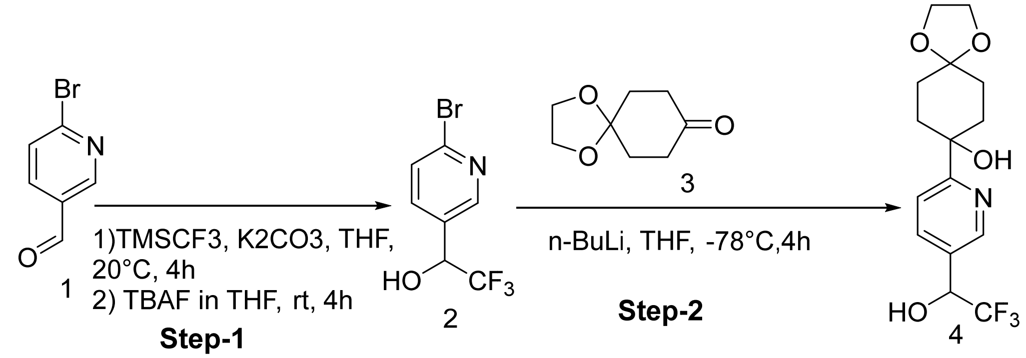
[0396] LCMS (ES) m/z: 199 [M+H]$^+$

Step-5: 8-{imidazo[1,5-a]pyridin-5-yl}-1,4-dioxaspiro[4.5]decan-8-ol

[0397] To a solution of 5-bromoimidazo[1,5-a]pyridine (0.4 g, 2.03 mmol) in oxolane (10 mL) at -78 °C, *n*-BuLi (20 mL, 1.2 eq., 2.44 mmol) was added dropwise. After being stirred at -78 °C for 2.5 h , a solution of 1,4-dioxaspiro[4.5]decan-8-one (317 mg, 2.03 mmol) in toluene (5mL) was added to the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (300 mL) and extracted with EtOAc (500 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford crude 8-{imidazo[1,5-a]pyridin-5-yl}-1,4-dioxaspiro[4.5]decan-8-ol (0.6 g, 41%).

[0398] LCMS (ES) m/z: 275.1 [M+H]$^+$

Procedure 44: Synthesis of 8-(5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step-1: 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethan-1-ol

[0399] To a solution of 6-bromopyridine-3-carbaldehyde (2 g, 10.8 mmol) in oxolane (5 mL) at 20 °C were added K_2CO_3 (149 mg, 0.1 eq., 1.08 mmol) and trimethyl(trifluoromethyl)silane (2.39 mL, 1.5 eq., 16.1 mmol) and stirred for 4 h. Then TBAF (9.37 mL, 3 eq., 32.3 mmol) was added dropwise stirred at room temperature for 4 h. The reaction mixture was quenched with ice cold water and extracted with EtOAc (100 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude which was purified by MPLC using 30% EA/heptane to afford 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethan-1-ol (1.5 g, 53%).

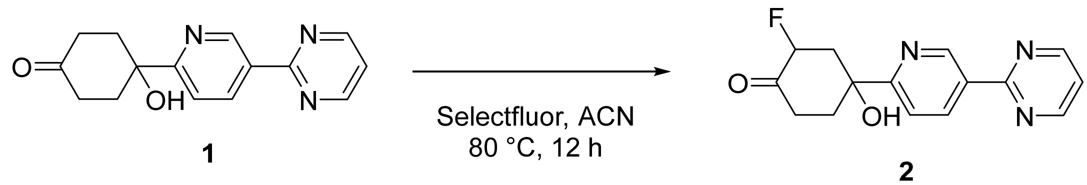
[0400] LCMS (ES) m/z: 257.9 $[M+H]^+$

Step-2: 8-[5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0401] To a solution of 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethan-1-ol (0.5 g, 1.95 mmol) in oxolane (5 mL) at -78 °C, *n*-BuLi (5 mL, 1.5 eq., 2.93 mmol) was added dropwise. After being stirred at -78 °C for 2.5 h, a solution of 1,4-dioxaspiro[4.5]decan-8-one (305 mg, 1.95 mmol) in THF (5mL) was added to the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (300 mL) and extracted with EtOAc (500 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude which was purified by MPLC using 60% EA/heptane to afford 8-[5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.6 g, 41%).

[0402] LCMS (ES) m/z: 334$[M+H]^+$

Procedure 45: Synthesis of 2-fluoro-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexan-1-one



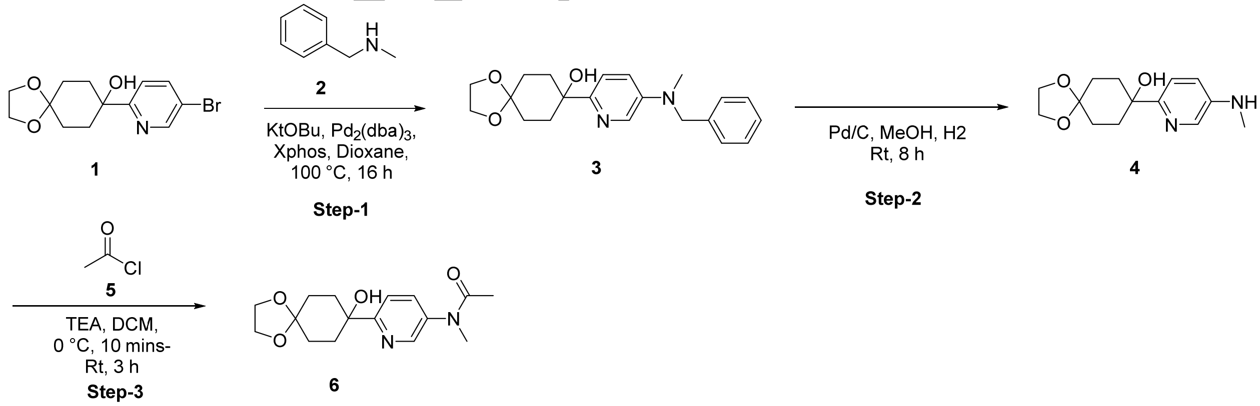
Step-1: Synthesis of 2-fluoro-4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one

[0403] To a solution of 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (1.5 g, 5.57 mmol) in acetonitrile (20 mL, 383 mmol) under N_2 atmosphere was added Selectfluor (3.95 g, 2 eq., 11.1 mmol). The resulting solution was stirred at 80 °C for 12 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with water, then brine, and evaporated under reduced pressure to afford the crude compound. The crude was purified by flash column MPLC using 5% MeOH in DCM as eluent to afford 2-fluoro-4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (430 mg, 27%) 200 mg (non-polar in TLC) and 230 mg (polar in TLC).

[0404] Non-polar isomer on TLC: LCMS (ES) m/z: 288.0 $[M+H]^+$

[0405] Polar isomer on TLC: LCMS (ES) m/z: 288.1 $[M+H]^+$

Procedure 46: Synthesis of N-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-N-methylacetamide



Step-1: Synthesis of 8-{5-[benzyl(methyl)amino]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol

[0406] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 1.59 mmol) and benzyl(methyl)amine (394 µL, 2 eq., 3.18 mmol) in 1,4-dioxane (8 mL, 93.8 mmol) were added potassium 2-methylpropan-2-olate (536 mg, 3 eq., 4.77 mmol) and dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (152 mg, 0.2 eq., 318 µmol) under N_2 atmosphere. The reaction mixture was purged with Ar for 5 minutes, then tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (146 mg, 0.1 eq., 159 µmol) was added under N_2 atmosphere, and the reaction mixture was stirred at 100 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was quenched with water (45 mL), extracted with ethyl acetate (2 x 30 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude was purified by silica gel column chromatography using EtOAc in *n*-hexane as eluent to afford 8-{5-[benzyl(methyl)amino]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (70 mg, 12%).

[0407] LCMS (ES) m/z: 355.2 $[M+H]^+$

Step 2: Synthesis 8-[5-(methylamino)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0408] To a stirred solution of 8-{5-[benzyl(methyl)amino]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (560 mg, 1.58 mmol) in methanol (8 mL) was added 10% palladium on carbon (0.2 g, 1.2 eq., 1.88 mmol), and the reaction mixture was stirred at room temperature for 5 h in H_2 atmosphere. Progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under vacuum to afford 8-[5-(methylamino)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (340 mg, yield: 65%).

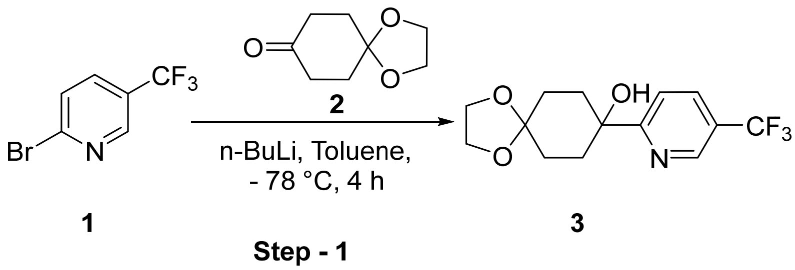
[0409] LCMS (ES) m/z: 265.2 $[M+H]^+$

Step 3: Synthesis of N-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N-methylacetamide:

[0410] To a stirred solution of 8-[5-(methylamino)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (320 mg, 1.21 mmol) in DCM (5 mL, 78.1 mmol) were added trimethylamine (145 µL, 1.5 eq., 1.82 mmol) and acetyl chloride (104 µL, 1.2 eq., 1.45 mmol) at 0 °C and stirred for 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred for another 3 h. The progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was quenched with water (25 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were washed with water, brine, and concentrated under reduced pressure to afford N-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N-methylacetamide (250 mg, Yield: 67%).

[0411] LC-MS (ES) m/z: 307.2 $[M+H]^+$

Procedure 47: Synthesis of 8-(5-(trifluoromethyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

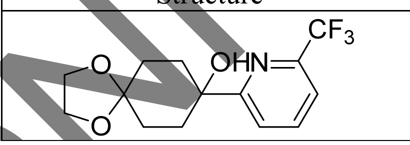


Step 1: Preparation of 8-(5-(trifluoromethyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

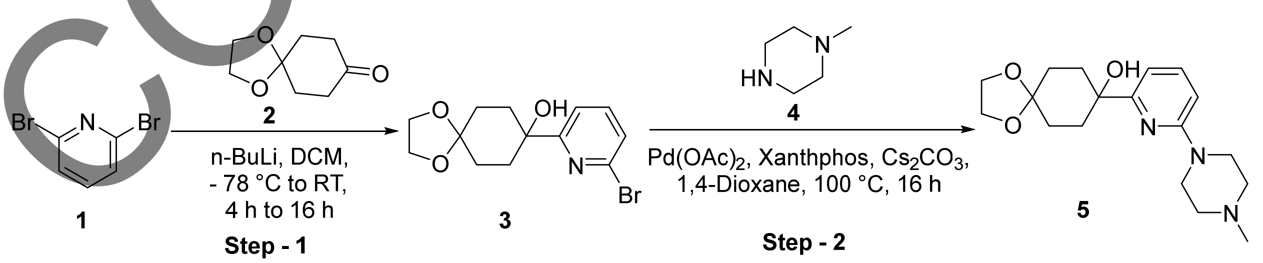
[0412] To a solution of 2-bromo-5-(trifluoromethyl)pyridine (0.25 g, 1.11 mmol, 1 eq) in toluene (10 mL) at -78 °C, *n*-BuLi (1.6 M, 0.83 mL, 1.33 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred at -78 °C for 2.5 h. Then a solution of 1,4-dioxaspiro[4.5]decan-8-one (0.173 g, 1.11 mmol, 1 eq) in toluene (5 mL) was added to the reaction mixture. The resulting mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (20 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum to yield the crude. The crude material was purified by flash column chromatography by using 0-20 % ethyl acetate in heptane as eluent to afford 8-[5-(trifluoromethyl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.12 g, 36%).

[0413] LC-MS (ES) m/z: 304.1 $[M+H]^+$

[0414] The following compound was made according to Procedure 47.

Structure	LCMS (ES) m/z
	304.1 $[M+H]^+$

Procedure 48: Synthesis of 8-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol:



Step-1: Synthesis of 8-(6-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

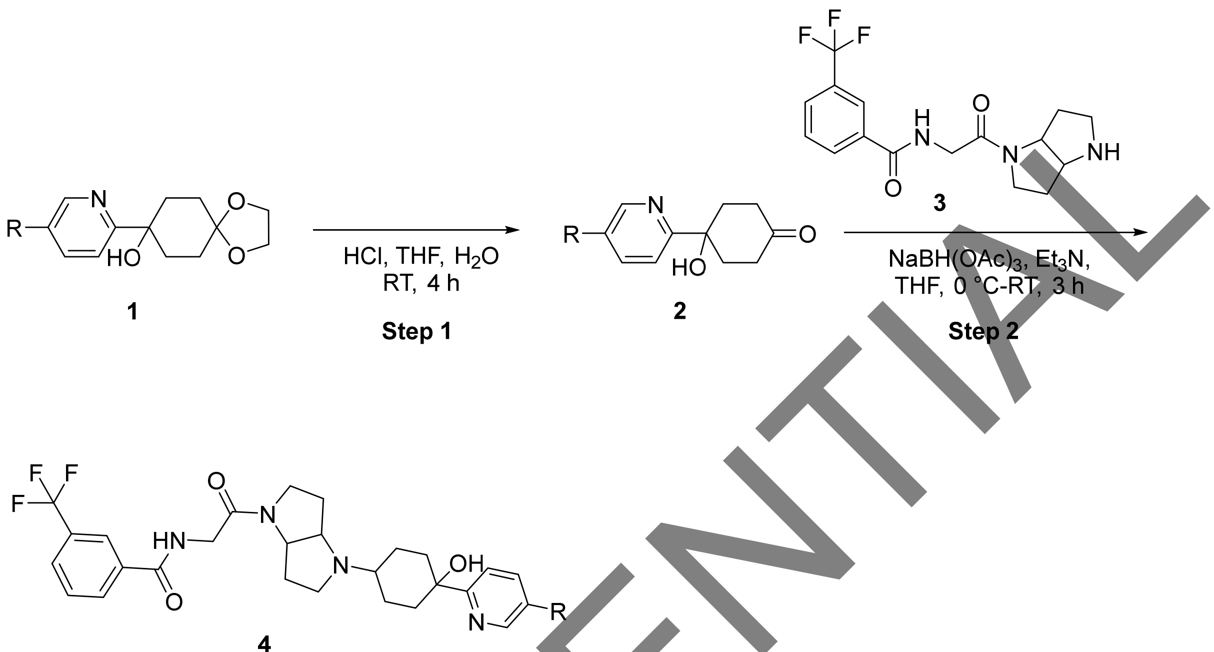
[0415] To a solution of 2,6-dibromopyridine (0.5 g, 2.11 mmol, 1 eq) in DCM (20 mL) at -78 °C, *n*-BuLi (1.6 M, 1.32 mL, 2.11 mmol, 1.0 eq) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h. Then a solution of 1,4-dioxaspiro[4.5]decan-8-one (0.297 g, 1.9 mmol, 0.9 eq) in DCM (10 mL) was added to the reaction mixture. The resulting mixture was stirred for 2 h at -78 °C and allowed to warm to room temperature slowly, then stirred for another 12 h. The reaction mixture was poured into aqueous NH_4Cl (30 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to yield the crude. The crude material was purified by flash column chromatography using 0-30 % ethyl acetate in heptane as eluent to afford 8-(6-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.55 g, 83%).

[0416] LC-MS (ES) m/z: 314.1 $[M+H]^+$

Step-2: Synthesis of 8-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol:

[0417] To a stirred solution of 8-(6-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.15 g, 0.477 mmol, 1 eq) in 1,4-dioxane (3 mL) were added 1-methylpiperazine (0.0956 g, 0.955 mmol, 2 eq) and cesium carbonate (0.467 g, 1.43 mmol, 3 eq). The reaction mixture was purged with Ar for 5 minutes, then [5-(diphenylphosphanyl)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphane (0.0415 g, 0.0716 mmol, 0.15 eq) and palladium(2+) diacetate (0.0107 g, 0.0477 mmol, 0.1 eq) were added portionwise under argon atmosphere. The reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to yield the crude compound, which was purified by flash column chromatography using 0-10 % MeOH in DCM as eluent to afford 8-[6-(4-methylpiperazin-1-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.15 g, 94%). LC-MS (ES) m/z: 334.1 $[M+H]^+$

Procedure 49: Compounds synthesized using Procedures 20 to 48 are converted into corresponding final compound using below general scheme



Step-1: General procedure for deprotection of 1,3-dioxalane group

[0418] To a stirred solution of Intermediate **1** (3 mmol) in THF (10 mL), 4N HCl in water (10 mL) was added dropwise at 0 ºC, then the reaction mixture was stirred at room temperature for 2 h. The reaction progress was monitored by TLC (50% EA in heptane). Upon completion the reaction mixture was concentrated under reduced pressure at rotavapor to yield the aqueous residue, which was basified with saturated aqueous Na_2CO_3 to pH 8~9 (pH paper), then the aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford Intermediate **2**.

Step-2: General procedure for reductive amination

[0419] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (**3**) (20 mmol) in THF (10 mL) at 0 °C were added the corresponding keto compound (Intermediate **2**) and triethylamine (100 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then sodium triacetoxy borohydride (20 mmol) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution at room temperature and diluted with water (10 mL). The aqueous layer was extracted using ethyl acetate (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield the crude product. Crude compound was further purified by preparative TLC using (1 to 10% methanolic ammonia in DCM or in ethyl acetate) to afford the non-polar and polar isomers.

[0420] The following compounds were prepared according to the procedures above using the appropriate starting materials.

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
82	N-(2-(4-(3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-yl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97 - 8.89 (m, 1 H), 8.18 (t, *J* = 11.6 Hz, 2 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.24 - 7.18 (m, 4 H), 4.92 (s, 2 H), 4.53 - 4.42 (m, 1 H), 4.25 - 3.92 (m, 2 H), 3.64 - 3.17 (m, 4 H), 2.96 - 2.87 (m, 1 H), 2.64 (s, 1 H), 2.12 - 1.21 (m, 12 H).	528.3
83	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-morpholinopyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.95 (tt, *J* = 12 Hz, *J* = 12 Hz, 1H), 8.22-8.14 (m, 3H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 20.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.35-7.32 (m, 1H), 4.85 (s, 1H), 4.47-4.27 (m, 1H), 4.20-3.96 (m, 2H), 3.75 (t, *J* = 9.6 Hz, 4H), 3.70-3.49 (m, 3H), 3.13 (t, *J* = 9.6 Hz, 4H), 2.99-2.91 (m, 1H), 2.33-2.31 (m, 2H), 2.14-2.06 (m, 1H), 1.95-1.51 (m, 10H), 1.26-1.24 (m,1H).	602.4
84	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-morpholinopyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.93 (tt, *J* = 10.6 Hz, *J* = 10.6 Hz, 1H), 8.22-8.17 (m, 3H), 7.93 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 15.6 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.33 (dd, *J* = 2.8 Hz, *J* = 2.8 Hz, 1H), 4.80 (s, 1H), 4.47-4.27 (m, 1H), 4.16-3.98 (m, 2H), 3.75 (t, *J* = 9.2 Hz, 4H), 3.57-3.55 (m, 3H), 3.14 (t, *J* = 9.2 Hz, 4H), 2.94-2.84 (m, 1H), 2.33-2.30 (m, 2H), 2.11-2.08 (m, 1H), 1.91-1.85 (m, 5H), 1.64-1.52 (m, 5H), 1.30-1.28 (m, 1H).	602.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
85	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(oxazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.10 (s, 1 H), 8.89- 8.99 (m, 1 H), 8.30- 8.33 (dd, *J* = 2.0 Hz, 10.4 Hz, 1 H), 8.29 (s, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.43 (s, 1 H), 5.14 (s, 1 H), 4.45- 4.48 (m, 1 H), 3.98- 4.29 (m, 3 H), 3.49- 3.62 (m, 3 H), 2.88 (d, *J* = 8.0 Hz, 1 H), 2.37 (s, 2 H), 2.07- 2.14 (m, 2 H), 1.81- 1.93 (m, 4 H), 1.62- 1.76 (m, 3 H), 1.43- 1.56 (m, 2 H).	584.3
86	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(oxazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.05 (s, 1 H), 8.90- 8.96 (m, 1 H), 8.28 (t, *J* = 8.0 Hz, 2 H), 8.17 (t, *J* = 12.0 Hz, 2 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.40 (s, 1 H), 5.13 (s, 1 H), 4.43 (d, *J* = 6.8 Hz, 1 H), 4.10- 4.25 (m, 2 H), 3.48- 3.64 (m, 3 H), 3.20 (d, *J* = 10.8 Hz, 1 H), 2.88 (s, 1 H), 2.30 (s, 1 H), 1.94- 2.05 (m, 4 H), 1.60- 1.82 (m, 7 H), 1.48 (s, 1 H).	584.3
87	N-(2-(4-((1r,4r)-4-(5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.17(s,1H), 8.98-8.88 (t, *J* = 8 Hz, 1H), 8.38-8.33 (dd, *J* = 4 Hz 1H), 8.24-8.17 (s, 4H), 7.93 (d, *J* = 4 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 5.13 (s, 1H), 4.31 (m, 1H), 4.03 (m, 2H), 3.57 (m, 3H), 2.80 (m, 1H), 2.39 (m, 1H), 2.30 (m, 1H), 1.96 (m, 5H), 1.76 (m, 4H), 1.55 (m, 3H)	584.4
88	N-(2-(4-((1s,4s)-4-(5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.12 (s,1H), 8.98-8.89 (t, *J*=8Hz, 1H), 8.35-8.33(dd, *J*=4Hz 1H), 8.20 (s, 4H), 7.91-7.83 (d, *J*=4Hz, 2H), 7.25 (t, *J*=8Hz,1H), 5.14 (s, 1H), 4.49 (m, 1H), 4.43-4.10 (m, 2H), 3.99 (m, 1H), 3.65 (m, 1H), 3.55 (m, 2H), 2.98 (m, 2H), 2.06 (m, 4H), 1.80 (m, 8H)	584.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
89	N-(2-oxo-2-(4-(2'-oxospiro[cyclohexane-1,3'-indolin]-4-yl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1H), 8.23 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.29 - 7.25 (m, 1H) 7.14 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.49 - 4.45 (m, 0.5 H), 4.33 - 4.28 (m, 0.5 H), 4.21- 4.12 (m, 1H), 4.04 - 3.97 (m, 1H), 3.69 - 3.44 (m, 3H), 3.00 - 2.89 (m, 1H), 2.26 - 2.02 (m, 3H), 1.99 - 1.82 (m, 3H), 1.77 - 1.63 (m, 6H), 1.58 - 1.50 (m, 2H).	541.4
90	N-(2-(4-((1r,4r)-4-(3-fluoro-[2,3'-bipyridin]-6'-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.02 (s, 1 H), 8.99 - 8.92 (m, 1 H), 8.61 - 8.59 (m, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 8 Hz, 1 H), 7.94 - 7.87 (m, 2 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.75 (t, *J* = 8.4 Hz, 1 H), 7.56 - 7.52 (m, 1 H), 5.11 (s, 1 H), 4.49 - 4.23 (m, 1 H), 4.18 - 3.98 (m, 2 H), 3.62 - 3.5 (m, 3 H), 2.87 - 2.81 (m, 1 H), 2.4 - 2.33 (m, 2 H), 2.26 - 1.92 (m, 2 H), 1.91 - 1.85 (m, 3 H), 1.84 - 1.76 (m, 4 H), 1.25 - 1.24 (m, 2 H).	612.3
91	N-(2-(4-((1s,4s)-4-(3-fluoro-[2,3'-bipyridin]-6'-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.6 - 8.59 (m, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J* = 8 Hz, 1 H), 7.95 - 7.92 (m, 1 H), 7.9 - 7.89 (m, 1 H), 7.84 (d, *J* = 8 Hz, 1 H), 7.76 (t, *J* = 16 Hz, 1 H), 7.56 - 7.52 (m, 1 H), 5.12 (s, 1 H), 4.5 - 4.27 (m, 1 H), 4.21 - 3.97 (m, 2 H), 3.71 - 3.49 (m, 3 H), 3.02 - 2.93 (m, 1 H), 2.16 - 1.97 (m, 4 H), 1.91 - 1.53 (m, 10 H).	612.3
92	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90 (s, 1 H), 8.22 (s, 2 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.44- 7.51 (m, 2 H), 4.88 (s, 1 H), 4.20- 4.55 (m, 1 H), 3.98- 4.18 (m, 2 H), 3.58 (s, 3 H), 3.29- 3.39 (m, 8 H), 2.67 (s, 4 H), 2.38- 2.55 (m, 3 H), 1.70- 2.15 (m, 5 H), 1.42- 1.69 (m, 6 H).	615.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
93	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.89- 8.97 (m, 1 H), 8.17- 8.22 (m, 3 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.75 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.30- 7.33 (dd, J =2.8 Hz, 11.6 Hz, 1 H), 4.83 (s, 1 H) , 4.25- 4.55 (m, 1 H), 3.92- 4.21 (m, 2 H), 3.52- 3.71 (s, 2 H), 3.42- 3.51 (m, 1 H), 3.15 (t, J = 4.4 Hz, 4 H), 2.91- 2.99 (m, 1 H), 2.39- 2.61 (m, 5 H), 2.33 (s, 3 H), 2.08- 2.19 (m, 1 H), 1.51- 2.10 (m, 12 H).	615.4
94	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(1-methyl-1H-imidazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97- 8.91 (m, 1 H), 8.84 (s, 1 H), 8.22 (s, 1 H), 8.18 (d, J = 8 Hz, 1 H), 8.09 (d, J = 8.4 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 2 H), 7.75 (t, J = 14.8 Hz, 2 H), 7.31 (s, 1 H), 7.03 (s, 1 H), 5.06 (s, 1 H), 4.49 - 4.3 (m, 1 H), 4.19 - 3.97 (m, 2 H), 3.84 - 3.74 (m, 3 H), 3.57 - 3.52 (m, 1 H), 3.43 - 3.41 (m, 1 H), 3.18 - 3.14 (m, 1 H), 3.03 - 2.99 (m, 1 H), 2.88 - 2.72 (m, 1 H), 2.4 - 2.37 (m, 2 H), 2.23 - 2.13 (m, 1 H), 2.02 - 1.64 (m, 4 H), 1.47 - 1.34 (m, 2 H), 1.3 - 1.24 (m, 2 H).	597.4
95	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(1-methyl-1H-imidazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.9 (m, 1 H), 8.81 (s, 1 H), 8.23 (s, 1 H), 8.19 (d, J = 8 Hz, 1 H), 8.02 (dd, J = 10.8 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.79 - 7.73 (m, 2 H), 7.31 (s, 1 H), 7.02 (s, 1 H), 5.08 (s, 1 H), 4.31 - 4.3 (m, 1 H), 4.18 - 3.98 (m, 2 H), 3.83 - 3.74 (m, 3 H), 3.69 - 3.58 (m, 1 H), 3.53 - 3.4 (m, 1 H), 3.01 - 2.93 (m, 1 H), 2.16 - 1.99 (m, 4 H), 1.92 - 1.77 (m, 4 H), 1.71 - 1.53 (m, 6 H).	597.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
96	N-(2-(4-((1r,4r)-4-carbamoyl-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90- 8.95 (m, 1 H), 8.58 (d, J = 3.6 Hz, 1 H), 8.17 (t, J = 11.6 Hz, 2 H), 7.92 (d, J = 7.6 Hz, 1 H), 7.71- 7.80 (m, 2 H), 7.49 (d, J = 7.2 Hz, 1 H), 7.25 (t, J = 6.0 Hz, 1 H), 6.84 (s, 1 H), 6.74 (s, 1 H), 4.18- 4.48 (m,1 H), 4.02- 4.10 (m, 1 H), 3.89- 4.01 (m, 1 H), 3.56 (s,1 H), 3.45 (s, 1 H), 3.17 (s,1 H), 2.78 (s, 1 H), 2.59- 2.71 (m, 2 H), 2.38 (s,1 H), 2.18 (s, 1 H), 2.07 (s, 1 H), 1.61- 1.92 (m, 5 H), 1.54 (s, 1 H), 1.38 (s, 1 H), 1.10- 1.32 (m, 3 H).	544.3
97	N-(2-(4-((1s,4s)-4-carbamoyl-4-(pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90- 8.99 (m, 1 H), 8.52 (d, J = 4.8 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.72- 7.76 (m, 2 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.21- 7.24 (m, 1 H), 7.16 (s, 1 H), 6.98 (s, 1 H), 4.25- 4.51 (m,1 H), 3.91- 4.20 (m, 2 H), 3.45- 4.10 (m, 3 H), 3.22- 3.32 (m,1 H), 2.83- 2.94 (m, 1 H), 2.33- 2.46 (m,2 H), 2.13- 2.16 (m, 1 H), 1.72- 2.17 (m, 4 H), 1.59- 1.62 (m, 2 H), 1.39- 1.57 (m, 2 H), 1.35 (s, 1 H), 1.12- 1.30 (m, 2 H).	544.3
98	N-(2-(4-((1r,4r)-4-hydroxy-4-(oxazol-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90 (s,1 H), 8.22 (s, 1 H), 8.18 (d, J= 8 Hz, 1 H), 8.01 (s, 1 H), 7.93 (d, J=8 Hz, 2 H), 7.74 (t, J=8 Hz, 1 H), 7.12(s,1 H), 5.34-5.33 (m,1 H), 4.01 (m, 3 H), 3.41-3.31 (m, 3 H), 2.68-2.56 (m, 1 H), 2.33-2.02 (m, 3 H), 1.78-1.62 (m, 11 H)	**507.4**
99	N-(2-(4-((1s,4s)-4-hydroxy-4-(oxazol-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.94-8.88 (s,1 H), 8.18 (s, 1 H), 8.14 (d, J= 7.6 Hz, 1 H), 8.02 (s, 1 H), 7.90 (d, J=7.6 Hz, 2 H), 7.71 (t, J=7.6 Hz, 1 H), 7.14 (s,1 H), 5.47 (s,1 H), 4.22-4.20 (m, 1 H), 4.09-3.94 (m, 4 H), 3.54-3.46 (m, 2 H), 2.71-2.65 (m, 2 H), 2.48-2.35 (m, 2 H), 2.30-2.05 (m, 2 H), 1.88-1.55 (m, 5 H), 1.28-1.21 (m, 3 H)	**507.4**

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
104	N-(2-(4-((1r,4r)-4-(5-(2,6-dimethylmorpholino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.91 - 8.97 (m, 1H), 8.17 - 8.27 (m, 3H), 7.93 (d, *J*= 8.0 Hz, 1H), 7.73 - 7.77 (m, 1H), 7.44 - 7.46 (m, 1H), 7.33 - 7.35 (m, 1H), 4.79 (s, 1H), 4.19 - 4.46 (m, 1H), 3.97 - 4.18 (m, 2H), 3.68 - 3.77 (m, 2H), 3.60 - 3.64 (m, 4H), 2.55- 2.56 (m, 2H), 2.31 - 2.40 (m, 4H), 2.18 - 2.26 (m, 1H), 2.07 - 2.13 (m, 1H), 1.66 - 1.87 (m, 5H), 1.53 - 1.66 (m, 3H), 1.34 - 1.43 (m, 2H), 1.12 - 1.15 (m, 6H).	**630.4**
105	N-(2-(4-((1s,4s)-4-(5-(2,6-dimethylmorpholino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.91 - 8.97 (m, 1H), 8.18 - 8.23 (m, 3H), 7.93 (d, *J*= 8.0 Hz, 1H), 7.73 - 7.77 (m, 1H), 7.47 - 7.49 (m, 1H), 7.32 - 7.35 (m, 1H), 4.84 (s, 1H), 4.29 - 4.47 (m, 1H), 4.11 - 4.20 (m, 1H), 3.96 - 4.13 (m, 1H), 3.58 - 3.69 (m, 3H), 3.51 - 3.67 (m, 3H), 3.50- 3.52 (m, 1H), 3.40 - 3.42 (m, 1H), 2.91 - 2.99 (m, 1H), 2.25 - 2.46 (m, 2H), 2.08 - 2.12 (m, 1H), 1.83 - 1.98 (m, 4H), 1.67 - 1.77 (m, 4H), 1.49 - 1.52 (m, 3H), 1.15 - 1.22 (m, 6H).	**630.4**
106	N-(2-(4-((1r,4r)-4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.0-8.92 (m, 1H), 8.23 (s, 1H), 8.18 (d, *J*=7.6Hz, 1H0, 8.09 (d, *J*=2.8Hz, 1H), 7.94 (d, *J*=8Hz, 1H), 7.75 (t, *J*=8Hz, 1H), 7.45 (d, *J*=8.8Hz, 1H), 7.24-7.21 (m,1H), 4.84 (s, 1H), 4.28-4.21 (m,3H), 4.19-3.96 (m, 2H), 3.67-3.49 (m, 3H), 2.99-2.81 (m, 2H), 2.34-2.14 (m, 1H), 2.08-1.97 (m, 3H), 1.94-1.84(m, 5H), 1.79-1.55 (m, 8H), 1.31-1.24 (m , 2H)	628.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
107	N-(2-(4-((1s,4s)-4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.93 (m, 1H), 8.23 (s, 1H), 8.2-8.14 (m, 1H), 8.09 (d, *J*=2.4 Hz, 1H), 7.93 (d, *J*=8 Hz, 1H), 7.75 (t, *J*=7.6Hz, 1H), 7.45 (d, *J*=8.8Hz, 1H), 7.28-7.21 (m, 1H), 4.84 (s, 1H), 4.44-4.20 (m, 3H), 4.19-4.11 (m, 1H), 4.08-3.96 (m, 1H), 3.79-3.52 (m, 3H), 3.43-3.40 (m, 2H), 3.0-2.73(m, 3H), 2.08-1.91(m, 4H), 1.84 (bs, 5H), 1.77-1.67(m, 6H), 1.58-1.5(m, 2H), 1.30-1.29(m,2H)	**628.8**
108	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(trifluoromethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.92 - 8.97 (m, 2H), 8.17 - 8.22 (m, 3H), 7.87 - 7.94 (m,2H), 7.73 - 7.77 (m, 1H), 5.22 (s, 1H), 4.47 - 4.49 (m, 1H), 4.23 - 4.31 (m, 1H), 3.98 - 4.17 (m, 2H), 3.51 - 3.63 (m, 2H), 3.34 - 3.44 (m, 1H), 2.79 - 2.86 (m, 1H), 2.33 - 2.46 (m, 2H), 2.08 - 2.18 (m, 1H), 1.78 - 2.07 (m, 4H), 1.54 - 1.77 (m, 4H), 1.43 - 1.5 (m, 2H).	**585.4**
109	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(trifluoromethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.89 - 8.98 (m, 2H), 8.18 - 8.22 (m, 3H), 7.90 - 7.94 (m,2H), 7.73 - 7.77 (m, 1H), 5.24 (s, 1H), 4.20 - 4.51 (m, 1H), 4.11 - 4.19 (m, 1H), 3.96 - 4.02 (m, 1H), 3.35 - 3.65 (m, 3H), 2.87 - 3.00(m, 1H), 2.07 - 2.15 (m, 1H), 1.82 - 2.08 (m, 3H), 1.70 - 1.91 (m, 4H), 1.53 - 1.70 (m, 5H), 1.41 - 1.54 (m, 1H).	**585.4**
110	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-(trifluoromethyl)morpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.88 (m, 1 H), 8.29 - 8.22 (m, 2 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.5 - 7.42 (m, 2 H), 4.81 (s,1 H), 4.47 - 4.26 (m, 2 H), 4.18 - 3.97 (m, 3 H), 3.83 - 3.75 (m, 2 H), 3.63 - 3.51 (m, 3 H), 3.4 - 3.34 (m, 1 H), 2.87 - 2.75 (m, 3 H), 2.46 - 2.3 (m, 3 H), 2.12 - 2.08 (m, 1 H), 1.92 - 1.74 (m, 4 H), 1.73 - 1.65 (m, 1 H), 1.64 - .41 (m, 3 H), 1.39 - 1.34 (m, 2 H), 1.24 (s, 1 H).	652.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
111	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-(trifluoromethyl)morpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J* = 8 Hz, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.53 (d, *J* = 8.8 Hz, 1 H), 7.44 (dd, 11.6 H), 4.87 (s, 1 H), 4.38 - 4.28 (m, 2 H), 4.19 - 3.98 (m, 3 H), 3.82 - 3.74 (m, 2 H), 3.68 - 3.58 (m, 3 H), 3.52 - 3.4 (m, 1 H), 2.3 - 2.912 (m, 1 H), 2.89 - 2.74 (m, 2 H), 2.17 - 2.15 (m, 1 H), 1.2 - 1.80 (m, 4 H), 1.77 - 1.72 (m, 2 H), 1.67 - 1.64 (m, 2 H), 1.60 - 1.52 (m, 2 H), 1.51 - 1.24 (m, 2 H).	652.4
112	6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)nicotinic acid	8.98 - 8.89 (m, 2 H), 8.25 - 8.15 (m, 3 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.84 - 7.73 (m, 2 H), 4.49 - 4.27 (m, 1 H), 4.20 - 4.11 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.70 - 3.35 (m, 2 H), 2.94 - 2.73 (m, 1 H), 3.02 - 2.88 (m, 4 H), 2.78 - 2.67 (m, 4 H), 2.56 - 1.52 (m, 8 H).	561.3
113	6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)nicotinic acid	13.19 (s, 1 H), 9.00 - 8.88 (m, 2 H), 8.25 - 8.17 (m, 3 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.78 - 7.72 (m, 2 H), 5.13 (s, 1 H), 4.48 - 3.99 (m, 3 H), 3.58 (t, *J* = 6.8 Hz, 2 H), 2.79 - 2.67 (m, 2 H), 2.10 - 2.07 (m, 2 H), 1.93 - 1.77 (m, 5 H), 1.63 - 1.16 (m, 7 H).	561.3
114	N-(2-(4-((1r,4r)-4-(5-(2H-tetrazol-5-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.13 (s, 1 H), 9.08 - 8.95 (m, 1 H), 8.31 - 8.28 (m, 1 H), 8.21 (t, *J* = 11.2 Hz, 2 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.76 (t, *J* = 7.6 Hz, 2 H), 5.30 - 5.21 (m, 1 H), 5.05 - 4.91 (m, 2 H), 4.67 - 4.00 (m, 3 H), 3.72 - 3.67 (m, 2 H), 2.88 (s, 5 H), 2.33 - 1.58 (m, 10 H).	585.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
115	N-(2-(4-((1s,4s)-4-(5-(2H-tetrazol-5-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.11 (s, 1 H), 9.00 - 8.92 (m, 1 H), 8.33 - 8.30 (m, 1 H), 8.20 (t, *J* = 11.2 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.76 - 7.73 (m, 2 H), 5.20 (d, *J* = 14.8 Hz, 1 H), 4.47 (s, 1 H), 4.19 - 3.98 (m, 3 H), 3.63 (d, *J* = 16.8 Hz, 2 H), 2.88 (s, 2 H), 2.33 - 1.91 (m, 6 H), 1.76 - 1.58 (m, 8 H)	585.3
116	(1r,4r)-1-(pyridin-2-yl)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexane-1-carboxylic acid	8.89- 8.98 (m, 1 H), 8.45- 8.50 (m, 1 H), 8.19 (t, *J* = 11.6 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.66- 7.76 (m, 2 H), 7.44 (d, *J* = 8.0 Hz, 0.5 H), 7.26 (t, *J* = 7.2 Hz, 0.5 H), 7.18 (t, *J* = 5.2 Hz, 1.0 H), 4.26- 4.47 (m, 1 H), 4.08- 4.21 (m, 1 H), 3.98- 4.05 (m, 1 H), 3.42- 3.67 (m, 3 H), 2.67- 2.94 (m, 2 H), 2.31- 2.40 (m, 1 H), 2.12- 2.33 (m, 1 H), 1.98- 2.07 (m, 1 H), 1.8- 2.03 (m, 4 H), 1.71 (s, 1 H), 1.55- 1.69 (m, 3 H), 1.41- 1.52 (m, 1 H), 1.19- 1.49 (m, 1 H).	545.3
117	(1s,4s)-1-(pyridin-2-yl)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexane-1-carboxylic acid	8.86- 8.97 (m, 1 H), 8.48-8.48 (d, *J* = 2.8 Hz, 1 H), 8.16- 8.22 (m, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.66- 7.76 (m, 2 H), 7.46 (d, *J* = 8.0 Hz, 0.5 H), 7.26 (t, *J* = 7.2 Hz, 0.5 H) , 7.12- 7.19 (m, 1.0 H), 4.19- 4.51 (m, 1 H), 4.04- 4.15 (m, 1 H), 3.92- 4.01 (m, 1 H), 3.50- 3.69 (m, 2 H), 3.35- 3.49 (m, 2 H), 2.85- 3.33 (m, 1 H), 2.74- 2.82 (m, 1 H), 2.62- 2.80 (m, 1 H), 2.30- 2.34 (m, 1 H), 2.10- 2.29 (m, 1 H), 1.89- 1.99 (m, 1 H), 1.81- 1.86 (m, 2 H), 1.63- 1.75 (m, 2 H), 1.49- 1.61 (m, 2 H), 1.39- 1.48 (m, 1 H), 1.11- 1.45 (m, 1 H).	545.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
118	N-(2-(4-((1r,4r)-4-hydroxy-4-(imidazo[1,5-a]pyridin-5-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.988.98-8.89 (m,1H), 8.80 (s, 1H), 8.23 (s, 1H), 8.20-8.18 (d, *J*=8Hz, 1H), 7.94-7.92 (d, *J*=8Hz, 1H), 7.77-7.73 (t, *J*=8Hz, 1H), 7.51-7.49 (d, *J*=8Hz,1H), 7.40 (s,1H), 6.79-6.75 (t, *J*=8Hz, 1H), 6.61-6.60 (d, *J*=4Hz, 1H), 5.13 (s, 1H), 4.48 (m, 1H), 4.30-4.12 (m, 2H), 3.69-3.51 (m, 2H), 3.02 (m, 1H), 2.33-2.22 (m, 2H), 1.98 (m, 2H), 1.78 (m, 4H), 1.60 (m, 1H), 1.38 (m, 1H), 1.24 (m, 4H)	556.3
119	N-(2-(4-((1s,4s)-4-hydroxy-4-(imidazo[1,5-a]pyridin-5-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.89 (m,1H), 8.80 (s, 1H), 8.23 (s, 1H), 8.20-8.18 (d, *J*=8Hz, 1H), 7.94-7.92 (d, *J*=8Hz, 1H), 7.77-7.73 (t, *J*=8Hz, 1H), 7.51-7.49 (d, *J*=8Hz,1H), 7.40 (s,1H), 6.79-6.75 (t, *J*=8Hz, 1H), 6.61-6.60 (d, *J*=4Hz, 1H), 5.13 (s, 1H), 4.48 (m, 1H), 4.30-4.12 (m, 2H), 3.69-3.51 (m, 2H), 3.02 (m, 1H), 2.33-2.22 (m, 2H), 1.98 (m, 2H), 1.78 (m, 4H), 1.60 (m, 1H), 1.38 (m, 1H), 1.24 (m, 4H)	556.3
120	N-(2-(4-((1r,4r)-4-(5-(1,1-dioxidothiomorpholino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90- 9.00 (m, 1 H), 8.30 (d, *J* = 2.0 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.67- 7.76 (m, 1 H), 7.42- 7.48 (m, 2 H), 4.82 (s, 1 H), 4.45- 4.51 (m, 1 H),4.31 (s, 1 H), 4.02- 4.19 (m, 2 H), 4.01 (s, 1 H), 3.80 (s, 4 H), 3.55- 3.57 (m, 2 H), 3.15 (s, 4 H), 2.71- 2.90 (m, 1 H), 2.29 (s, 1 H), 2.12 (s, 1 H), 1.72- 2.11 (m, 3 H), 1.65 (s, 1 H), 1.54 (s, 2 H), 1.39 (s, 2 H), 1.21- 1.35 (m, 3 H).	650.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
121	N-(2-(4-((1s,4s)-4-(5-(1,1-dioxidothiomorpholino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.91- 9.00 (m, 1 H), 8.26 (d, *J* = 2.4 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.42- 7.45 (dd, *J* = 11.6 Hz, 2.8 Hz,1 H), 4.89 (s, 1 H), 4.45- 4.51 (m, 0.5 H), 4.25- 4.32 (m, 0.5 H), 4.02- 4.31 (m, 2 H), 3.92- 4.01(m, 2 H), 3.80 (s, 4 H), 3.60- 3.72 (m, 1 H), 3.52 (s, 1 H), 3.49 (s, 1 H), 3.15 (s, 4 H), 2.97- 3.01 (m, 0.5 H), 2.89- 2.92 (m, 0.5 H), 2.15 (s, 1 H), 1.97 (s, 2 H), 1.52- 1.89 (m, 9 H).	650.4
122	N-(2-(4-(4-hydroxy-1-methyl-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.44 (s, 1 H), 8.95 - 8.89 (m, 3 H), 8.67 - 8.65 (m, 1 H), 8.23 -8.18 (m, 2 H), 7.94 - 7.92 (m, 1 H), 7.86 - 7.84 (m, 1 H), 7.77 - 7.73 (m, 1 H), 7.50 (t, *J* = 4.8 Hz, 1 H), 5.10 -5.09 (m, 1 H), 4.38 - 3.98 (m, 3 H), 3.68 - 3.40 (m, 3 H), 3.01 - 2.86 (m, 3 H), 2.33 - 2.25 (m, 1 H), 2.07 - 1.96 (m, 3 H), 1.86 (s, 3 H), 1.85 - 1.71 (m, 2 H), 1.44 - 1.10 (m, 2 H), 0.88 -0.86 (m, 3 H).	367
123	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-methylmorpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 (bs,1H), 8.22-8.13 (m, 2H), 7.95-7.93 (d, *J*=8Hz, 1H), 7.77-7.67 (m, 2H), 7.50-7.48 (d, *J*=8Hz,1H), 7.31-7.29 (s,1H), 4.86 (s, 1H), 4.44 (m, 1H), 4.29-4.16 (m, 2H),4.14 (m, 1H), 4.10 (m, 2H), 4.01-3.87 (m, 3H), 3.71 (m, 1H), 3.22 (m, 1H), 3.02 (m, 1H), 2.08 (m, 2H), 1.91-1.44 (m, 4H), 1.39-1.32 (m, 6H), 1.05-1.03 (d, *J*=8Hz, 3H)	556.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
124	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-methylmorpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 (bs,1H), 8.22-8.14 (m, 2H), 7.94-7.92 (d, *J*=8Hz, 1H), 7.76-7.67 (m, 2H), 7.46-7.44 (m, 1H), 7.31 (m,1H), 4.86 (s, 1H), 4.44 (m, 1H), 4.29-4.16 (m, 2H), 4.14 (m, 1H), 4.10 (m, 2H), 4.01-3.87 (m, 3H), 3.71 (m, 1H), 3.22 (m, 1H), 3.02 (m, 1H), 2.08 (m, 2H), 1.91-1.44 (m, 4H), 1.39-1.32 (m, 6H), 1.05-1.03 (d, *J*=8Hz, 3H)	556.3
125	N-(2-(4-((1r,4r)-4-hydroxy-4-(6-(trifluoromethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.87 (m, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz,1 H), 8.07 (t, *J* = 7.6 Hz,1 H), 7.93 (t, *J* = 7.6 Hz, 2 H), 7.76-7.67 (m, 2 H), 5.21 (s, 1 H), 4.08-4.01 (m, 1 H), 3.99-3.95 (m, 1 H), 3.62-3.49 (m, 2 H), 3.42-3.39 (m, 1 H), 2.86-2.68 (m, 1 H), 2.46-2.42(m, 2 H), 2.12-2.09 (m, 1 H), 1.92-1.88 (m, 4 H), 1.87-1.68(m, 5 H), 1.62-1.36(m, 2 H), 1.24-0.86(m, 1 H)	585.4
126	N-(2-(4-((1s,4s)-4-hydroxy-4-(6-(trifluoromethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.89 (m, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz,1 H), 8.07 (t, *J* = 7.6 Hz,1 H), 7.99 (t, *J* = 8 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.77-7.69 (m, 2 H), 5.21 (s, 1 H), 4.16-4.11 (m, 1 H), 4.03-3.96 (m, 1 H), 3.67-3.54 (m, 4 H), 3.00-2.89 (m, 1 H), 2.15-2.03 (m, 1 H), 1.99-89(m, 3 H), 1.87-1.65 (m, 7 H), 1.56-1.38 (m, 3 H)	585.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
129	N-(2-(4-(4-hydroxy-4-(6-(4-methylpiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.92-8.98 (m, 1H), 8.23 (s, 1H), 8.18 (d, *J*=7.6Hz, 1H), 7.93 (d, *J*=8Hz, 1H), 7.73-7.77 (m, 1H), 7.48-7.52 (m, 1H), 6.84-6.91(m, 1H), 6.63-6.65 (m, 1H), 4.80-4.83 (m, 1H), 4.27-4.29 (m, 1H), 4.11-4.16 (m, 1H), 3.97-4.03 (m, 1H), 3.61-3.72 (m, 2H), 3.51-3.60 (m, 2H), 3.45-3.65 (m, 4H), 2.85-3.01 (m, 1H), 2.38-2.45 (m, 4H), 2.21-2.25 (s, 3H), 1.8-2.0 (m, 4H), 1.70-1.79 (m, 2H), 1.63-1.70 (m, 2H), 1.47-1.60 (m, 3H).	**615.4**
130	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-methylmorpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.92 (m, 1 H), 8.20 (t, *J* = 12.0 Hz, 3 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.76 - 7.69 (m, 2 H), 7.48 - 7.39 (m, 2 H), 7.33 (d, *J* = 6.4 Hz, 1 H), 4.80 (s, 1 H), 4.29 - 4.18 (m, 1 H), 4.16 - 3.91 (m, 4 H), 3.67 - 3.42 (m, 7 H), 2.85 - 2.68 (m, 1 H), 2.40 - 2.26 (m, 3 H), 1.87 - 1.64 (m, 5 H), 1.39 - 0.91 (m, 8 H).	616.4
131	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-methylmorpholino)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00 - 8.91 (m, 1 H), 8.22 (s, 1 H), 8.19 (d, *J* = 3.2 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 7.35 - 7.32 (m, 1 H), 4.86 (s, 1 H), 4.86 - 4.27 (m, 2 H), 4.19 - 3.90 (m, 3 H), 3.66 - 3.37 (m, 6 H), 2.99 - 2.89 (m, 1 H), 2.70 - 2.55 (m, 2 H), 2.46 - 2.32 (m, 3 H), 1.98 - 1.19 (m, 14 H).	616.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
134	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-methyl-3-oxopiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.91 (m, 1 H), 8.20 (t, *J* = 12.0 Hz, 3 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.37 - 7.35 (m, 1 H), 4.80 (s, 1 H), 4.47 - 4.45 (m, 1 H), 4.30 - 3.97 (m, 3 H), 3.80 (s, 2 H), 3.56 - 3.51 (m, 6 H), 2.90 (s, 3 H), 2.85 - 2.67 (m, 1 H), 2.46 - 2.30 (m, 3 H), 2.11 - 2.10 (m, 1 H), 1.91 - 1.65 (m, 4 H), 1.63 - 1.24 (m, 6 H).	629.3
135	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-methyl-3-oxopiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.91 (m, 1 H), 8.22 - 8.17 (m, 3 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.77 - 7.72 (m, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.37 - 7.34 (m, 1 H), 4.87 (s, 1 H), 4.86 - 4.46 (m, 1 H), 4.45 - 3.97 (m, 3 H), 3.79 (s, 2 H), 3.67 - 3.40 (m, 7 H), 2.90 (s, 3 H), 2.33 - 2.14 (m, 1 H), 1.98 - 1.52 (m, 12 H), 1.51 - 1.26 (m, 1 H).	629.3
136	N-(2-(4-(4-hydroxy-4-(1-methyl-6-oxo-1,6-dihydro-[2,3'-bipyridin]-6'-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.0 - 8.91 (m, 1 H), 8.64 - 8.63 (m, 1 H), 8.22 - 8.17 (m, 2 H), 7.97 - 7.92 (m, 2 H), 7.78 - 7.73 (m, 2 H), 7.49 - 7.45 (m, 1 H), 6.49 - 6.47 (m,1 H), 6.22 (d, *J* = 6.8 Hz 1 H), 5.12 (s, 1 H), 4.5 - 4.23 (m, 1 H), 4.15 - 4 (m, 2 H), 3.63 - 3.48 (m, 2 H), 3.43 - 3.38 (m, 1 H), 3.28 - 3.26 (m, 3 H), 2.86 - 2.78 (m, 1 H), 2.59 - 2.61 (m, 1 H), 2.38 - 2.41 (m, 1 H), 2.14 - 2.1 (m, 1 H), 1.95 - 1.89 (m, 4 H), 1.84 - 1.76 (m, 1 H), 1.74 - 1.65 (m, 3 H), 1.57 - 1.54 (m, 1 H), 1.52 - 1.43 (m, 2 H).	624.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
137	N-(2-(4-((1r,4r)-4-(5'-fluoro-[2,3'-bipyridin]-6'-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.28 (s, 1H), 8.99 (d, *J*=4.8 Hz, 2H), 8.95-8.92 (m, 1H), 8.40-8.37 (m, 1H), 8.23 (s, 1H), 8.20-8.18 (m, 1H), 7.95-7.93 (m, 1H), 7.75 (t, *J*=8Hz, 1H), 7.57 (t, *J*=5.2 Hz, 1H), 5.23-5.22 (m, 1H), 4.46-4.29 (m, 1H), 4.25-4.14 (m, 1H), 4.12-3.98 (m, 1H), 3.68-3.52 (m, 3H), 3.50-3.42 (m, 1H), 3.01-2.91 (m, 1H), 2.30-2.16 (m, 1H), 2.04-1.95 (m, 5H), 1.90-1.85 (m, 2H), 1.78-1.53 (m, 4H), 1.50-1.48 (m, 1H)	613.4
138	N-(2-(4-((1s,4s)-4-(5'-fluoro-[2,3'-bipyridin]-6'-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.28 (s, 1H), 8.98 (d, *J*=5.2Hz, 2H), 8.94-8.92 (m, 1H), 8.40-8.37 (m, 1H), 8.23 (s, 1H), 8.20-8.18 (m, 1H), 7.95-7.93 (m, 1H), 7.75 (t, *J*=8Hz, 1H), 7.57 (t, *J*=4.8Hz, 1H), 5.23-5.22 (m, 1H), 4.48-4.27 (m, 1H), 4.18-4.12 (m,, 1H), 4.03-3.99 (m, 1H), 3.68-3.52 (m, 3H), 3.48-3.44 (m, 1H), 3.01-2.91 (m, 2H), 2.19-2.15 (m, 1H), 2.01-1.95 (m, 4H), 1.90-1.87 (m, 2H), 1.84-1.65 (m, 4H), 1.64-1.53 (m, 1H)	613.4
139	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-oxopyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.91-8.98 (m, 1H), 8.73 (d, *J*=2.4Hz, 1H), 8.23 (s, 1H), 8.18 (d, *J*=7.6Hz, 1H), 8.04-8.07 (m, 1H), 7.93 (d, *J*=8Hz, 1H), 7.74 (t, *J*=15.6Hz, 1H), 7.6 (d, *J*=8.8Hz, 1H), 4.96 (s, 1H), 4.28-4.50 (m, 1H), 4.08-4.20 (m, 1H), 3.95-4.03 (m, 1H), 3.87 (t, *J*=10 Hz, 2H), 3.38-3.63 (m, 3H), 2.71-2.90 (m, 1H), 2.25-2.41 (m, 4H), 2.25-2.0 (m, 4H), 1.76-2.0 (m, 4H), 1.49-1.71 (m, 4H), 1.36-1.48 (m, 2H).	600.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
140	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-oxopyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90-9.0 (M, 1H), 8.73 (d, *J*=2.4Hz, 1H), 8.22 (s, 1H), 8.18 (d, *J*=3.6Hz, 1H), 8.04-8.07 (m, 1H), 7.93 (d, *J*=8Hz, 1H), 7.55 (t, *J*=14Hz, 1H), 7.6 (d, *J*=8.8Hz, 1H), 4.99 (s, 1H), 4.40-4.52 (m, 1H), 4.23-4.39 (m, 1H), 4.11-4.19 (m, 1H), 3.97-4.05 (m, 1H), 3.86 (t, *J*=6.8Hz, 2H), 3.60-3.72 (m, 1H), 3.50-3.60 (m, 1H), 3.38-3.45 (m, 1H), 2.85-3.03 (m, 2H), 2.01-2.28 (m, 4H), 1.98-2.0 (m, 2H), 1.7-1.9 (m, 4H), 1.56-1.70 (m, 4H), 1.40-1.50 (m, 1H).	600.3
141	N-(2-(4-((1r,4r)-4-(5-(4,4-difluoropiperidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 (m, 1H), 8.28-8.22 (m, 2H), 8.19-8.17 (m, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.77-7.67 (m, 1H), 7.48-7.39 (m, 2H), 4.81 (s, 1H), 4.67-4.12 (m, 3H), 4.10-3.97 (m, 2H), 3.79-3.50 (m, 4H), 2.84-2.77 (m, 1H), 2.45-2.26 (m, 2H), 2.12-2.08 (m, 4H), 2.02-1.77 (m, 4H), 1.74-1.65 (m, 1H), 1.63-1.38 (m,4H), 1.34-1.28 (m, 1H), 1.24-1.11(m, 2H), 0.88-0.84 (m, 1H)	636.4
142	N-(2-(4-((1s,4s)-4-(5-(4,4-difluoropiperidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98- 8.92 (m, 1H), 8.26-8.18 (m, 3H), 7.93 (d, *J* = 8 Hz, 1H), 7.75 (t, *J* = 8 Hz, 1H), 7.51-7.49 (m, 1H), 7.43-7.40 (m, 1H), 4.68 (bs, 1H), 4.50-4.45 (m, 1H), 4.30-4.28 (m, 1H), 4.17-4.12 (m, 1H), 4.03-3.99 (m, 1H), 3.77-3.62 (m, 1H), 3.61-3.51 (m, 2H), 3.50-3.47 (m, 2H), 3.34-3.22 (m, 2H), 3.18-2.90 (m, 1H), 2.15-2.08 (m, 5H), 2.01-1.79 (m, 4H), 1.71-1.67 (m, 4H), 1.64-1.49 (m, 3H).	636.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
143	N-(2-(4-((1r,4r)-4-hydroxy-4-(1-methyl-6-oxo-1,6-dihydro-[2,3'-bipyridin]-6'-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.91 (m, 1 H), 8.62 (s, 1 H), 8.17 (t, *J* = 20 Hz, 2 H), 7.94 - 7.9 (m, 2 H), 7.76 - 7.71 (m, 2 H), 7.47 - 7.43 (m, 1 H), 6.46 (d, *J* = 9.2 Hz, 1 H), 6.19 (d, *J* = 6.4 Hz, 1 H), 5.1 (s, 1 H), 4.52 - 4.27 (m, 2 H), 4.15 - 3.91 (m, 2 H), 3.61 - 3.56 (m, 2 H), 3.5 - 3.41 (m, 1 H), 3.31 - 3.24 (m, 3 H), 2.84 - 2.77 (m, 1 H), 2.65 - 2.57 (m, 1 H), 2.1 - 2.06 (m, 2 H), 1.89 - 1.76 (m, 3 H), 1.63 - 1.52 (m, 3 H), 1.42 - 1.32 (m, 2 H), 1.26 - 1.22 (m, 1 H).	624.4
144	N-(2-(4-((1s,4s)-4-hydroxy-4-(1-methyl-6-oxo-1,6-dihydro-[2,3'-bipyridin]-6'-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.9 (m, 1 H), 8.59 (s, 1 H), 8.18 (t, *J* = 20.2 Hz, 2 H), 7.95 - 7.91 (m, 2 H), 7.79 - 7.71 (m, 2 H), 7.46 - 7.42 (m, 1 H), 6.45 (d, *J* = 9.6 Hz, 1 H), 6.19 (d, *J* = 6.8 Hz, 1 H), 5.12 (s, 1 H), 4.44 - 4.42 (m, 1 H), 4.3 - 4.25 (m, 1 H), 4.17 4.11 (m, 1 H), 4.0 - 3.94 (m, 1 H), 3.68 - 3.61 (m, 1 H), 3.56 - 3.48 (m, 1 H), 3.45 - 3.31 (m, 1 H), 3.23 - 3.18 (m, 3 H), 3.06 - 2.9 (m, 1 H), 2.13 - 2.07 (m, 1 H), 2.03 - 1.89 (m, 3 H), 1.83 - 1.63 (m, 7 H), 1.48 - 1.52 (m, 1 H).	624.4
147	6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)-2-methylnicotinamide	8.99 - 8.92 (m, 1 H), 8.20 (t, *J* = 12.4 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.83 (s, 1 H), 7.76 - 7.68 (m, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 5.02 (s, 1 H), 4.47 - 4.25 (m, 1 H), 4.18 - 3.92 (m, 2 H), 3.58 - 3.37 (m, 2 H), 2.87 - 2.80 (m, 1 H), 2.33 - 2.27 (m, 2 H), 2.12 - 1.87 (m, 4 H), 1.78 - 1.52 (m, 4 H), 1.41 - 1.14 (m, 8 H).	574.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
148	6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)-2-methylnicotinamide	9.00 - 8.92 (m, 1 H), 8.21 (t, J = 12.0 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.83 (s, 1 H), 7.77 - 7.71 (m, 2 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.46 (s, 1 H), 5.04 (d, *J* = 2.8 Hz, 1 H), 4.47 - 4.27 (m, 1 H), 4.20 - 3.97 (m, 2 H), 3.67 - 3.27 (m, 3 H), 2.99 - 2.91 (m, 1 H), 2.46 - 2.45 (m, 3 H), 2.14 - 1.56 (m, 14 H).	574.3
149	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-methylpyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.4 (s, 1H), 8.99-8.96 (m, 1H), 8.79 (d, *J* = 8 Hz, 1H), 8.65-8.63 (d, *J* = 8 Hz, 1H), 8.22-8.17 (m, 2H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.80-7.72 (m, 2H), 7.38-7.37 (d, *J* = 8 Hz, 1H), 5.11 (s, 1H), 4.49-4.31 (m, 1H),4.10-3.94 (m, 3H), 3.92-3.58 (m, 3H), 2.86-2.80 (m, 1H), 2.42-2.33 (m, 2H), 2.33-2.29 (m, 1H), 2.14-2.09 (m, 1H), 1.93-1.85 (m, 5H), 1.79-1.77 (m, 4H), 1.69-1.52 (m, 3H)	609.1
150	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-methylpyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.41 (s, 1H), 8.98-8.92 (m, 1H), 8.78-8.77 (d, *J* = 4 Hz, 1H), 8.65-8.64 (d, *J* = 4 Hz, 1H), 8.22-8.18 (m, 2H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.85-7.83 (d, *J* = 8 Hz, 1H), 7.75-7.71 (t, *J* = 8 Hz, 1H), 7.38-7.37 (d, *J* = 8 Hz, 1H), 5.12 (s, 1H), 4.48-4.30 (m, 2H), 4.21-4.13 (m, 3H), 3.65-3.41 (m, 3H), 3.01-2.68 (m, 1H), 2.11-1.91 (m, 5H), 1.86-1.68 (m, 6H), 1.52-1.43 (m, 1H), 1.38-1.34 (m, 4H).	609.1

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
151	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.88 (m, 1 H), 8.22 - 8.17 (m, 3 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.30 (m, 1 H), 4.76 (s,1 H), 4.67 (d, *J* = 4.4 Hz, 1 H), 4.47 - 4.28 (m, 1 H), 4.18 - 4.04 (m, 1 H), 4.03 - 3.99 (m, 1 H), 3.67 - 3.6 (m, 2 H), 3.57 - 3.53 (m, 3 H), 3.41 - 3.4 (m, 2 H), 2.91 - 2.84 (m, 2 H), 2.72 - 2.8 (m, 1 H), 2.34 - 2.25 (m, 2 H), 2.14 - 2.08 (m, 1 H), 1.91 - 1.75 (m, 6 H), 1.54 - 1.52 (m, 1 H), 1.51 - 1.46 (m, 4 H), 1.44 - 1.38 (m, 2 H).	616.4
152	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1 H), 8.23 (s, 1 H), 8.19 (d, *J* = 7.2 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.3 (m, 1 H), 4.81 (s, 1 H), 4.66 (d, *J* = 4.4 Hz, 1 H), 4.47 - 4.28 (m, 1 H), 4.19 - 4.11 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.67 - 3.6 (m, 2 H), 3.56 - 3.52 (m, 3 H), 3.42 - 3.4 (m, 1 H), 3.25 - 3.23 (m, 1 H), 2.99 - 2.83 (m, 3 H), 2.15 - 2.08 (m, 1 H), 1.97 - 1.91 (m, 2 H), 1.89 - 1.80 (m, 4 H), 1.76 - 1.56 (m, 2 H), 1.52 - 1.51 (m, 2 H), 1.5 - 1.46 (m, 4 H).	616.4
153	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00-8.90 (m, 1H), 8.59 (s, 1H), 8.22 (s, 1H), 8.19-8.17 (dd, *J* = 8 Hz, 1H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.88-7.86 (d, *J* = 8 Hz, 1H), 7.76-7.68 (m, 2H), 6.97-6.95 (d, *J* = 8 Hz, 1H), 5.28-5.25 (m, 1H), 5.03 (s, 1H), 4.48-4.29 (m, 2H), 4.18-3.97 (m, 2H), 3.58-3.50 (m, 3H), 2.86-2.68 (m, 1H), 2.33-2.08 (m, 3H), 1.91-1.80 (m, 4H), 1.70-1.58 (m, 3H), 1.41-1.21 (m, 3H).	615.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
154	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00-8.91 (m, 1H), 8.57 (s, 1H), 8.23 (s, 1H), 8.20-8.18 (dd, *J* = 8 Hz, 1H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.88-7.86 (d, *J* = 8 Hz, 1H), 7.77-7.71 (m, 2H), 6.96-6.95 (d, *J* = 4 Hz, 1H), 5.28-5.25 (m, 1H), 5.04 (s, 1H), 4.47-4.19 (m, 1H), 4.17-3.9 6(m, 2H), 3.67-3.49 (m, 3H), 3.23 (m, 1H), 3.00-2.89 (m, 1H), 2.15-2.13 (m, 1H), 2.08-1.97 (m, 3H), 1.94-1.68 (m, 8H), 1.60 (m, 1H).	615.3
155	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.50 (d, *J* = 1.6 Hz, 1 H), 9.40 (s, 2 H), 8.99 - 8.90 (m, 1 H), 8.74 - 8.71 (m, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 7.94 - 7.86 (m, 2 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 5.18 (s, 1 H), 4.47 - 4.30 (m, 1 H), 4.14 - 3.92 (m, 2 H), 3.63 - 3.51 (m, 3 H), 2.86 - 2.80 (m, 1 H), 2.33 - 2.27 (m, 2 H), 2.14 - 2.08 (m, 1 H), 1.95 - 1.90 (m, 4 H), 1.85 - 1.77 (m, 4 H), 1.65 - 1.07 (m, 3 H).	663.4
156	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(5-(trifluoromethyl)pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.48 (d, *J* = 2.0 Hz, 1 H), 9.39 (s, 2 H), 9.00 - 8.91 (m, 1 H), 8.74 - 8.71 (m, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 7.93 (d, J = 9.2 Hz, 2 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 5.19 (s, 1 H), 5.19 - 4.48 (m, 1 H), 4.46 - 4.12 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.68 - 3.52 (m, 3 H), 3.01 - 2.91 (m, 1 H), 2.45 - 2.33 (m, 1 H), 2.33 - 1.71 (m, 4 H), 1.69 - 1.24 (m, 9 H).	663.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
157	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.27-9.22 (m, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 8.08 (d, *J* = 2.4 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 7.17 (dd, J = 8.8 Hz, J = 2.4 Hz, 1 H), 4.73 (s, 1 H), 4.46-4.44 (m, 1 H), 4.03-3.98 (m, 2 H), 3.56 - 3.52 (m, 2 H), 3.39 - 3.36 (m, 2 H), 3.21 (s, 2H), 2.83 (d, *J* = 8.6 Hz, 2 H), 2.34 - 2.33 (m, 2 H), 2.23 (S, 3H), 2.0-1.79 (m, 8 H), 1.63 (d, *J* = 7.2 Hz, 2 H), 1.51 (S, 4H), 1.52 - 1.32 (m, 4 H).	641.4
158	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.91 (m, 2 H), 8.20 (s, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.06 (s, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 7.19 (m, 1 H), 4.82 (s, 1 H), 4.44-4.42 (m, 1 H), 4.13-3.98 (m, 2 H), 3.62 - 3.54 (m, 2 H), 3.39 - 3.36 (m, 5 H), 2.89 (brS, 3 H), 2.34 - 2.33 (m, 2 H), 2.12-2.52 (m, 14 H).	641.4
161	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyridazin-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.27-9.22 (m, 2 H), 9.00-8.91 (m, 1 H), 8.53 - 8.50 (m, 1 H), 8.32 - 8.29 (m, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.88-7.82 (m, 2 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 5.15 (d, *J* = 4.0 Hz, 1 H), 4.45 - 4.32 (m, 1 H), 4.27 - 4.12 (m, 1 H), 4.04 - 3.96 (m, 1 H), 3.71 - 3.43 (m, 3 H), 3.37 - 3.21 (m, 1 H), 3.03 - 2.91 (m, 1 H), 2.19 - 1.96 (m, 4 H), 1.92 - 1.66 (m, 8 H), 1.56 - 1.49 (m, 1 H).	595.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
162	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyridazin-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.27-9.24 (m, 2 H), 9.00 - 8.90 (m, 1 H), 8.53 - 8.51 (m, 1 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.85 - 7.82 (m, 2 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 5.14 (s, 1 H), 4.49 - 4.30 (m, 1 H), 4.19 - 3.98 (m, 2 H), 3.63 - 3.43 (m, 3 H), 2.87 - 2.81 (m, 1 H), 2.56 - 2.36 (m, 4 H), 2.14 - 2.12 (m, 1 H), 2.08 - 1.78 (m, 4 H), 1.77 - 1.58 (m, 3 H), 1.53 - 1.45 (m, 2 H).	595.3
163	N-(2-(4-((1R,2S,4R)-2-fluoro-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.44 (s, 1 H), 8.90-9.00 (m, 3 H), 8.67 (d, *J* = 8.4 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 5.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 5.40 (t, *J* = 3.2 Hz, 1 H), 4.90 - 5.15 (m, 1 H), 4.22-4.51 (m, 1 H), 4.0-4.21 (m, 2 H), 3.68- 3.95 (m, 1 H), 3.51-3.62 (m, 1 H), 3.39-3.50 (m, 1 H), 2.89-3.00 (m, 1 H), 2.71-2.98 (m, 3 H), 2.23 (s, 1 H), 2.02 (s, 1 H), 1.67-2.01 (m, 5 H), 1.52- 1.72 (m, 1 H), 1.32- 1.51 (m, 1 H).	613.3
164	N-(2-(4-((1R,2S,4S)-2-fluoro-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.45 (d, *J* = 2.0 Hz, 1 H), 8.90-9.01 (m, 3 H), 8.68-8.71 (dd, *J* = 2.0 Hz, 10.4 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 5.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 4.8 Hz, 1 H), 5.49 (d, *J* = 3.6 Hz, 1 H), 4.69 - 5.21 (m, 1 H), 4.21- 4.52 (m, 1 H), 4.12-4.21 (m, 1 H), 3.95- 4.05 (m, 1 H), 3.52-3.90 (m, 2 H), 3.42-3.52 (m, 1 H), 3.12 (s, 1 H), 2.89 -3.09 (m, 2 H), 2.75 (s, 1 H), 2.62 (s, 1 H), 2.32 (s, 1 H), 2.15 (s, 2 H), 2.02 (s, 2 H), 1.85 (s, 2 H), 1.71 (s, 1 H).	613.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
165	N-(2-(4-((1R,2R,4R)-2-fluoro-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.42 (d, *J* = 2.0 Hz, 1 H), 8.91-8.99 (m, 3 H), 8.66-8.69 (dd, *J* = 2.0 Hz, 10.4 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 5.20 (s, 1 H), 4.29 - 4.60 (m, 1 H), 4.10- 4.25 (m, 1 H), 3.96- 4.08 (m, 1 H), 3.61- 3.78 (m, 1 H), 3.49- 3.59 (m, 1 H), 3.01- 3.17 (m, 1 H), 2.72- 2.89 (m, 1 H), 2.33- 2.37 (m, 2 H), 2.14- 2.28 (m, 3 H), 1.97- 2.10 (m, 1 H), 1.75- 1.80 (m, 1 H), 1.73 (s, 2 H), 1.63 (s, 2 H), 1.51 (s, 1 H), 1.25 (s, 1 H).	613.3
166	N-(2-(4-((1R,2R,4S)-2-fluoro-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.42 (d, *J* = 2.0 Hz, 1 H), 8.91-8.99 (m, 3 H), 8.66-8.69 (dd, *J* = 2.0 Hz, 10.4 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 5.03 (s, 1 H), 4.21 - 4.51 (m, 1 H), 4.10- 4.20 (m, 1 H), 3.96- 4.08 (m, 1 H), 3.61- 3.78 (m, 2 H), 3.51 (s, 1 H), 3.01- 3.17 (m, 1 H), 2.72- 2.89 (m, 1 H), 1.99- 2.39 (m, 6 H), 1.82-1.97 (m, 1 H), 1.75 (s, 1 H), 1.65 (s, 2 H), 1.49- 1.53 (m, 1 H), 1.25 (s, 1 H).	613.3
167	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3,3,4-trimethylpiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.92 (m, 1 H), 8.22 - 8.17 (m, 3 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.43 (d, *J* = 8 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 4.79 (s,1 H), 4.47 - 4.28 (m, 1 H), 4.18 - 3.97 (m, 2 H), 3.57 - 3.56 (m, 2 H), 3.18 - 3.17 (m, 2 H), 2.92 - 2.78 (m, 3 H), 2.34 - 2.30 (m, 4 H), 2.10 - 2.08 (m, 1 H), 1.91 - 1.76 (m, 8 H), 1.66 - 1.60 (m, 1 H), 1.526 (s, 3 H), 1.40 - 1.34 (m, 2 H), 1.09 (s, 6 H).	643.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) [M+H]$^+$
168	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3,3,4-trimethylpiperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.91 (m, 1 H), 8.23 - 8.16 (m, 3 H), 7.94 (d, *J* = 8 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.3 (dd, *J* = 11.6 Hz, 1 H), 4.85 (s, 1 H), 4.77 - 4.45 (m, 1 H), 4.43 - 4.08 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.7 - 3.63 (m, 1 H), 3.57 - 3.47 (m, 1 H), 3.42 - 3.38 (m, 1 H), 3.25 - 3.18 (m, 1 H), 3.13 (s, 2 H), 2.99 - 2.89 (m, 3 H), 2.6 - 2.57 (m, 2 H), 2.17 (s, 3 H), 2.08 - 1.83 (m, 5 H), 1.8 - 1.74 (m, 2 H), 1.67 - 1.64 (m, 2 H), 1.58 - 1.52 (m, 3 H), 1.08 (s, 6 H).	643.4
169	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.91 (m, 1H), 8.21-8.17 (m, 3H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.77-7.73 (t, *J* = 8 Hz, 1H), 7.49-7.47 (d, *J* = 8 Hz, 1H), 7.34-7.31 (d, *J* = 8 Hz, 1H), 4.79 (s, 1H), 4.46-4.27 (m, 1H), 4.16-3.97 (m, 2H), 3.56-3.55 (m, 2H), 3.32 (m, 1H), 3.26-3.23 (m, 3H), 3.18 (m, 4H), 2.84-2.76 (m, 5H), 2.33-2.27 (m, 1H), 1.91-1.84 (m, 5H), 1.66-1.63 (m, 2H), 1.52-1.38 (m, 2H) 1.15 (m, 3H)	683.3
170	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.91 (m, 1H), 8.22-8.18 (m, 3H), 7.94-7.92 (d, *J* = 8 Hz, 1H), 7.77-7.73 (t, *J* = 8 Hz,1H), 7.45-7.42 (d, *J* = 8 Hz, 1H), 7.34-7.32 (d, *J* = 8 Hz, 1H), 4.85 (s, 1H), 4.46-4.26 (m, 1H), 4.16-3.97 (m, 2H), 3.69-3.62 (m, 3H), 3.40-3.32 (m, 3H), 3.35-3.32 (m, 4H), 3.16-3.01 (m, 1H), 2.99 (m, 4H), 2.77 (m, 1H), 2.67 (m, 1H), 2.51-2.50 (m, 4H), 1.92-1.67 (m, 7H).	683.3

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
171	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-oxoimidazolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.89 (m, 1H), 8.61 (d, *J*=2.4Hz, 1H), 8.22 (s, 1H), 8.19 (d, *J*=7.6Hz, 1H), 8.04-8.01 (m, 1H), 7.94-7.92 (m, 1H), 7.75 (t, *J*=8Hz, 1H), 7.55 (d, *J*=8.8Hz, 1H), 7.05 (s, 1H), 4.88 (s, 1H), 4.47-4.55 (m, 1H), 4.30-4.14 (m, 1H), 4.13-3.98 (m, 1H), 3.91-3.87 (m, 2H), 3.57-3.54 (m, 2H), 3.47-3.40 (m, 3H), 2.85-2.78 (m, 1H), 2.44-2.41 (m, 3H), 2.38-2.33 (m, 2H), 2.12-2.08 (m, 1H), 1.94-1.78 (m, 4H), 1.67-1.55 (m, 3H), 1.53-1.14 (m, 2H)	601.3
172	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-oxoimidazolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.0-8.91 (m, 1H), 8.61 (d, *J*=2.4Hz, 1H), 8.23 (s, 1H), 8.2-8.18 (m, 1H), 8.0-7.93 (m, 2H), 7.75 (t, *J*=8 Hz, 1H), 7.59 (d, *J*=8.8Hz, 1H), 7.05 (s, 1H), 4.49 (bs, 1H), 4.47-4.46 (m, 1H), 4.44-4.28 (m, 1H), 4.25-4.00(m, 2H), 3.99-3.86 (m, 2H), 3.57-3.49 (m, 3H), 3.0-2.98 (m, 1H), 2.3-2.15 (m, 1H), 2.01-1.83 (m, 5H), 1.81-1.68 (m, 4H), 1.65-1.49 (m, 3H)	601.3
173	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.91 (m, 1 H), 8.63 (t, *J* = 2.4 Hz, 1 H), 8.20 (t, *J* = 11.6 Hz, 2 H), 8.02 - 7.99 (m, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, i = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 4.88 (s, 1 H), 4.47 - 4.28 (m, 1 H), 4.18 - 3.97 (m, 2 H), 3.83 (t, *J* = 7.6 Hz, 2 H), 3.57 - 3.34 (m, 5 H), 2.85 - 2.78 (m, 4 H), 2.37 - 2.19 (m, 3 H), 2.10 - 2.07 (m, 4 H), 1.89 - 1.54 (m, 4 H), 1.54 - 1.40 (m, 2 H).	615.3

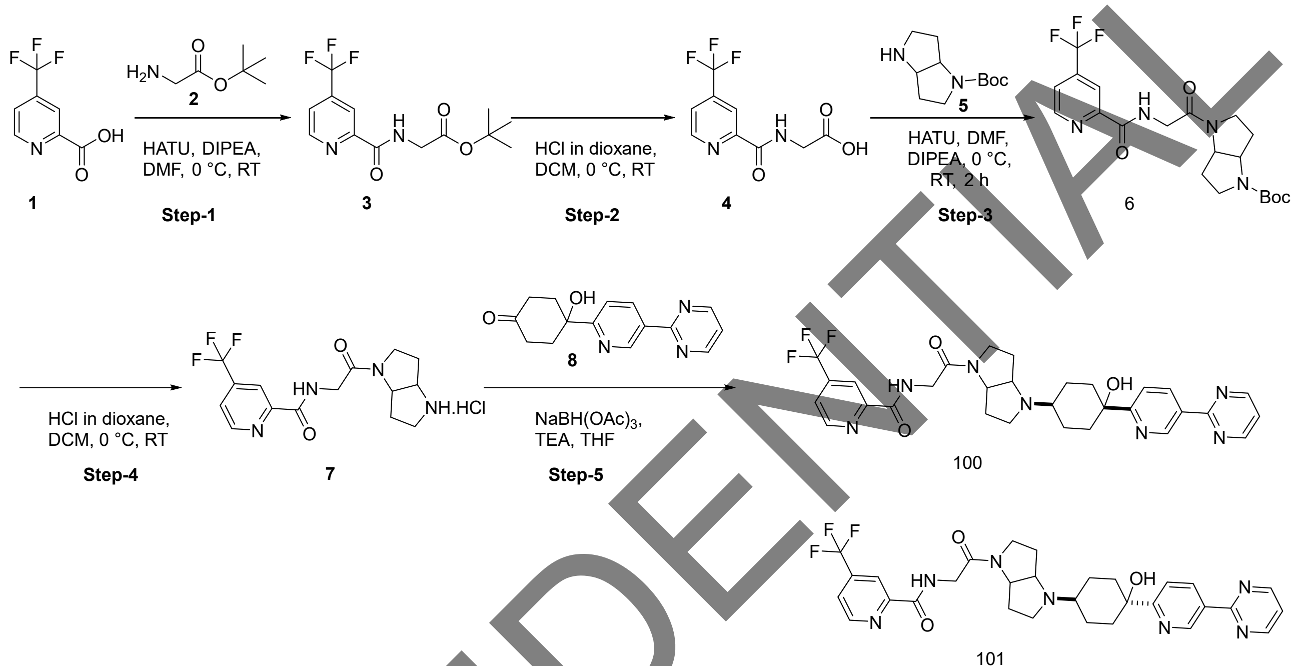
Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
174	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-methyl-2-oxoimidazolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.90 (m, 1 H), 8.64 (d, *J* = 4.0 Hz, 1 H), 8.21 (t, J = 11.6 Hz, 2 H), 7.98-7.92 (m, 2 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 4.92 (d, *J* = 3.2 Hz, 1 H), 4.47 - 4.28 (m, 1 H), 4.20 - 4.17 (m, 1 H), 4.03 - 3.97 (m, 1 H), 3.80 (t, *J* = 7.2 Hz, 2 H), 3.64 - 3.51 (m, 1 H), 3.49 - 3.42 (m, 3 H), 3.01 - 2.89 (m, 1 H), 2.78 (s, 3 H), 2.15 - 2.01 (m, 1 H), 1.98 - 1.58 (m, 11 H), 1.58 - 1.49 (m, 1 H).	615.3
175	N-(2-(4-((1r,4r)-4-hydroxy-4-(1'-methyl-2'-oxo-1',2'-dihydro-[3,4'-bipyridin]-6-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00 - 8.90 (m, 1 H), 8.87 (s, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 8.13 (dd, *J* = 2.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.82 - 7.72 (m, 3 H), 6.77 (s, 1 H), 7.64 (d, i = 6.8 Hz, 1 H), 5.08 (s, 1 H), 4.51 - 4.27 (m, 1 H), 4.18 - 3.98 (m, 2 H), 3.63 - 3.51 (m, 2 H), 3.49 - 3.37 (m, 4 H), 2.86 - 2.67 (m, 3 H), 2.41 - 2.33 (m, 2 H), 2.27 - 1.88 (m, 5 H), 1.83 - 1.15 (m, 5 H).	624.3
176	N-(2-(4-((1s,4s)-4-hydroxy-4-(1'-methyl-2'-oxo-1',2'-dihydro-[3,4'-bipyridin]-6-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00 - 8.91 (m, 1 H), 7.84 (d, *J* = 2.0 Hz, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 8.13 (dd, *J* = 2.4 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.82 - 7.73 (m, 3 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 7.64 (dd, J = 2.0 Hz, 1 H), 5.11 (s, 1 H), 4.47 - 4.20 (m, 1 H), 4.19 - 3.96 (m, 2 H), 3.70 - 3.43 (m, 6 H), 3.35 - 3.20 (m, 1 H), 3.02 - 2.92 (m, 1 H), 2.15 - 1.50 (m, 13 H).	624.3
177	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(N-methylacetamido)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90- 8.99 (m, 1 H), 8.51 (s, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.71- 7.76 (m, 3 H), 5.05 (s, 1 H), 4.28- 4.46 (m, 1 H), 4.12- 4.14 (m, 1 H), 3.99- 4.08 (m, 1 H), 3.50- 3.61 (m, 2 H), 3.50 (s, 1 H), 3.17 (d, *J* = 5.2 Hz, 2 H), 2.67-2.86 (m, 1 H), 2.55 (s,1 H), 2.25- 2.38 (m, 3 H), 2.08- 2.13 (m, 1 H), 1.89- 1.91 (m, 3 H), 1.79 (s, 3 H),1.61- 1.72 (m, 4 H), 1.51- 1.54 (m, 3 H).	588.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
178	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(N-methylacetamido)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90- 8.99 (m, 1 H), 8.49 (s, 1 H), 8.22 (s, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 3 H), 5.06 (s, 1 H), 4.28- 4.47 (m, 1 H), 4.11- 4.20 (m, 1 H), 3.96- 4.03 (m, 1 H), 3.59- 3.67 (m, 2 H), 3.54- 3.57 (m, 1 H), 3.27 (s, 1 H), 3.16 (s, 3 H), 2.90- 3.02 (m,1 H), 2.15- 2.18 (m, 1 H), 2.08- 2.18 (m, 3 H), 1.52- 2.02 (m, 10 H), 1.24- 1.30 (m, 2 H).	588.4
183	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(1-methyl-2-oxopiperidin-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.90 (m, 1 H), 8.43 (s, 1 H), 8.20 (t, *J* = 12.0 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.76 - 7.67 (m, 2 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 4.94 (s, 1 H), 4.53 - 4.28 (m, 2 H), 4.14 - 3.99 (m, 2 H), 3.57 - 3.26 (m, 4 H), 3.26 - 3.09 (m, 1 H), 2.86 - 2.78 (m, 4 H), 2.46 - 2.27 (m, 4 H), 2.12 - 1.66 (m, 7 H), 1.57 - 1.14 (m, 87 H).	628.4
184	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(1-methyl-2-oxopiperidin-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00 - 8.92 (m, 1 H), 8.41 (d, *J* = 1.6 Hz, 1 H), 8.21 (t, *J* = 12.0 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.77 - 7.68 (m, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 4.98 (s, 1 H), 4.47 - 4.28 (m, 1 H), 4.20 - 3.96 (m, 2 H), 3.69 - 3.37 (m, 4 H), 3.29 - 3.00 (m, 3 H), 2.46 - 2.33 (m, 3 H), 2.15 - 1.58 (m, 15 H), 1.51 - 1.24 (m, 4 H).	628.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
185	N-(2-(4-((1r,4r)-4-(5-(3,3-difluoropyrrolidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.91 (m, 2H), 8.22-8.17 (m, 2H), 7.94-7.92 (m, 2H), 7.75 (t, *J*=8 HZ, 1H), 7.43 (d, *J*=8.8 Hz, 1H), 7.05-7.01 (m, 1H), 4.77 (s, 1H), 4.47-4.27 (m, 1H), 4.14-3.98 (m, 2H), 3.76-3.70 (m , 3H), 3.57-3.49 (m, 6H), 3.21-3.17 (m, 1H), 2.84-2.77 (m, 1H), 2.33-2.28 (m, 2H), 2.11-2.08 (m, 1H), 1.89-1.75 (m, 5H), 1.53-1.52 (m, 2H), 1.40-1.38 (m, 2H)	622.4
186	N-(2-(4-((1s,4s)-4-(5-(3,3-difluoropyrrolidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.92 (m, 2H), 8.23-8.19 (m, 2H), 7.95-7.91 (m, 2H), 7.75 (t, *J*=7.6 Hz, 1H), 7.48 (d, *J*=4.8 Hz, 1H), 7.05-7.02 (m, 1H), 4.84 (s, 1H), 4.17-4.12 (m, 1H), 4.03-3.98 (m, 1H), 3.75- 3.57 (m, 4H), 3.54-3.48 (m, 4H), 3.01-2.89 (m, 1H), 2.59-2.55 (m, 2H), 2.34-2.15 (m, 1H), 1.99-1.83 (m, 5H), 1.80-1.71 (m, 2H), 1.67-1.59 (m, 2H), 1.56-1.51 (m, 2H)	622.4
187	N-(2-(4-((1r,4r)-4-(5-(bicyclo[1.1.1]pentan-1-ylamino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.91 (m, 1 H), 8.20 (t, *J* = 12.0 Hz, 2 H), 7.97-7.92 (m, 2 H), 7.76-7.69 (m, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.06 (m, 1 H), 6.48 (s, 1 H), 4.68 (s, 1 H), 4.46 - 4.25 (m, 1 H), 4.18 - 3.92 (m, 2 H), 3.56 - 3.55 (m, 2 H), 2.85-2.76 (m, 1 H), 2.27 - 2.26 (m, 2 H), 2.04 (s, 7 H), 1.90 - 1.81 (m, 4 H), 1.76 - 1.63 (m, 1 H), 1.63 - 1.51 (m, 4 H), 1.38 - 1.34 (m, 3 H), 1.32 - 1.11 (m, 1 H).	598.4
188	N-(2-(4-((1s,4s)-4-(5-(bicyclo[1.1.1]pentan-1-ylamino)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.978-8.91 (m, 1 H), 8.18 (t, *J* = 12 Hz, 2 H), 7.91 (d, *J* = 8.4 Hz, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.32 (d, i = 8.4 Hz, 1 H), 7.03 - 7.01 (m, 1 H), 6.44(s, 1 H), 4.74 (s, 1 H), 4.42 - 4.25 (m, 1 H), 4.16 - 3.92 (m, 2 H), 3.61-3.30 (m, 3 H), 3.25 - 3.21 (m, 1 H), 2.96 - 2.87 (m, 1 H), 2.48 - 2.44 (m, 2 H), 2.12 - 2.00 (m, 7 H), 1.91 - 1.51 (m, 11 H).	598.4

Ex.	IUPAC name	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
189	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-methoxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.92 (m, 2 H), 8.22 (s, 2 H), 8.18 (d, *J* = 8 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.43 - 7.35 (m, 2 H), 4.77 (s,1 H), 4.45 - 4.29 (m, 1 H), 4.18 - 3.97 (m, 2 H), 3.53 - 3.45 (m, 5 H), 3.29 (s, 3 H), 2.95 - 2.91 (m, 2 H), 2.85 - 2.72 (m, 1 H), 2.34 - 2.29 (m, 2 H), 2.19 - 2.02 (m, 1 H), 1.95 - 1.76 (m, 6 H), 1.65 - 1.49 (m, 6 H), 1.48 - 1.3 (m, 2 H), 0.87 - 0.84 (m, 2 H).	630.6
190	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-methoxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9 - 8.92 (m, 1 H), 8.23 (s, 1 H), 8.2 - 8.18 (m, 2 H), 7.93 (d, *J* = 7.5 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.35 - 7.32 (m, 1 H), 4.85 (s, 1 H), 4.46 - 4.3 (m, 1 H), 4.2 - 4.12 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.8 - 3.35 (m, 2 H), 3.7 - 3.65 (m, 1 H), 3.52 - 3.45 (m, 4 H), 3.27 (s, 3 H), 2.94 - 2.88 (m, 3 H), 2.34 - 2.33 (m, 1 H), 2.17 - 2.13 (m, 1 H), 1.95 - 1.83 (m, 6 H), 1.8 - 1.66 (m, 4 H), 1.6 - 1.48 (m, 5 H).	630.6

Procedure 50: N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide (100) and N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide (101)



Step 1: Preparation of *tert*-butyl (4-(trifluoromethyl)picolinoyl)glycinate

[0421] To a stirred solution of 4-(trifluoromethyl)pyridine-2-carboxylic acid (1 g, 5.23 mmol, 1 eq) in DMF (15 mL) were added *tert*-butyl 2-aminoacetate (0.82 g, 6.28 mmol, 1.2 eq), ethylbis(propan-2-yl)amine (2.74 mL, 15.7 mmol, 3 eq), and hexafluoro-λ^5-phosphanuide 1-[bis(dimethylamino)methylidene]-1H-1λ^5-[1,2,3]triazolo[4,5-b]pyridin-3-ium-1-ylium-3-olate (3.98 g, 10.5 mmol, 2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and progress of the reaction was checked by TLC monitoring. After completion of the reaction, the reaction mixture was poured into cold water (30 mL), extracted with ethyl acetate (2 x 100 mL), and concentrated *in vacuo* to yield the crude. The crude was purified by flash column chromatography using 20% EtOAc/heptane as eluent to afford *tert*-butyl 2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetate (1.1 g, 69% yield).

[0422] LCMS (ES) m/z: 249.1 $[M-t-Bu]^+$

Step 2: Preparation of (4-(trifluoromethyl)picolinoyl)glycine

[0423] To a stirred solution of *tert*-butyl 2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetate (0.9 g, 2.96 mmol, 1eq) in DCM (10 mL), 4N HCl in 1,4-dioxane (8 mL) was added dropwise at 0 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude material was triturated with *n*-pentane and diethyl ether, the solvent was decanted and dried to afford 2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetic acid (0.6 g, 81% yield).

[0424] LCMS (ES) m/z**: 249.1 [M+H]$^+$**

Step-3: Preparation of *tert*-butyl 4-((4-(trifluoromethyl)picolinoyl)glycyl)hexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate

[0425] To a stirred solution of 2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetic acid (0.4 g, 1.61 mmol, 1 eq) in DMF (6 mL) were added *tert*-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.2 g, 0.94 mmol, 1 eq), ethylbis(propan-2-yl)amine (0.4 mL, 2.83 mmol, 3 eq), and [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (0.7 g, 1.88 mmol, 2 eq) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into cold water (30 mL) and extracted with EtOAc (2 x 100 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude. The crude was purified by flash column chromatography eluted on 50 % EtOAc/heptane to afford *tert*-butyl 4-(2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.35 g, 83% yield).

[0426] LCMS (ES) m/z: 443.2 [M+H]$^+$

Step-4 Preparation of N-(2-(hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide hydrochloride.

[0427] To a stirred solution of *tert*-butyl 4-(2-{[4-(trifluoromethyl)pyridin-2-yl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.4 g, 0.90 mmol, 1eq) in DCM (6 mL), 4N HCl in 1,4-dioxane (6 mL) was added dropwise 0 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude material was triturated with n-pentane and diethyl ether, the solvent was decanted and dried to afford N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-4-(trifluoromethyl)pyridine-2-carboxamide (0.3 g, 96% yield).

[0428] LCMS (ES) m/z: 343.2 [M+H]$^+$

Step-5 Preparation of N-(2-(4-(4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide

[0429] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-4-(trifluoromethyl)pyridine-2-carboxamide hydrochloride (0.1 g, 0.26 mmol, 1 eq) in THF (4 mL) were added 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (0.08 g, 0.31 mmol, 1.2 eq) and triethylamine (0.2 mL, 1.58 mmol, 6 eq) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, cooled to 0 °C, then sodium bis(acetyloxy)boranuidyl acetate (0.1 g, 0.52 mmol, 2 eq) was added and stirred at room temperature for 1 h. Progress of the reaction mixture was checked by TLC monitoring. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, extracted with DCM (2 x 50 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by prep TLC. Non-polar and polar bands of compound were separated and isolated to afford both geometrical isomers, i.e., non-polar isomer N-[2-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]-4-(trifluoromethyl)pyridine-2-carboxamide (0.007 g, 5% yield) and polar isomer N-[2-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]-4-(trifluoromethyl)pyridine-2-carboxamide (0.01 g, 6% yield). LCMS (ES) m/z: 596.3 $[M+H]^+$

[0430] Following the general protocol of Procedure 50 below compounds were synthesized.

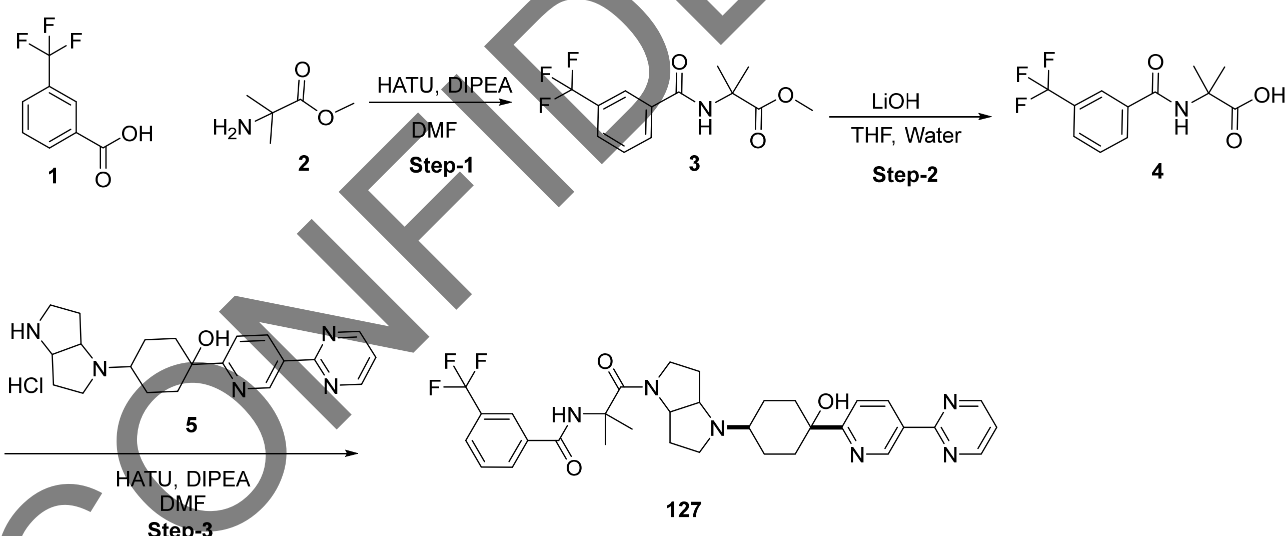
Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
100	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide	9.43 (d, *J* = 1.6 Hz, 1 H), 9.00 - 8.89 (m, 4 H), 8.67 - 8.65 (m, 1 H), 8.25 (s, 1 H), 8.06 (d, *J* = 4.0 Hz, 1 H), 8.85 (d, *J* = 8.4 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 5.12 (s, 1 H), 4.46 - 4.02 (m, 3 H), 3.71 - 3.46 (m, 4 H), 3.01 - 2.93 (m, 1 H), 2.33 - 1.97 (m, 5 H), 1.87 - 1.58 (m, 8 H).	596.4

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
101	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-4-(trifluoromethyl)picolinamide	9.44 (d, *J* = 2 Hz, 1 H), 9.00 - 8.88 (m, 4 H), 8.67 - 8.64 (m, 1 H), 8.25 (s, 1 H), 8.06 (t, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 5.11 (s, 1 H), 4.46 - 4.04 (m, 4 H), 3.61 - 3.35 (m, 3 H), 2.86 - 2.60 (m, 1 H), 2.46 - 2.16 (m, 3 H), 2.15 - 1.24 (m, 9 H).	596.4
102	2-fluoro-N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-5-(trifluoromethyl)benzamide	9.44 (d, *J* = 1.6 Hz, 1 H), 8.95 (d, *J* = 4.8 Hz, 2 H), 8.67 - 8.65 (m, 1 H), 8.63 - 8.56 (m, 1 H), 8.01 - 7.96 (m, 2 H), 7.83 (d, *J* = 10.8 Hz, 1 H), 7.59 (t, *J* = 18.4 Hz, 1 H), 7.51 (t, *J* = 9.6 Hz, 1 H), 5.06 (s, 1 H), 4.46 - 4.3 (m, 1 H),4.22 - 4.15 (m, 1 H), 4.13 - 3.99 (m, 1 H), 3.62 - 3.52 (m, 2 H), 3.47 - 3.42 (m, 1 H), 2.87 - 2.80 (m, 1 H), 2.42 - 2.38 (m ,4 H), 2.17 - 2.08 (m, 1 H), 1.98 - 1.77 (m, 5 H), 1.69 - 1.55 (m, 4 H), 1.244 - 1.18 (m, 2 H).	613.4
103	2-fluoro-N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-5-(trifluoromethyl)benzamide	9.43 (d, *J* = 1.6 Hz, 1 H), 8.95 (d, *J* = 4.8 Hz, 2 H), 8.66 (dd, *J* = 10.2 Hz, 1 H), 8.62 - 8.57 (m, 1 H), 8.01 - 7.97 (m, 2 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 18.8 Hz, 1 H), 7.51 (t, *J* = 9.6 Hz, 1 H), 5.1 (s, 1 4.45 - 4.29 (m, 1 H), 4.23 - 4.13 (m, 1 H), 4.06 - 3.98 (m, 1 H), 3.73 - 3.59 (m, 2 H), 3.54 - 3.40 (m, 1 H), 3.03 - 2.91 (m, 1 H), 2.20 - 1.97 (m ,4 H), 1.89 - 1.65 (m, 10 H).	613.4

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
145	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-5-(trifluoromethyl)nicotinamide	9.44 (d, *J* = 1.6 Hz, 1 H), 9.30 (d, *J* = 1.6 Hz, 1 H), 9.20 - 9.10 (m, 2 H), 8.95 (d, *J* = 5.2 Hz, 2 H), 8.67 - 8.65 (m, 1 H), 8.60 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.52 - 7.49 (m, 1 H), 5.12 (s, 1 H), 4.49 - 4.48 (m, 1 H), 4.32 - 4.28 (m, 1 H), 4.22 - 4.02 (m, 3 H), 3.63 - 3.52 (m, 2 H), 3.46 - 3.36 (m, 1 H), 2.86 - 2.80 (m, 1 H), 2.46 - 2.33 (m, 3 H), 2.16 - 2.13 (m, 1 H), 2.11 - 1.45 (m, 8 H).	596.4
146	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-5-(trifluoromethyl)nicotinamide	9.42 (d, *J* = 2.0 Hz, 1 H), 9.31 (d, *J* = 1.2 Hz, 1 H), 9.21 - 9.12 (m, 2 H), 8.96 (t, *J* = 8.8 Hz, 2 H), 8.67 - 8.65 (m, 1 H), 8.60 (s, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.51 (t, *J* = 4.8 Hz, 1 H), 4.47 (s, 1 H), 4.31 - 4.18 (m, 1 H), 4.17 - 4.00 (m, 2 H), 3.71 - 3.42 (m, 3 H), 3.01 - 2.92 (m, 1 H), 2.16 - 2.04 (m, 4 H), 2.00 - 1.65 (m, 6 H), 1.52 - 1.19 (m, 4 H).	596.4
159	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide	9.49 (bs, 1H), 8.97 (d, *J*=4.8Hz, 2H), 8.73-8.71 (m, 2 H), 8.36-8.33 (m, 2 H), 8.35-8.31 (m, 2H), 8.17-8.15 (m, 1H), 7.87- 7.85 (m, 1H), 7.55-7.53 (m, 1H), 5.47 (s, 1H), 4.69-4.67 (m, 1H), 4.47-4.21 (m, 1H), 4.17-4.05 (m, 1H), 3.81-3.55 (m, 4H), 2.46-2.45 (m, 2 H), 2.34-2.19 (m, 4H), 1.92 (m, 1H), 1.81-1.52 (m, 5H),1.48-1.41 (m, 1H), 1.24-1.19 (m, 1H)	596.3

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
160	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide	9.43 (bs, 1H), 8.95 (d, *J*=4.8Hz, 2H), 8.77-8.73 (m, 1H), 8.68-8.66 (m, 1H), 8.35-8.31 (m, 2H), 8.17-8.15 (m, 1H), 7.85 (d, *J*=8.4Hz, 1H), 7.51 (t, *J*=4.8 Hz, 1H), 5.14 (s, 1H), 4.46-4.29 (m, 1H), 4..25-4.19 (m, 1H), 4.18-4.06 (m, 1H), 3.72-3.60 (m, 1H), 3.52-3.46 (m, 1H), 3.18-2.93 (m, 1H), 2.46-2.34 (m, 1H), 2.33-2.08 (m,4H), 1.87-1.78 (m, 1H), 1.69-1.58 (m, 5H), 1.56 (m, 1H)	596.3

Procedure 51: Synthesis of N-(1-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-methyl-1-oxopropan-2-yl)-3-(trifluoromethyl)benzamide (127)



Step-1: Synthesis of methyl 2-methyl-2-(3-(trifluoromethyl)benzamido)propanoate:

[0431] To a stirred solution of 3-(trifluoromethyl)benzoic acid (1 g, 5.26 mmol) in DMF (15 mL) were added HATU (3 g, 1.5 eq., 7.89 mmol), methyl 2-amino-2-methylpropanoate (678 mg, 1.1 eq., 5.79 mmol), and ethylbis(propan-2-yl)amine (2.75 mL, 3 eq., 15.8 mmol) at 0 °C and reaction mixture was stirred at room temperature for 2 h. The reaction progress was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude. The crude product was purified by flash column chromatography with 30% ethyl acetate in hexane as eluent to afford methyl 2-methyl-2-{[3-(trifluoromethyl)phenyl]formamido}propanoate (1.1 g, 70% yield).

[0432] LCMS (ES) m/z: 290.1 $[M+H]^+$

Step-2: Synthesis of 2-methyl-2-(3-(trifluoromethyl)benzamido)propanoic acid:

[0433] To a stirred solution of 2-methyl-2-{[3-(trifluoromethyl)phenyl]formamido}propanoate (1 g, 3.46 mmol) in THF (15 mL, 41.6 mmol) was added methanol (1 mL, 24.7 mmol). The reaction mixture was cooled to 0 °C and lithium hydroxide (523 mg) in water (5 mL) was added. The reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, reaction mixture was acidified by 1N HCl in water. The precipitated white compound was filtered and dried to afford 2-methyl-2-{[3-(trifluoromethyl)phenyl]formamido}propanoic acid (928 mg, 97% yield).

[0434] LCMS (ES) m/z: 276.0 $[M+H]^+$

Step-3: Synthesis of N-(1-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-methyl-1-oxopropan-2-yl)-3-(trifluoromethyl)benzamide

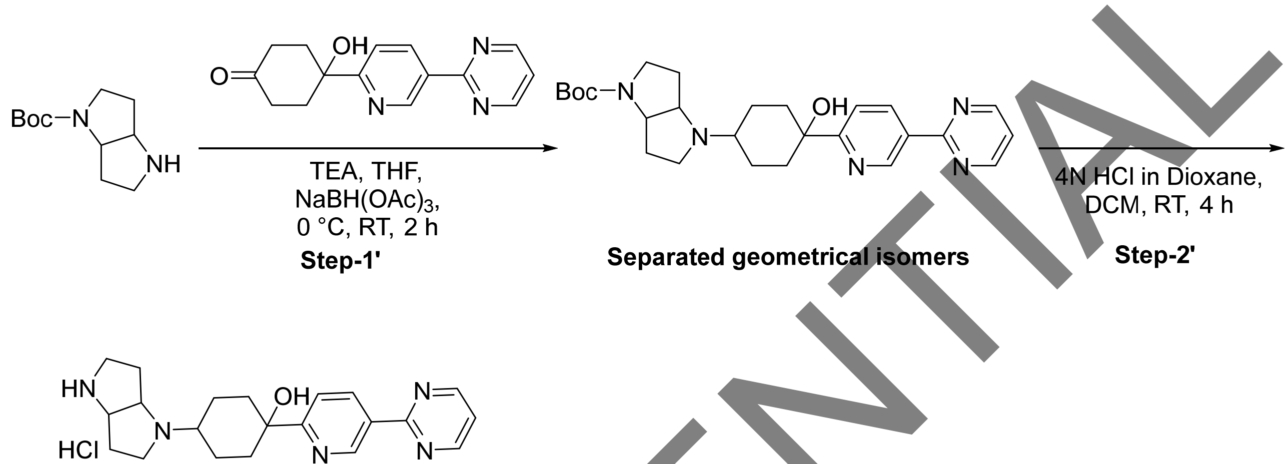
[0435] To a solution of 2-methyl-2-{[3-(trifluoromethyl)phenyl]formamido}propanoic acid (64 mg, 233 µmol), 4-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-1-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-ol (85 mg, 233 µmol) in DMF (4 mL, 51.7 mmol), [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (106 mg, 1.2 eq., 279 µmol), and ethylbis(propan-2-yl)amine (90.2 mg, 3 eq., 698 µmol) were added at 0 °C and reaction mixture was stirred at room temperature for 3 h. The reaction progress was monitored by TLC and LCMS. After completion of the reaction the reaction mixture was quenched with cold water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude. The crude product was purified by flash column chromatography using 5% MeOH in DCM as eluent to afford N-[1-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-methyl-1-oxopropan-2-yl]-3-(trifluoromethyl)benzamide (25 mg, 17%)

[0436] LC-MS (ES) m/z: 623.4. $[M+H]^+$

[0437] ^{1}HNMR (400 MHz, DMSO-d_6): **δ ppm**; 9.43 (s,1H), 8.96 (d, *J*=5.2Hz. 2H), 8.75 (s,1H), 8.60-8.63 (m, 1H), 8.14-8.17 (m, 1H), 7.91 (d, *J*=8Hz. 1H), 7.68-7.76 (m, 2H), 7.51 (t, 4.8Hz, 1H), 5.08 (s,1H), 4.36-

4.38 (m, 1H), 3.58-3.68 (m, 1H), 2.3-2.4 (m, 4H), 2.11-2.18 (m, 1H), 1.65-1.95 (m, 4H), 1.50-1.64 (m, 4H), 1.35-1.49 (m, 9H), 1.22-1.28 (m, 1H).

[0438] Intermediate 5 for use in Procedure 51 is prepared as follows. The polar isomer separated at Step-1' was converted into corresponding deBoc compound using Step-2'. Further following procedure of step-3 of Procedure 51 corresponding polar isomer was synthesized.



5

Step-1': Synthesis of *tert*-butyl 4-(4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrole-1(2*H*)-carboxylate

[0439] To a stirred solution of *tert*-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.3 g, 1.41 mmol) in THF (7 mL) at 0 °C were added 4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexan-1-one (381 mg, 1.41 mmol) and triethylamine (985 µL, 5 eq., 7.07 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then sodium triacetoxyborohydride (359 mg, 1.2 eq., 1.7 mmol) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with water (50 mL), and extracted using ethyl acetate (50 mL x 2). The organic layer was dried over Na*2*SO*4*, filtered, and evaporated under reduced pressure to yield the crude product. The crude product was purified by combiflash 45%-90% ethyl acetate in hexane as eluent to afford *tert*-butyl 4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (0.16 g, non-polar spot). The same crude also eluted using 10% MeOH in DCM to afford *tert*-butyl 4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-*b*]pyrrole-1-carboxylate (0.4 g, polar spot).

[0440] LCMS (ES) m/z: 466.1 $[M+H]^+$ (Non-polar isomer)

[0441] LCMS (ES) m/z: 466.3 $[M+H]^+$ (Polar isomer)

Step-2': Synthesis of 4-(hexahydropyrrolo[3,2-b]pyrrol-1(2*H*)-yl)-1-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexan-1-ol hydrochloride

[0442] To a stirred solution of *tert*-butyl 4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (160 mg, 344 µmol) in DCM (5 mL), 4N HCl in 1,4-dioxane (2.58 mL) was added dropwise to the reaction solution at 0 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude material was triturated with n-pentane and diethyl ether combination, the solvent was decanted and dried to afford 4-{octahydropyrrolo[3,2-*b*]pyrrol-1-yl}-1-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-ol (0.14 g, crude). LCMS (ES) m/z: 366.1 $[M+H]^+$.Step-2: Synthesis of 4-(hexahydropyrrolo[3,2-b]pyrrol-1(2*H*)-yl)-1-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexan-1-ol hydrochloride

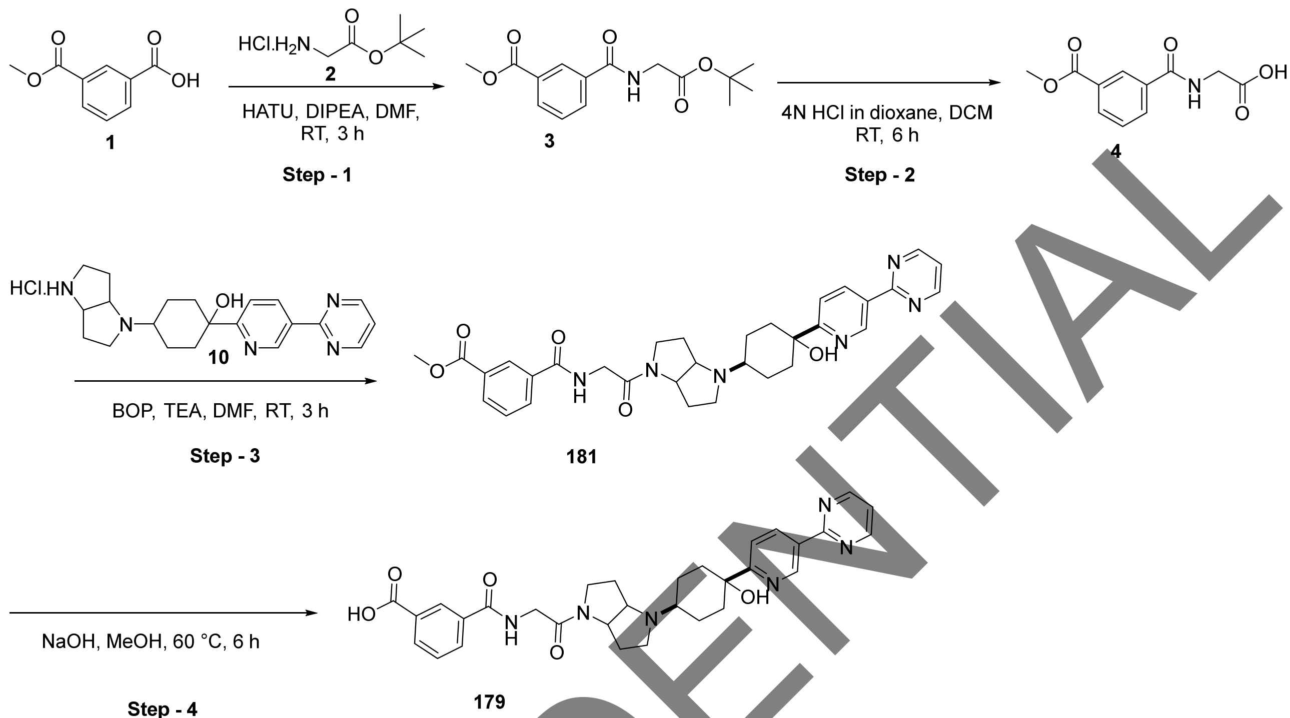
[0443] To a stirred solution of *tert*-butyl 4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (160 mg, 344 µmol) in DCM (5 mL), 4N HCl in 1,4-dioxane (2.58 mL) was added dropwise to the reaction solution at 0 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude material was triturated with n-pentane and diethyl ether combination, the solvent was decanted and dried to afford 4-{octahydropyrrolo[3,2-*b*]pyrrol-1-yl}-1-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-ol (0.14 g, crude). LCMS (ES) m/z: 366.1 $[M+H]^+$.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
128	N-(1-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-methyl-1-oxopropan-2-yl)-3-(trifluoromethyl)benzamide	9.40-9.42 (M, 1H), 8.949 (d, *J*=4.8Hz. 2H), 8.90 (s, 1H), 8.67-8.70 (m, 1H), 8.22-8.29 (m, 2H), 7.95-7.97 (m, 1H), 7.76-7.86 (m, 2H), 7.52 (t, *J*=10Hz, 1H), 5.41-5.49 (m, 1H), 4.76-4.78 (m1 1H), 4.15-4.21 (m, 1H), 3.93-3.95 (m, 1H), 3.51-3.57 (m, 1H), 2.32-2.39 (m, 2H), 2.01-2.13 (m, 5H), 1.81-2.0 (m, 6H), 1.65-1.80 (m, 4H), 1.45-1.55 (m, 8H), 1.18-132 (m, 4H), 0.8-0.9 (m, 2H).	623.4

[0444] The following compounds were synthesize using Procedure 51.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
132	3-fluoro-N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)benzamide	9.45(s,1H), 9.01-9.00 (d, *J*=4Hz, 2H), 8.79-8.86 (m, 2H), 7.83-7.81 (d, *J*=8Hz, 1H), 7.74-7.72 (d, *J*=8Hz,1H), 7.67-7.65 (d, *J*=8Hz,1H), 7.57-7.50 (m, 2H), 7.43-7.38 (m, 1H), 5.13 (s, 1H), 4.48-4.11 (m, 1H), 4.10-3.97 (m, 2H), 3.75-3.65 (m, 2H), 3.08-2.97 (m, 1H), 2.45-2.40 (m, 2H), 2.33-2.29 (m, 2H), 2.08 (bs, 3H), 1.63-1.47 (m, 6H), 3.02 (m, 1H), 2.08 (m, 2H)	545.6
133	3-fluoro-N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)benzamide	9.45 (s,1H), 9.01-9.00 (d, *J*=4Hz, 2H), 8.79-8.86 (m, 2H), 7.83-7.81 (d, *J*=8Hz, 1H), 7.74-7.72 (d, *J*=8Hz,1H), 7.67-7.65 (d, *J*=8Hz,1H), 7.57-7.50 (m, 2H), 7.43-7.38 (m, 1H), 5.13 (s, 1H), 4.48-4.11 (m, 1H), 4.10-3.97 (m, 2H), 3.75-3.65 (m, 2H), 3.08-2.97 (m, 1H), 2.45-2.40 (m, 2H), 2.33-2.29 (m, 2H), 2.08 (bs, 3H), 1.63-1.47 (m, 6H), 3.02 (m, 1H), 2.08 (m, 2H)	545.6

Procedure 52: Synthesis of 3-((2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)carbamoyl)benzoic acid (179)



Step 1: Synthesis of methyl 3-{[2-(*tert*-butoxy)-2-oxoethyl]carbamoyl}benzoate

[0445] To a stirred solution of 3-(methoxycarbonyl)benzoic acid (1 g, 5.55 mmol) in DMF (10 mL) were added hexafluoro-λ⁵-phosphanuide 1-[bis(dimethylamino)methylidene]-1H-1λ⁵-[1,2,3]triazolo[4,5-b]pyridin-3-ium-1-ylium-3-olate (3.17 g, 1.5 eq., 8.33 mmol), *tert*-butyl 2-aminoacetate (874 mg, 1.2 eq., 6.66 mmol), and ethylbis(propan-2-yl)amine (2.91 mL, 3 eq., 16.7 mmol). The reaction mixture was stirred at room temperature for 3 h. The progress of the reaction mixture was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was diluted with cold water (50 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under vacuum to yield the crude compound. The crude compound was purified by flash column MPLC by using 0-25% ethyl acetate in hexane as eluent to afford methyl 3-{[2-(tert-butoxy)-2-oxoethyl]carbamoyl}benzoate (750 mg, 46%). LCMS (ES) m/z**:** 238.0 $[M+H]^+$ (tertiary butyl cleavage mass)

Step 2: Synthesis of 2-{[3-(methoxycarbonyl)phenyl]formamido}acetic acid

[0446] To a stirred solution of methyl 3-{[2-(tert-butoxy)-2-oxoethyl]carbamoyl}benzoate (750 mg, 2.56 mmol) in DCM (10 mL), 4N HCl in 1,4-dioxane (7.0 mL) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was concentrated under reduced pressure to yield the crude compound. The crude material was triturated with n-pentane and diethyl ether, decanted, and dried to get 2-{[3-(methoxycarbonyl)phenyl]formamido}acetic acid (650 mg, 77%).

[0447] LCMS (ES) m/z**:** 238.0 $[M+H]^+$.

Step 3: methyl 3-((2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)carbamoyl)benzoate (181)

[0448] To a stirred solution of 2-{[3-(methoxycarbonyl)phenyl]formamido}acetic acid (50 mg, 211 µmol) in DMF (2.5 mL) were added (1H-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)phosphanium; hexafluoro-λ^5-phosphanuide (93.2 mg, 211 µmol) and 4-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-1-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-ol (77 mg, 211 µmol), followed by the addition of triethylamine (118 µL, 4 eq., 843 µmol). The reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was diluted with water and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to yield the crude which was purified by MPLC column using 5% MeOH in DCM as eluent to afford methyl 3-{[2-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]carbamoyl}benzoate (17 mg, 14%).

[0449] LCMS (ES) m/z: 585.4 $[M+H]^+$

[0450] ^{1}HNMR (400 MHz, DMSO-d_6): δ ppm: 9.44 (s, 1 H), 8.95 (d, J = 4.8 Hz, 2 H), 8.88- 8.91 (m, 1 H), 8.65-8.67 (dd, J = 10.0 Hz, 1.6 Hz, 1 H), 8.47 (s, 1 H), 8.13 (t, J = 8.8 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 1 H) , 7.63- 7.71 (m, 1.0 H), 7.51 (t, J = 4.8 Hz, 1 H), 5.12 (s, 1 H), 4.18- 4.48 (m, 1 H), 3.96-4.13 (m, 3 H), 3.90 (s, 3 H), 3.43- 3.59 (m, 2 H), 2.58- 2.86 (m, 2 H), 2.33 (s, 3 H), 2.27- 2.33 (m, 2 H), 2.12 (s, 1 H), 1.91 (s, 3 H), 1.71 (s, 2 H), 1.56 (s, 2 H).

Step 4: Synthesis of 3-((2-(4-((1r,4r)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)carbamoyl)benzoic acid (179)

[0451] To a solution of methyl 3-{[2-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]carbamoyl}benzoate (120 mg, 205 µmol) in methanol (2 mL, 49.4 mmol) was added sodium hydroxide (24.6 mg, 3 eq., 616 µmol). The reaction mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was complete, the reaction mixture was concentrated under reduced pressure to yield the crude. The crude compound was triturated with diethyl ether, then purified by prep HPLC and lyophilized to afford 3-{[2-(4-{4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]carbamoyl}benzoic acid (26 mg, 22%).

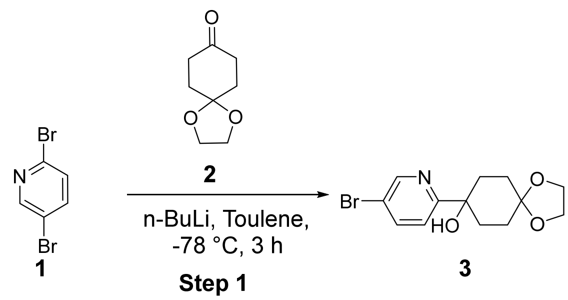
[0452] LCMS (ES) m/z: 571.4 $[M+H]^+$

[0453] ^{1}HNMR (400 MHz, DMSO-d_6): δ ppm: 9.44 (d, *J* = 2.0 Hz, 1 H), 8.95 (d, *J* = 4.8 Hz, 2 H), 8.65- 8.72 (m, 2 H), 8.41 (s, 1 H), 8.03 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H) , 7.46- 7.52 (m, 2 H), 5.13 (s, 1 H), 4.23- 4.49 (m, 1 H), 3.94 -4.13 (m, 2 H), 3.40- 3.67 (m, 4 H), 2.79- 2.86 (m, 1 H), 2.67 (s, 1 H), 2.30- 2.39 (m, 3 H), 2.11- 2.15 (m, 1 H), 1.82- 1.98 (m, 3 H), 1.72- 1.80 (m, 1 H), 1.52- 1.76 (m, 2 H), 1.39- 1.50 (s, 2 H).

[0454] Intermediate 10 was provided as in Step-1' and Step-2' of Procedure 51. Further following procedure of step-3 and step-4 of Procedure 52 corresponding polar isomer was synthesized.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
182	methyl 3-((2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)carbamoyl)benzoate	9.42 (d, *J* = 2.0 Hz, 1 H), 8.96 (d, *J* = 4.8 Hz, 2 H), 8.82- 8.94 (m, 1 H), 8.65-8.67 (dd, *J* = 10.0 Hz, 1.6 Hz, 1 H), 8.48 (s, 1 H), 8.13 (t, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.4 Hz, 1 H) , 7.64- 7.71 (m, 1 H), 7.50 (t, *J* = 4.8 Hz, 1 H), 5.12 (s, 1 H), 4.29- 4.48 (m, 1 H), 4.10- 4.16 (m, 1 H), 3.97- 4.02 (m, 1 H), 3.90 (s, 3 H), 3.59- 3.69 (m, 1 H), 3.36-3.52 (m, 1 H), 3.21 (s, 1 H), 2.91- 3.01 (m, 1 H), 2.10- 2.22 (m, 1 H), 1.98- 2.10 (s, 3 H), 1.95 (s, 2 H), 1.78 (s, 2 H),1.65- 1.77 (m, 4 H), 1.51- 1.53 (m, 2 H)	585.4
180	3-((2-(4-((1s,4s)-4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)carbamoyl)benzoic acid	9.43 (d, *J* = 2.0 Hz, 1 H), 8.95 (d, *J* = 4.8 Hz, 2 H), 8.60- 8.67 (m, 2 H), 8.40 (s, 1 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 7.84- 7.88 (m, 2 H), 7.50 (t, *J* = 9.6 Hz, 1 H) , 7.43 (t, *J* = 7.6 Hz, 1 H), 5.14 (s, 1 H), 4.12- 4.31 (m, 1 H), 4.07- 4.09 (m, 1 H), 3.94- 4.00 (m, 1 H), 3.58- 3.69 (m, 2 H), 3.68 (s, 1 H), 3.22 (s, 1 H), 2.90- 3.00 (m, 1 H), 2.04- 2.16 (m, 5 H), 1.64- 1.89 (m, 7 H), 1.51- 1.53 (m, 1 H).	571.4

Procedure 53: Synthesis of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

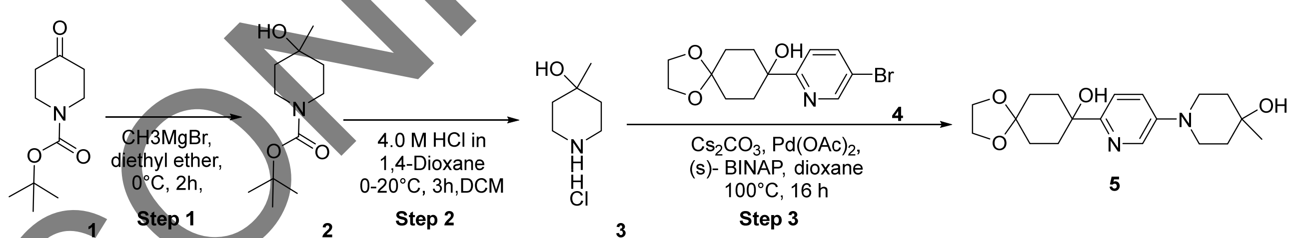


Step-1: 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0455] To a solution of 2,5-dibromopyridine (40 g, 168.8 mmol, 1 *eq*) in anhydrous toluene (300 mL) at -78 °C, n-BuLi (1.6 M, 126.4 mL, 202.8 mmol, 1.2 *eq*) was added dropwise. After being stirred at –78 °C for 2.5 hours, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (26.4 g, 168.8 mmol, 1 *eq*) in toluene (40 mL) was added in to the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. After completion of the reaction mixture was poured into aqueous $NaHCO_3$ (400 mL) and extracted with EtOAc (600 mL x 2). The organic extracts were combined, dried over $NaSO_4$, filtered and concentrated under vacuum at rotavapor. The resulting product was purified by using combiflash using eluent of 0 - 15 % ethyl acetate/n-hexane to afford 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (34.3 g, 64 %).

[0456] LCMS (ES) m/z: 316.1 $[M+H]^+$

Procedure 54: Synthesis of 1-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-4-methylpiperidin-4-ol



Step 1: Synthesis of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate

[0457] To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (3 g, 5.02 mmol) in diethyl ether (25 mL) at 0°C was added methyl magnesium bromide (7.53 mL, 5.1 mmol). After 2 h, the reaction mixture was quenched with $NaHCO_3$ (25 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over sodium sulphate and filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 35% of EtOAc : hex to afford the title compound (2.2 g, 68%).

[0458] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm**:** 5.31 (s, 1 H), 4.12 - 3.87 (m, 4 H), 3.28 – 3.21 (m, 4 H), 1.50 (s, 3 H), 1.24 (s, 9 H).

Step 2: Synthesis of 4-methylpiperidin-4-ol hydrochloride

[0459] To a stirred solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (2.2 g, 10.2 mmol) in DCM (10 mL) at 0°C was added 4 M HCl in dioxane (8 mL, 10.2 mmol) and stirred for 3 h. Then the reaction mixture was evaporated under reduced pressure to get the crude product (1.2 g, 80%) as HCl salt. The crude product was taken for next step without any purification.

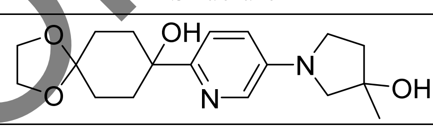
[0460] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm**:** 8.97 – 8.85 (bd, 2H), 5.53 (s, 1 H), 3.74 - 3.39 (m, 4 H), 1.71 – 1.43 (m, 4 H), 1.11 (s, 3 H).

Step 3: Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-4-methylpiperidin-4-ol

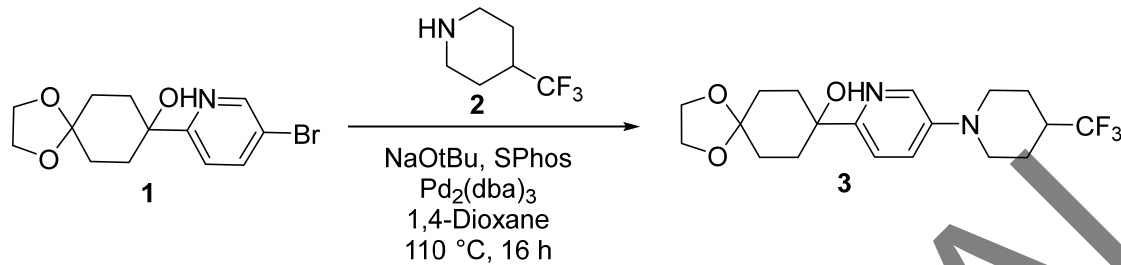
[0461] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2.59 g, 8.24 mmol) and 4-methylpiperidin-4-ol hydrochloride (1.2 mg, 8.24 mmol) in dioxane (40 mL) were added dicesium(1+) carbonate (8.06g, 8.24 mmol). The reaction mixture was purged with argon for 15 min and then added (S)-BINAP (1.03 g, 8.24 mmol) and $Pd(OAc)_2$ (185 mg, 8.24 mmol). The reaction mixture was stirred at 100 °C for 16 h. After the completion of the reaction, the reaction mixture was quenched with water (50 mL) extracted with ethyl acetate (2 x 250 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude material. The crude material was purified by flash column chromatography using 60-64% of EtOAc:hex to afford title compound (400 mg, 14%).

[0462] LCMS (ES) m/z: 349.1 $[M+H]^+$

[0463] The following compounds were synthesized using Procedure 54:

Structure	LCMS (ESI) m/z
	335.3 $[M+H]^+$

Procedure 55: Synthesis of 8-(5-(4-(trifluoromethyl)piperidin-1-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



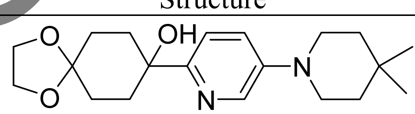
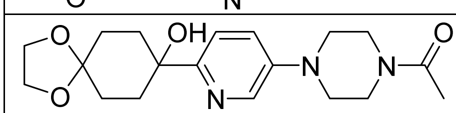
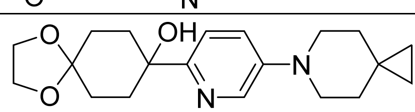
Step 1: 8-(5-(4-(trifluoromethyl)piperidin-1-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0464] To a solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.6 g, 1.91 mmol), in 1,4-dioxane (25 mL, 293 mmol). Then sodium t-butoxide (551 mg, 3 eq., 5.73 mmol), dicyclohexyl({2',6'-dimethoxy-[1,1'-biphenyl]-2-yl})phosphane (78.4 mg, 0.1 eq., 191 µmol), tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (175 mg, 0.1 eq., 191 µmol) were added and purged for 5 minutes. Then 4-(trifluoromethyl)piperidine (292 mg, 1.91 mmol) was added to the reaction mixture and stirred at 100°C for 16 h in a sealed tube. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the solvent was removed under reduced pressure. The residue was quenched with water (30 mL) extracted by ethyl acetate (2 X 25 mL), washed with brine solution (20 mL) dried over by sodium sulphate the combined organic layers were concentrated to get crude product, the crude product was purified with flash column chromatography using 20% - 40% ethyl acetate in heptane as eluent to afford 8-{5-[4-(trifluoromethyl)piperidin-1-yl]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (300 mg, 40%).

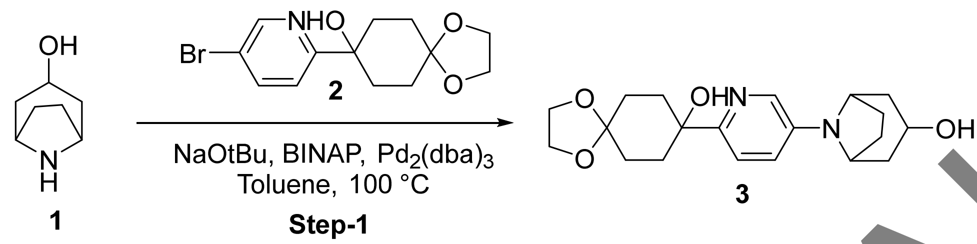
[0465] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 4.05 - 3.98 (m, 4H), 3.77 (d, 2H, J = 12.4 Hz), 2.81 - 2.74 (m, 2H), 2.25 - 2.00 (m, 6H), 1.83 - 1.69 (m, 7H).

[0466] LCMS (ES) m/z: 387.2 $[M+H]^+$

[0467] The following compounds were synthesized using Procedure 55.

Structure	LCMS (ESI) m/z
	347.3 $[M+H]^+$
	362.2 $[M+H]^+$
	345.3 $[M+H]^+$

Procedure 56: Synthesis of 8-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-ol

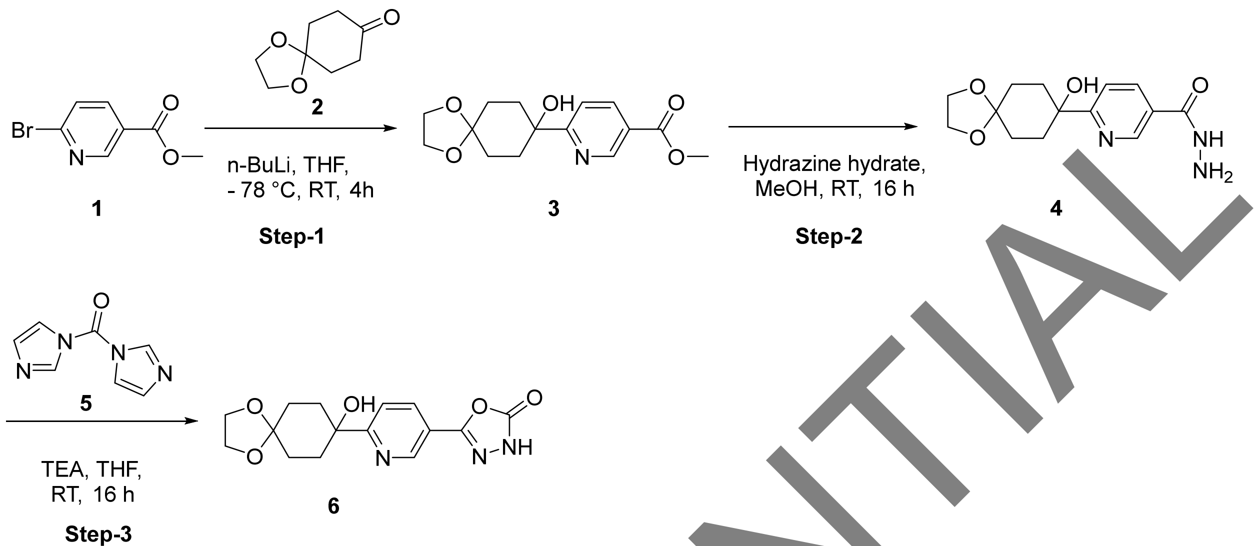


Step-1: 8-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-ol

[0468] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1 g, 3.18 mmol) in toluene (20 mL, 169 mmol). 8-azabicyclo[3.2.1]octan-3-ol (405 mg, 3.18 mmol), sodium 2-methylpropan-2-olate (918 mg, 3 eq., 9.55 mmol) and [2'-(diphenylphosphanyl)-[1,1'-binaphthalen]-2-yl]diphenylphosphane (198 mg, 0.1 eq., 318 µmol) were added to the reaction mixture and under nitrogen condition, reaction mixture was purged with argon for 5 minutes, after that tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (146 mg, 0.05 eq., 159 µmol) was added under nitrogen atmosphere, the reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction was diluted with ethylacetate (2* 50 mL) and washed water (10 mL), the organic layer was dried over Na_2SO_4, and concentrated in vacuum to get the crude material. The crude material was purified by combi column chromatography (24 g cartridge), and the product eluted at 0-5% MeOH in DCM to afford 8-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-ol (230 mg, impure).

[0469] LCMS (ES) m/z: 361.1 $[M+H]^+$

Procedure 57: Synthesis of 5-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one



Step 1: Preparation of methyl 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)nicotinate

[0470] To a solution of methyl 6-bromopyridine-3-carboxylate (0.5 g, 2.31 mmol, 1 eq) in DCM (8 mL) at -78 °C, n-BuLi (1.11 mL, 2.78 mmol, 1.2 eq) was added dropwise. After being stirred at –78 °C for 2.5 hours, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (0.43 g, 2.78 mmol, 1.2 eq) in DCM (2 mL) was added in to the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (50 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting product was purified by using combiflash and eluent used as 0 - 15 % ethyl acetate/n-hexane to afford methyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carboxylate (400 mg, 58 %).

[0471] LCMS (ES) m/z: 294.1 $[M+H]^+$

Step 2: Preparation of 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)nicotinohydrazide

[0472] To a stirred solution of methyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carboxylate(0.4 g, 1.7 mmol, 1 eq) in methanol (20 mL). was added hydrazine hydrate 50% (0.82 mL, 8.52 mmol, 5 eq), and the reaction mixture was stirred at RT for 8 h. After completion, the reaction mixture was transferred to a round bottom flask and the solvent evaporated under reduced pressure, filtered and washed with the same solvent, to afford 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carbohydrazide (300 mg, 60 %).

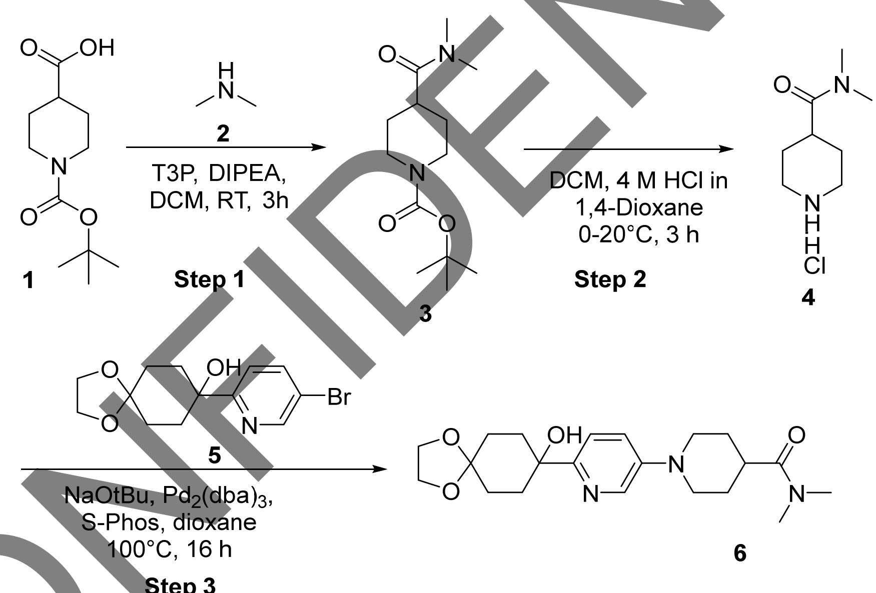
[0473] LCMS (ES) m/z: 294.2 $[M+H]^+$

Step 3: Preparation of 5-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one

[0474] To a stirred solution of 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carbohydrazide (0.3 g, 1.36 mmol, 1 eq) in THF (8 mL) were added triethylamine (0.57 mL, 4.09 mmol, 3 eq) and 1-(1H-imidazole-1-carbonyl)-1H-imidazole (0.44 g, 2.73 mmol, 2 eq). The reaction mixture was stirred at 80 °C for 16 h. Progress of the reaction mixture was checked by TLC monitoring, after completion of the reaction, The reaction mixture was evaporated under reduced pressure to obtain the crude product. The crude was purified by flash column chromatography eluted on 5% MeOH - DCM to afford 5-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-2,3-dihydro-1,3,4-oxadiazol-2-one (25 mg, 57 %).

[0475] LCMS (ES) m/z: 320.0 $[M+H]^+$

Procedure 58: Synthesis of 1-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide



Step 1: Synthesis of tert-butyl 4-(dimethylcarbamoyl)piperidine-1-carboxylate

[0476] To a stirred solution of 1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid (3 g, 13.1 mmol) in DCM (30 mL) were added T3P (17 mL, 13.1 mmol) and DIPEA (7 mL, 13.1 mmol) followed by the addition of dimethylamine (6.5 mL, 13.1 mmol) at 0°C. Stirred the reaction mixture at rt for 12 hours. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (5 mL) and extracted with DCM (2x20 mL) concentrated in vacuo to get the crude. The crude material was purified by flash column chromatography using 10% MeOH/DCM to afford mixture (2.2

g). This mixture was quenched with $NaHCO_3$ (20 mL) and extracted with ethyl acetate (2 x 100 mL) to obtain the title compound (1 g, 30%).

[0477] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.16 – 4.12 (m, 2 H), 3.07 (s, 3 H), 2.96 (m, 3 H), 2.77 – 2.69 (m, 2 H), 1.74 – 1.70 (m, 4 H), 1.27 (s, 9 H).

Step 2: Synthesis of N,N-dimethylpiperidine-4-carboxamide hydrochloride

[0478] To a stirred solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (1 g, 3.9 mmol) in DCM (15 mL) at 0°C was added 4 M HCl in Dioxane (3 mL, 11.7 mmol) and stirred for 3 h. Then reaction mixture was evaporated under reduced pressure to get the crude (725 mg, 96%) as HCl salt. Crude product was taken for next step without any purification.

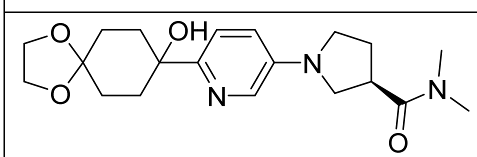
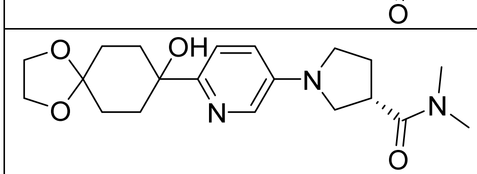
[0479] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.14 (bs, 1 H), 8.72 (bs, 1 H), 3.24 (d, J = 12.0 Hz, 2 H), 2.98 (s, 3 H), 2.96 – 2.89 (m, 2 H), 2.85 (s, 3 H), 1.76 – 1.67 (m, 4 H).

Step 3: Synthesis of 1-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide

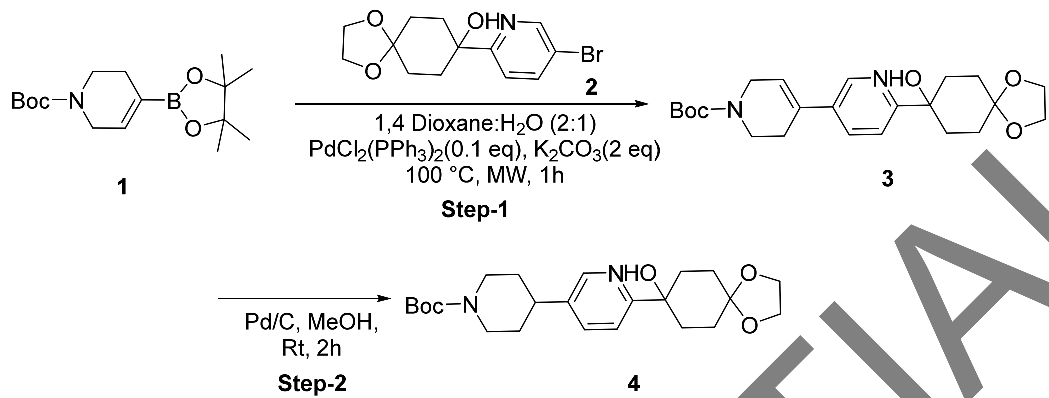
[0480] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (978 mg, 3.11 mmol) and 4-methylpiperidin-4-ol hydrochloride (600 mg, 3.11 mmol) in dioxane (20 mL) were added NaOtBu (898 mg, 3.11 mmol). The reaction mixture was purged with argon for 15 min and then added S-Phos (384 mg, 3.11 mmol) and $Pd_2(dba)_3$ (15 mg, 0.07 mmol). The reaction mixture was stirred at 100°C for 16 h. After the completion of the reaction, the reaction mixture was quenched with water (25 mL) extracted with ethyl acetate (2 x 200 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude material. The crude material was purified by flash column chromatography using 7-8% MeOH/DCM to afford the title compound (260 mg, 21%).

[0481] LCMS (ES) m/z: 390.1 $[M+H]^+$

[0482] The following compounds were synthesized using Procedure 58.

Structure	LCMS (ESI) m/z
	376.1 $[M+H]^+$
	376.1 $[M+H]^+$

Procedure 59: Synthesis of tert-butyl 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)piperidine-1-carboxylate



Step 1: Synthesis of tert-butyl 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate

[0483] To a stirred solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.5 g, 1.62 mmol) and 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (508 mg, 1.62 mmol) in 1,4-dioxane (20 mL, 234 mmol) and water (10 mL, 555 mmol)at room temperature purged with nitrogen for 10 min further dipotassium carbonate (670 mg, 3 eq., 4.85 mmol) and palladium(2+) bis(triphenylphosphane) dichloride (113 mg, 0.1 eq., 162 µmol) and again purged with nitrogen for 5 min and stirred for 1h at 100 °C in microwave . Progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture is filtered and evaporated using reduced vacuum, and purified in column chromatography using ethyl acetate in n-heptane as eluents (45-50 %) to afford tert-butyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-1'-carboxylate (625 mg, 93 %)

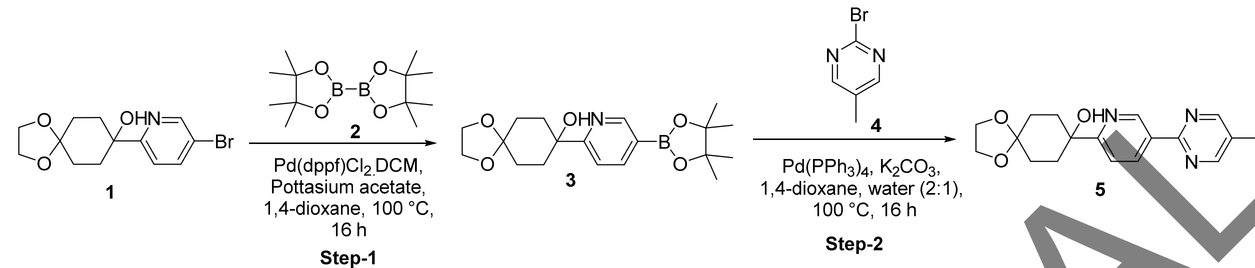
[0484] LCMS (ES) m/z: 417.3 $[M+H]^+$

Step 2: Synthesis of tert-butyl 4-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)piperidine-1-carboxylate

[0485] To a stirred solution of tert-butyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1',2',3',6'-tetrahydro-[3,4'-bipyridine]-1'-carboxylate (1.2 g, 2.88 mmol) in methanol (75 mL, 1.85 mol) at room temperature Palladium on carbon (307 mg, 2.88 mmol) was added and degassed using nitrogen for 5 min and further the reaction mixture is allowed to stir for 16 h at room temperature under H_2 atmosphere at 50 -60 psi pressure in parallel hydrogenation instrument, progress of the reaction monitored using TLC and LCMS. After completion, the reaction mixture was then filtered and concentrated using reduce vacuum, to yield tert-butyl 4-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidine-1-carboxylate (1 g, 85 %)

[0486] LCMS (ES) m/z: 419.1 $[M+H]^+$

Procedure 60: Synthesis of 8-(5-morpholinopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step 1: Synthesis of 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

[0487] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (0.4 g, 1.27 mmol) in 1,4-dioxane (8 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (388 mg, 1.2 eq., 1.53 mmol) followed by potassium acetate (375 mg, 3 eq., 3.82 mmol), reaction mixture was purged with nitrogen atmosphere for 10 mins, after that 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (104 mg, 0.1 eq., 127 µmol), then reaction mixture was stirred at 100 °C for 16 h, after completion of the reaction, reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (2 x 20 mL), combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (650 mg, 38 %).

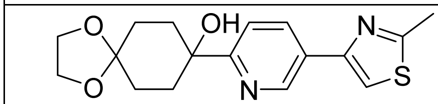
[0488] LCMS (ES) m/z: 280.2 $[M+H]^+$ (boronic acid mass)

Step 2: Synthesis of 8-[5-(5-methylpyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol

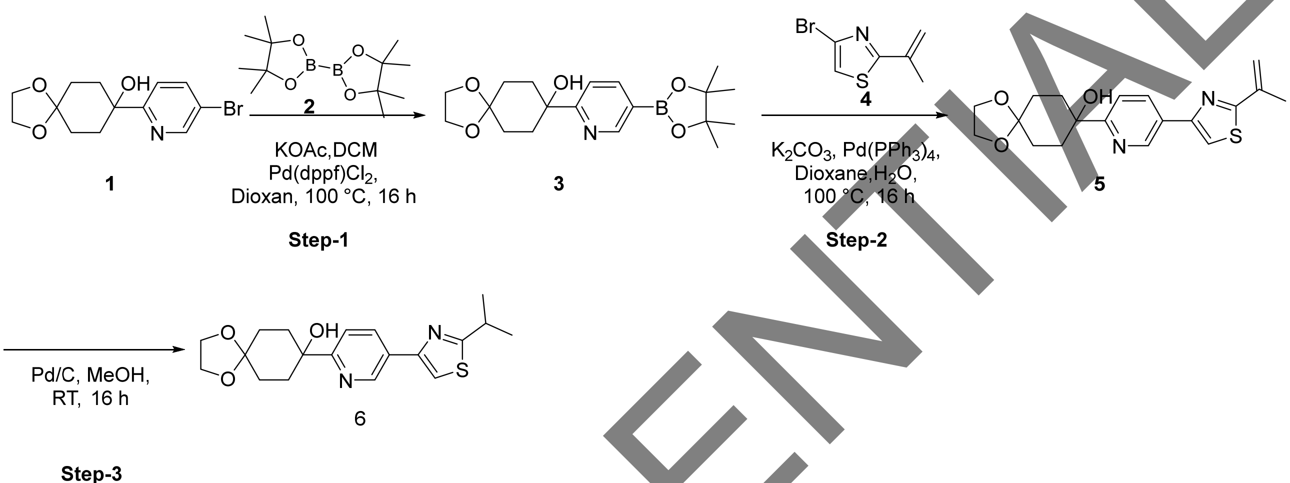
[0489] To a stirred solution of 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (0.5 g, 1.38 mmol, 1 eq) in 1,4-dioxane (8 mL) and water (4 mL) was added 2-bromo-5-methylpyrimidine (239 mg, 1.38 mmol, 1 eq) and dipotassium carbonate (574 mg, 4.15 mmol, 3 eq), reaction mixture was purging under N_2 atmosphere for 10 mins, after that tetrakis(triphenylphosphane) palladium (160 mg, 0.138 mmol, 0.05 eq) was added portion wise. The reaction mixture was stirred at 100 °C for 16h. After completion of the reaction, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (2 x 15 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude which was purified by column chromatography (0-40% EtOAc in hexane) to afford the 8-[5-(5-methylpyrimidin-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (330 mg, 64%).

[0490] LCMS (ES) m/z: 328.1 $[M+H]^+$

[0491] Following compounds were synthesized using Procedure 60.

Structure	LCMS (ESI) m/z
	333.2 $[M+H]^+$

Procedure 61: Synthesis of 8-(5-(2,6-dimethylmorpholino)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step 1: Preparation of 8-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol.

[0492] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2 g, 6.37 mmol, 1 eq) in 1,4-dioxane (20 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.94 g, 7.64 mmol, 1.2 equiv) followed by potassium acetate (1.87 g, 19.1 mmol, 3 equiv). The reaction mixture was purged with nitrogen atmosphere for 10 mins. After that 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (0.51 g, 0.63 mmol, 0.1 equiv). Then the reaction mixture was stirred at 100 °C for 16 h. after completion of the reaction. The reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (2 x 100 mL), combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (1.6 g, 69 %).

[0493] LCMS (ES) m/z: 280.2 $[M+H]^+$ (boronic acid mass)

Step 2: Preparation of 8-(5-(2-(prop-1-en-2-yl)thiazol-4-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol.

[0494] To a stirred solution of 4-bromo-2-(prop-1-en-2-yl)-1,3-thiazole (1 g, 4.9 mmol, 1 eq) in Dioxane (15 mL) and water (5 mL) were added 8-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (2.12 g, 5.88 mmol, 1.2 eq), K_2CO_3 (2.03 g, 14.7 mmol, 3 eq) and reaction mixture was purged with Argon for 10 mins. Tetrakis(triphenylphosphine) palladium (0.56 g, 0.49 mmol, 0.1 eq) was added and reaction mixture was heated at 100 °C for 16 h. Reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (2 x 100 mL), combined organic layer were dried with anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford crude compound. The crude was purified by flash column chromatography eluted on 30 % EtOAc - heptane to afford 8-{5-[2-(prop-1-en-2-yl)-1,3-thiazol-4-yl]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (700 mg, 39 %).

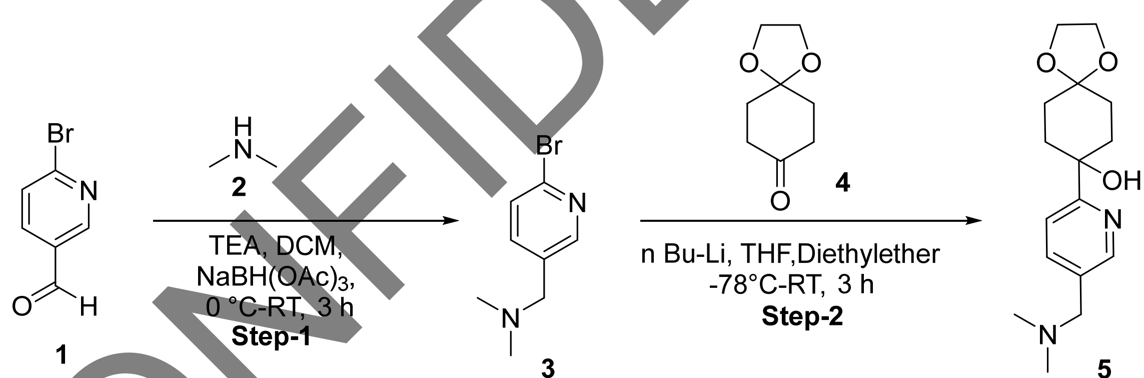
[0495] LCMS (ES) m/z: 359.2 $[M+H]^+$

Step 3: Preparation of 8-(5-(2-isopropylthiazol-4-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol.

[0496] To a stirred solution of 8-{5-[2-(prop-1-en-2-yl)-1,3-thiazol-4-yl]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (0.7 g, 2.23 mmol, 1 eq) in methanol (10 mL) was added palladium on carbon (0.47 g, 4.46 mmol, 2 eq) and allowed to stir at rt for 16 h under hydrogen atmosphere. The reaction mixture was filtered through celite bed and washed with methanol. The methanol was concentrated *in vacuo* to give crude 8-{5-[2-(propan-2-yl)-1,3-thiazol-4-yl]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (600 mg, 87 %).

[0497] LCMS (ES) m/z: 361.2 $[M+H]^+$

Procedure 62: Synthesis of 8-(5-((dimethylamino)methyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



Step 1: Preparation of [(6-bromopyridin-3-yl)methyl]dimethylamine

[0498] To a solution of 6-bromopyridine-3-carbaldehyde (3 g, 16.1 mmol) in dichloromethane (20 mL) were added dimethylamine (2.18 g, 3 eq., 48.4 mmol) after stirring for 5 min was added triethylamine (13.6 mL, 6 eq., 96.8 mmol).The resulting mixture was stirred at RT for 30 min, after that sodium bis(acetyloxy)boranuidyl acetate (6.84 g, 2 eq., 32.3 mmol) were added and stirred at rt for 3 h, the reaction mixture was diluted with water (2x 50mL) and extracted with DCM (2x 100mL), the organic layer was dried over Na2SO4, and concentrated in vacuum to get the crude. The crude was purified by flash column chromatography by using 5% methanol/DCM as an eluent to afford as [(6-bromopyridin-3-yl)methyl]dimethylamine (2.8 g, 81%)

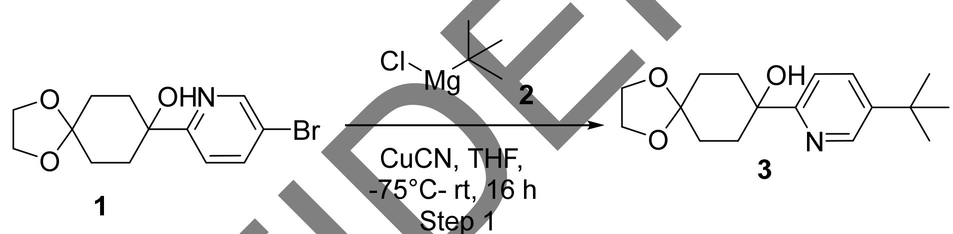
[0499] LCMS (ES) m/z: 604.1 $[M+H]^+$

Step 2: Preparation of 8-{5-[(dimethylamino)methyl]pyridin-2-yl}-1,4 dioxaspiro[4.5]decan-8-ol

[0500] To a solution of [(6-bromopyridin-3-yl)methyl]dimethylamine (1 g, 4.65 mmol) in oxolane (30 mL) and diethylether (80 mL) at -78 °C, lithium(1+) butan-1-ide (357 mg, 1.2 eq., 5.58 mmol) was added dropwise. After being stirred at –78 °C for 2.5 hours, a solution of 1,4-dioxaspiro[4.5]decan-8-one (871 mg, 1.2 eq., 5.58 mmol) in oxolane (10 mL) was added into the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (150 mL) and extracted with EtOAc (150 mL x 3). The organic extracts were combined, dried over $NaSO_4$, filtered and concentrated under vacuum to get crude. The crude was purified by flash column chromatography by using 10% methanol/DCM as an eluent to afford as 8-{5-[(dimethylamino)methyl]pyridin-2-yl}-1,4-dioxaspiro[4.5]decan-8-ol (100 mg, 5 %).

[0501] LCMS (ES) m/z: 293.1 $[M+H]^+$

Procedure 63: Synthesis of 8-(5-((dimethylamino)methyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

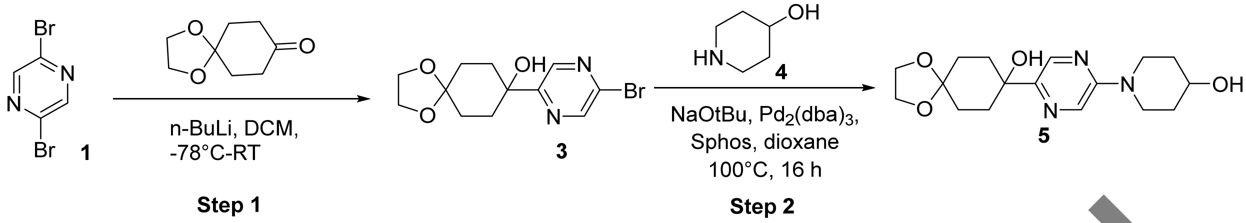


Step 1: Synthesis of 8-(5-(tert-butyl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0502] To a stirred solution of Copper(I) Cyanide (1.14 g, 4 eq., 12.7 mmol) in dry tetrahydrofuran (10 mL, 123 mmol) at - 78°C under nitrogen atmosphere added tert-butylmagnesium chloride 2.0 M (1.27 mL, 8 eq, 2.55mmol) and allowed to stir for 45 min under nitrogen atmosphere further 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1 g, 3.18 mmol) dissolved in tetrahydrofuran (10 mL, 123 mmol) is added dropwise to the reaction mixture and allowed to stir for 16 h at room temperature. The progress of the reaction was monitored by TLC and LCMS. The reaction product was purified from column chromatography using {ethyl acetate in n-heptane (0 - 50 %)} as eluents to afford 8-(5-tert-butylpyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (122 mg, 13 %).

[0503] LCMS (ES) m/z: 292.1 $[M+H]^+$

Procedure 64: Synthesis of 1-(5-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyrazin-2-yl)piperidin-4-ol



Step 1: Preparation of 8-(5-bromopyrazin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0504] To a solution of 2,5-dibromopyrazine (1 g, 4.2 mmol) in dichloromethane (30 mL)at -78 °C, lithium(1+) butan-1-ide (269 mg, 4.2 mmol) was added dropwise. After being stirred at –78 °C for 20 min, a solution of 1,4-dioxaspiro[4.5]decan-8-one (657 mg, 4.2 mmol) in dichloromethane(10 mL) was added into the reaction mixture. The resulting mixture was stirred for 30 min at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (150 mL) and extracted with EtOAc (100 mL x 3). The organic extracts were combined, dried over $NaSO_4$, filtered, and concentrated under vacuum to get crude. The crude was purified by flash column chromatography using 30% EtOH/Hexane as an eluent to afford as 8-(5-bromopyrazin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (350 mg, 27 %).

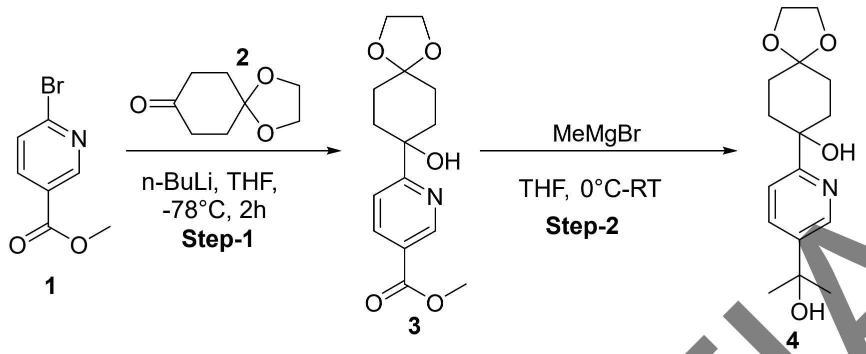
[0505] ^{1}H NMR($CDCl_3$, 400 MHz) δ ppm; 8.60-8.58 (m, 2 H), 4.03(s, 1H), 3.39-4.02 (m, 4 H), 8.19 2.24-2.00(m, 8 H).

Step 2: Preparation of 1-(5-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyrazin-2-yl)piperidin-4-ol

[0506] To a stirred solution of 8-(5-bromopyrazin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1 g, 3.17 mmol) and piperidin-4-ol (481 mg, 1.5 eq., 4.76 mmol) in 1,4-dioxane (60 mL, 703 mmol)was added sodium 2-methylpropan-2-olate (915 mg, 3 eq., 9.52 mmol) and dicyclohexyl({2',6'-dimethoxy-[1,1'-biphenyl]-2-yl})phosphane (261 mg, 0.2 eq., 635 µmol) under nitrogen condition, reaction mixture was purged with argon for 5 minutes, after that tris((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) dipalladium (291 mg, 0.1 eq., 317 µmol) was added under nitrogen atmosphere, reaction mixture was stirred at 100 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS data. The reaction was extracted with ethylacetate(2* 150 mL) and water(150 mL), the organic layer was dried over Na_2SO_4, and concentrated in vacuum to get the crude. The crude was purified by flash column chromatography using 10 % MeOH/ DCM as an eluent to afford 1-(5-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyrazin-2-yl)piperidin-4-ol (450 mg, 42 %)

[0507] LC-MS (ES) m/z: 336.2 $[M+H]^+$

Procedure 65: Synthesis of Synthesis of 4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexan-1-one



Step-1: Synthesis of methyl 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)nicotinate:

[0508] To a solution of methyl 6-bromopyridine-3-carboxylate (2 g, 9.26 mmol) in THF (40 mL) at -78 °C, butyllithium (1.19 g, 2 eq., 18.5 mmol) in Hexane 7.4 mL was added dropwise. After being stirred at –78 °C for 0.5 hours, a solution of 1,4-dioxaspiro[4.5]decan-8-one (1.74 g, 1.2 eq., 11.1 mmol) in THF (10 mL) was added in to the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (20 mL) and extracted with EtOAc (100 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting product was purified by using combiflash and eluent used as 0 - 15 % ethyl acetate/n-hexane to afford methyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carboxylate (0.5 g, 18 %).

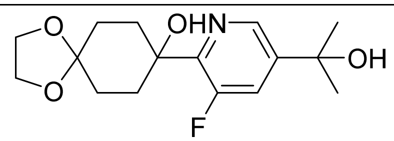
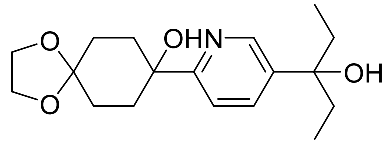
[0509] LC-MS (ES) m/z : 294.1 $[M+H]^+$

Step-2: Synthesis of 8-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol:

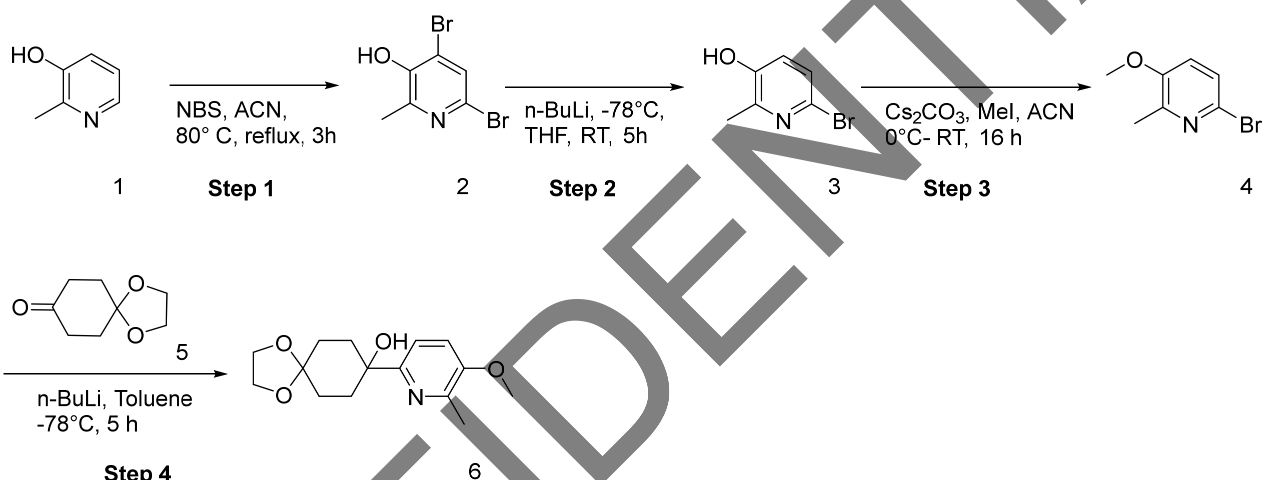
[0510] To a stirred solution of methyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carboxylate (0.4 g, 1.36 mmol) in tetrahydrofuran (15 mL) at room temperature under nitrogen atmosphere, the reaction mixture was cooled 0°C and methylmagnesium bromide solution 3.0 M in diethyl ether 1.64 mL was added dropwise and stirred for 16 hrs at room temperature. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction the reaction mixture was quenched with saturated ammonium chloride 20 mL and extracted with ethyl acetate 2 X 20 mL and washed with brine solution dried over by sodium sulphate. The combined organic layers were concentrated under reduced pressure to get crude product. The crude product was purified by column chromatography using 40% ethyl acetate in hexane as eluent to afford pure product of 8-[5-(2-hydroxypropan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (245 mg, 61 % yield).

[0511] LC-MS (ES) m/z : 294.2 $[M+H]^+$

[0512] Following compounds were synthesized using Procedure 65.

Structure	LCMS (ESI) m/z
	312.0 $[M+H]^+$
	322.2 $[M+H]^+$

Procedure 66: Synthesis of 4-hydroxy-4-(5-methoxy-6-methylpyridin-2-yl)cyclohexan-1-one



Step 1: Synthesis of 4,6-dibromo-2-methylpyridin-3-ol:

[0513] To a stirred solution of 2-methylpyridin-3-ol (2 g, 18.3 mmol) in ACN (20mL) was added a solution of NBS (6.52 mg, 36.7 mmol) in ACN (10 mL). The reaction mixture was heated at reflux for 2 hours at 80° C. After the completion of the reaction, the reaction mixture was quenched with sodium bicarbonate (20 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over sodium sulphate and filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 10-25% of EtOAc:hex to afford the title compound (0.8 g, 16%) and mixture (1 g).

[0514] LC-MS (ES) m/z : 267.8 $[M+H]^+$

Step 2: Synthesis of N,N-dimethylpiperidine-4-carboxamide hydrochloride

[0515] 4,6-dibromo-2-methylpyridin-3-ol (1 g, 3.75 mmol) was dissolved in THF (10 mL). The solution was cooled to -78°C and n-BuLi (9 mL, 22.5 mmol) was added drop-wise keeping the temperature at -78°C. The mixture was allowed to stir at that temperature for 2 h. The mixture was quenched with NH_4Cl (20 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over sodium sulphate and filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 25-30% of EtOAc:Hex to afford title compound (325 mg, 46%).

[0516] LC-MS (ES) m/z : 190.0 $[M+2]^+$

Step 3: Synthesis of 6-bromo-3-methoxy-2-methylpyridine

[0517] To a stirred solution of 6-bromo-2-methylpyridin-3-ol (650 mg, 3.46 mmol) in ACN (6 mL) was added Cs_2CO_3 (3.38 g, 10.4 mmol). After 30 min, reaction mixture was cooled to 0°C and added methyl iodide (0.3 mL, 5.19 mmol) and stirred at 50°C for 2 h. After the completion of the reaction, reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure to get the crude (675 mg, 91%).

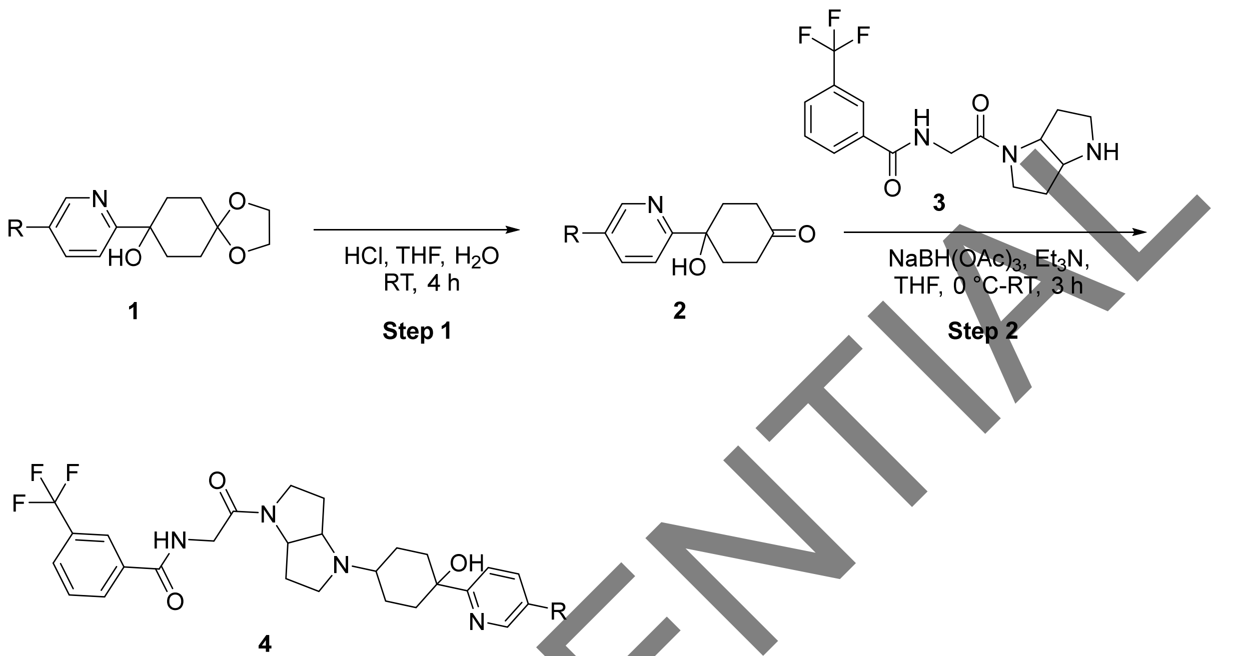
[0518] LC-MS (ES) m/z : 203.9 $[M+2]^+$

Step 4: Synthesis of 8-(5-methoxy-6-methylpyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol:

[0519] To a solution of 6-bromo-3-methoxy-2-methylpyridine (600 mg, 2.97 mmol) in THF (15 mL) at -78 °C, n-BuLi (2.4 mL, 5.94 mmol) was added dropwise. After being stirred at –78 °C for 1.5 hours, a solution of 1,4-dioxaspiro[4.5]decan-8-one (464 mg, 0.37 mmol) in THF (5 mL) was added into the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (25 mL) and extracted with EtOAc (100 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under vacuum to get the crude compound. The crude material was purified by flash column chromatography using 25-35% of EtOAc:Hex. to get the tittle product (95 mg, 11%).

[0520] LC-MS (ES) m/z : 280.2 $[M+H]^+$

Procedure 67: Compounds synthesized using Procedures 53-66 are converted into corresponding final compound using below general scheme



Step-1: General procedure for de-protection of 1,3-dioxalane group

[0521] To a stirred solution of Intermediate **1** (3 mmol) in THF (10 mL), 4N HCl in water (10 mL) was added drop wise under cooling condition (0 ºC), then the reaction mixture was stirred at room temperature for 2 h, reaction progress was monitored by TLC (50% E.A in heptane). Upon completion reaction mixture was concentrated under reduced pressure at rotavapor to get the aqueous residue, which was basified with saturated Na_2CO_3 to pH 8~9 (pH paper), then the aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the Intermediate **2**.

Step-2: General procedure for reductive amination

[0522] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (**3**) (20 mmol) in THF (10 mL) at 0 °C were added corresponding keto compound (Intermediate **2**) and triethylamine (100 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then sodium triacetoxy borohydride (20 mmol) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aq sodium bicarbonate solution at RT and diluted with water (10 mL). Aqueous layer was extracted using ethyl acetate (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to get the crude product. Crude compound was further purified using preparative TLC using (1 to 10% methanolic ammonia in DCM or in ethylacetate) to afford non polar and polar isomer.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
191	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00-8.90 (m, 1 H), 8.22-8.17 (m, 3 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.75 (t, J = 8.0 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.76 (s, 1 H), 4.56 - 4.44 (m, 1 H), 4.31 - 4.08 (m, 3 H), 4.04 - 3.97 (m, 1 H), 3.58 - 3.47 (m, 3 H), 3.27 - 3.15 (m, 2 H), 2.85 - 2.67 (m, 1 H), 2.66 - 2.40 (m, 2 H), 2.33 - 2.31 (m, 1 H),1.93 - 1.84 (m, 4 H), 1.78 - 1.52 (m, 6 H), 1.39 - 1.37 (m, 2 H), 1.30 - 1.26 (m, 1 H), 1.26 - 1.23 (m, 3 H).	630.5
192	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.00-8.91 (m, 1 H), 8.22-8.18 (m, 3 H), 7.93 (d, J = 8.0 Hz, 1 H), 7.75 (t, J = 8.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.83 (s, 1 H), 4.83 - 4.43 (m, 1 H), 4.30 - 4.26 (m, 2 H), 4.19 - 4.11 (m, 1 H), 4.03 - 3.95 (m, 1 H), 3.69 - 3.62 (m, 1 H), 3.56 - 3.47 (m, 1 H), 3.43 - 3.41 (m, 1 H), 3.29 - 3.19 (m, 2 H), 3.15 - 3.11 (m, 2 H), 3.09 - 2.89 (m, 1 H), 2.36 - 2.33 (m, 2 H), 2.14 - 2.08 (m, 1 H), 1.97 - 1.89 (m, 4 H), 1.79 - 1.63 (m, 5 H), 1.59 - 1.51 (m, 7 H), 1.15 (s, 3 H).	630.5
193	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-(trifluoromethyl)piperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.91 (m, 1H), 8.22-8.17 (m, 3H), 7.93 (d, 1H, *J* = 7.6 Hz), 7.74 (t, 1H, *J* = 12 Hz), 7.44 (d, 1H, *J* = 13.2 Hz), 7.36 (d, 1H, *J* = 12.4 Hz), 4.79 (s, 1H), 4.46-4.27 (m, 1H), 4.13-3.98 (m, 2H), 3.82 (d, 2H, *J* = 12.4 Hz), 3.56 (d, 2H, *J* = 6.4 Hz), 3.38 (s, 1H), 2.84-2.72 (m, 3H), 2.49 (s, 2H), 2.33-2.29 (m, 2H), 2.11-2.08 (m, 1H), 1.91-1.75 (m, 6H), 1.64-1.53 (m, 6H), 1.38 (br, 2H).	668.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
194	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(oxazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99-8.92 (m, 1H), 8.22-8.17 (m, 3H), 7.93 (d, 1H, *J* = 7.6 Hz), 7.75 (t, 1H, *J* = 16 Hz), 7.48 (d, 1H, *J* = 8.8 Hz), 7.35 (dd, 1H, *J* = 2.8 Hz, 2.8 Hz), 4.85 (s, 1H), 4.46-4.27 (m, 1H), 4.19-3.97 (m, 2H), 3.81 (d, 2H, *J* = 12.4 Hz), 3.64-3.41 (m, 3H), 3.18 (s, 1H), 2.99-2.67 (m, 4H), 2.15-2.08 (m, 1H), 1.98-1.50 (m, 16H).	668.6
195	N-(2-(4-(4-hydroxy-4-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	12.7 (s, 1 H), 9.00 - 8.88 (m, 2 H), 8.22 (s, 1 H), 8.19 - 8.14 (m, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.86 - 7.80 (m, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 5.19 - 5.17 (m, 1 H), 4.47 - 4.26 (m, 1 H), 4.19 - 4.11 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.68 - 3.47 (m, 2 H), 3.00 - 2.90 (m, 1 H), 2.33 - 2.00 (m, 5 H), 1.96 - 1.41 (m, 10 H).	601.5
196	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(5-methylpyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.41 (d, *J* = 2 Hz, 1 H), 9.00 - 8.9 (m, 1 H), 8.79 (s, 2 H), 8.63 (dd, *J* = 10 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.8 - 7.73 (m, 2 H), 5.11 (s, 1 H), 4.49 - 4.29 (m, 1 H), 4.19 - 3.98 (m, 2 H), 3.62 - 3.43 (m, 2 H), 2.86 - 2.8 (m, 1 H), 2.68 - 2.67 (m, 1 H), 2.38 - 2.34 (m, 2 H), 2.28 - 2.22 (m, 3 H), 2.14 - 2.08 (m, 1 H), 1.91 - 1.82 (m, 4 H), 1.79 - 1.76 (m, 1 H), 1.75 - 1.53 (m, 4 H), 1.45 - 1.3 (m, 2 H).	609.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
197	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(5-methylpyrimidin-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.4 (d, *J* = 1.6 Hz, 1 H), 9.0 - 8.91 (m, 1 H), 8.7 (s, 2 H), 8.63 (dd, *J* = 10 Hz, 1 H), 8.23 - 8.18 (m, 2 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 8 Hz, 1 H), 7.75 (t, *J* = 13.6 Hz, 1 H), 5.12 (s, 1 H), 4.48 - 4.29 (m, 1 H), 4.18 - 4.12 (m, 1 H), 4.04 - 3.98 (m, 1 H), 3.69 - 3.43 (m, 4 H), 3.03 - 2.91 (m, 1 H), 2.33 (s, 3 H), 2.17 - 1.96 (m, 4 H), 1.89 - 1.84 (m, 2 H), 1.8 - 1.77 (m, 2 H), 1.71 - 1.65 (m, 4 H), 1.54 - 1.51 (m, 1 H).	609.5
198	1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide	8.96-8.90 (m, 1 H), 8.21-8.16 (m, 3 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.76 (s, 1 H), 4.46 - 4.27 (m, 1 H), 4.15 - 3.97 (m, 2 H), 3.74 (d, J = 12.0 Hz, 2 H), 3.56 - 3.50 (m, 2 H), 3.41 - 3.36 (m, 1 H), 3.04 (s, 3 H), 2.81 - 2.66 (m, 5 H), 2.50 - 2.24 (m, 5 H), 2.11 - 2.07 (m, 1 H), 1.92 - 1.83 (m, 5 H), 1.78 - 1.58 (m, 4 H), 1.52 - 1.40 (m, 2 H), 1.40 - 1.38 (m, 2 H).	671.4
199	1-(6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide	8.95-8.88 (m, 1 H), 8.21-8.17 (m, 3 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.81 (d, *J* = 8.0 Hz, 1 H), 4.27 - 4.10 (m, 1 H), 4.02 - 3.96 (m, 2 H), 3.73 (d, *J* = 16.0 Hz, 2 H), 3.63 - 3.41 (m, 3 H), 3.41 - 3.29 (m, 1 H), 3.04 - 2.90 (m, 4 H), 2.81 - 2.73 (m, 6 H), 2.33 - 2.32 (m, 1 H), 2.13 - 1.79 (m, 5 H), 1.75 - 1.51 (m, 11 H).	671.4

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
200	N-(2-(4-((1r,4r)-4-(5-(4,4-dimethylpiperidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.96-8.89 (m, 1 H), 8.22-8.17 (m, 3 H), 7.92 (d, J = 7.6 Hz,1 H), 7.74 (t , J =7.6 Hz,1 H), 7.44 (d, J = 8.4 Hz, 1 H) ,7.32-7.29 (m, 1 H) 4.97 (s, 1 H), 4.47-4.42 (m, 1 H), 4.13-3.97 (m, 2 H), 3.56-3.36 (m, 3 H), 3.18-3.15 (m, 4 H), 2.84-2.66(m, 1 H), 2.32-2.28 (m, 3 H), 2.10-2.07(m, 1 H), 1.88-1.64(s, 5 H),1.51-1.39(m, 90 H), 0.95 (s, 6 H)	628.6
201	N-(2-(4-((1s,4s)-4-(5-(4,4-dimethylpiperidin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.96-8.89 (m, 1 H), 8.21-8.16 (m, 3 H), 7.92 (d, **J** = 7.6 Hz,1 H), 7.73 (t ,**J** =8 Hz,1 H), 7.41-7.38 (m, 1 H) ,7.32-7.29 (m, 1 H) 4.8 (s, 1 H), 4.46-4.18 (m, 2 H), 4.16-4.10 (m, 1 H), 4.02-3.96 (m, 1 H), 3.66-3.61 (m, 1 H), 3.56-3.40 (m, 2 H), 3.24-3.14 (m, 5 H), 2.98-2.90 (m, 1 H), 2.33-2.32(m, 2 H), 1.96-1.90(m, 4 H), 1.86-1.58(m, 6 H), 1.55-1.42(m, 4 H), 0.95(s, 6 H).	628.6
202	N-(2-(4-((1r,4r)-4-(5-(1-acetylpiperidin-4-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88 - 8.98 (m, 1 H), 8.40 (s, 1H), 8.21 (s, 1H), 8.16-8.18 (d, J = 8Hz, 1H), 7.91 - 7.93 (d, J = 8Hz, 1H), 7.74 (t, J = 3.0 Hz, 1H), 7.63-7.65 (d, J = 8Hz, 1H), 7.53-7.55 (d, J = 8Hz, 1H), 4.43-4.52 (m, 2H), 4.25-4.29 (m, 1H), 3.97-4.16 (m, 2H), 3.90-3.93 (m, 1H), 3.32-3.50(m, 1H), 3.13 (t, J = 12.8 Hz, 1H), 2.81 (t, J = 12 Hz, 1H), 2.56-2.68 (m, 1H), 2.28-2.33 (m, 2H), 2.02-2.13 (m, 1H), 2.02 (s, 3H), 1.75-1.89 (m, 6H), 1.54-1.63 (m, 5H), 1.39-1.45 (m, 3H)	642.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
203	N-(2-(4-((1s,4s)-4-(5-(1-acetylpiperidin-4-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.89 - 8.98 (m, 1 H), 8.37 (s, 1H), 8.22 (s, 1H), 8.17-8.19 (d, J = 8Hz, 1H), 7.91 - 7.93 (d, J = 8Hz, 1H), 7.74 (t, J = 3.0 Hz, 1H), 7.63-7.66 (d, J = 8Hz, 1H), 7.57-7.59 (d, J = 8Hz, 1H), 4.93-4.94 (m, 1H), 4.51-4.54 (m, 1H), 4.25-4.46 (m, 1H), 4.12-4.19 (m, 1H), 3.90-4.02(m, 2H), 3.40-3.67 (m, 3 H), 3.12 (t, J = 12.8 Hz, 1H), 2.89- 3.09 (m, 1H), 2.79 (t, J = 12 Hz, 1H), 2.56-2.68 (m, 1H), 2.28-2.33 (m, 2H), 2.07-2.13 (m, 1H), 2.07 (s, 3H), 1.75-1.89 (m, 6H), 1.54-1.98 (m, 10H), 1.39-1.57 (m, 2H), 1.23 (s, 1H)	642.6
204	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-isopropylthiazol-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.06 - 8.88 (m, 3 H), 8.26 - 8.16 (m, 3 H), 8.06 (s, 1 H), 7.92 (d, J = 7.6 Hz, 1 H), 7.76 - 7.68 (m, 2 H), 5.02 (s, 1 H), 4.47 - 3.98 (m, 3 H), 3.58 - 3.34 (m, 4 H), 2.86 - 2.65 (m, 1 H), 2.40 - 2.32 (m, 4 H), 2.12 - 1.76 (m, 4 H), 1.68 - 1.44 (m, 3 H), 1.42 - 1.22 (m, 8 H).	642.5
205	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-isopropylthiazol-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide.	9.03 - 8.26 (m, 2 H), 9.03 - 8.89 (m, 2 H), 8.29 - 8.17 (m, 3 H), 8.06 (s, 1 H), 7.92 (d, J = 7.6 Hz, 1 H), 7.76 - 7.72 (m, 2 H), 5.04 (s, 1 H), 5.04 - 3.96 (m, 3 H), 3.68 - 3.25 (m, 3 H), 2.91 - 2.67 (m, 1 H), 2.17 - 2.00 (m, 4 H), 1.99 - 1.62 (m, 9 H), 1.55 - 1.22 (m, 7 H).	642.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
206	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.89 (m, 1 H), 8.19 (t, *J* = 12.0 Hz, 2 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.79 - 7.72 (m, 2 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 4.79 (s, 1 H), 4.69 (s, 1H), 4.45 - 3.95 (m, 3 H), 3.55 - 3.51 (m, 2 H), 3.38 - 3.14 (m, 4 H), 2.83 - 2.66 (m, 1 H), 2.50 - 2.07 (m, 6 H), 1.97 - 1.82 (m, 6 H), 1.75 - 1.35 (m, 9 H).	616.5
207	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.90 (m, 1 H), 8.20 (t, *J* = 12.4 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.76 - 7.72 (m, 2 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 6.87 - 6.83 (m, 1 H), 4.46 - 3.95 (m, 3 H), 3.66 - 3.32 (m, 4 H), 3.28 - 2.67 (m, 3 H), 2.32 - 2.08 (m, 3 H), 1.95 - 1.50 (m, 14 H), 1.33 - 1.34 (m, 5 H).	616.5
208	N-(2-(4-((1r,4r)-4-(5-((dimethylamino)methyl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.89 (m, 1 H), 8.35 (s, 1 H), 8.19 (t, *J* = 11.6 Hz,2 H), 7.93 (d ,*J* =7.6 Hz,1 H), 7.74 (d, *J* =8 Hz, 1 H), 7.67 (d, *J* =7.6 Hz, 1 H), 7.59 (d,*J* =8 Hz, 1 H), 4.95(s, 1 H) , 4.47-4.46(m, 1 H), 4.30-4.28 (m, 1 H),4.16-4.08 (m, 1 H) 4.04-3.97(m, 1 H)3.58-3.57 (m, 2 H), 3.51-3.31 (m, 3 H), 2.85-2.67 (m, 2 H), 2.36-2.28 (m, 3 H), 2.16-2.07(m, 6 H), 1.90-1.75 (m, 4 H), 1.69-1.57(m, 3 H), 1.39-1.24 (m, 2 H).	574.4
209	N-(2-(4-((1s,4s)-4-(5-((dimethylamino)methyl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.95-8.93 (m, 1 H), 8.37 (s, 1 H), 8.23-8.18 (m,2 H), 7.93 (d, *J* =8 Hz, 1 H), 7.75 (t, *J* =8 Hz, 1 H), 7.68-7.61 (m, 2 H), 4.99-4.89(m, 1 H) , 4.29-4.17(m, 1 H), 4.16-4.3.97 (m, 2 H),3.67-.3.32 (m, 3 H) 3.30-3.24(m, 1 H), 2.91-2.66(m, 2 H), 2.33-1.24 (m, 20 H).	574.4

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
214	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88-8.98 (m, 1H), 8.58-8.59 (d, J=2.4 Hz, 1H), 8.21 (s, 1H), 8.16-8.18 (d, J=8 Hz, 1H), 7.91-7.93 (d, J=7.6 Hz, 1H), 7.79-7.82 (m, 1H), 7.72-7.76 (m, 1H), 7.52-7.56 (d, J=8 Hz, 1H), 5.11 (s, 1H), 4.9 (s, 1H), 4.26-4.47 (m, 1H), 3.98-4.17 (m, 2H), 3.51-3.56 (m, 2H), 3.33-3.34 (m, 1H), 2.77-2.85 (m, 1H),2.41-2.43 (m, 2H), 2.25-2.32 (m, 2H), 2.05-2.15 (1H), 1.55-1.98 (m, 5H), 1.51-1.62(m, 2H), 1.3-1.1.48(m, 8H).	575.5
215	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88-8.98 (m, 1H), 8.58-8.59 (d, J=2.4 Hz, 1H), 8.21 (s, 1H), 8.16-8.18 (d, J=8 Hz, 1H), 7.91-7.93 (d, J=7.6 Hz, 1H), 7.79-7.82 (m, 1H), 7.72-7.76 (m, 1H), 7.52-7.56 (d, J=8 Hz, 1H), 5.11 (s, 1H), 4.9 (s, 1H), 4.26-4.47 (m, 1H), 3.98-4.17 (m, 2H), 3.51-3.56 (m, 2H), 3.33-3.34 (m, 1H), 2.77-2.85 (m, 1H),2.41-2.43 (m, 2H), 2.25-2.32 (m, 2H), 2.05-2.15 (1H), 1.55-1.98 (m, 5H), 1.51-1.62(m, 2H), 1.3-1.1.48(m, 8H).	575.5
216	N-(2-(4-((1r,4r)-4-(5-(tert-butyl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88 - 8.98 (m, 1H), 8.16 - 8.56 (m, 1H), 8.21 (s, 1H), 8.18 - 8.21 (m, 1H) 7.91 - 7..93 (d, **J** = 8Hz, 1H), 7.72 - 7.78 (m, 2H), 7.52 - 7.54 (d, **J** = 8Hz, 1H), 4.89 (s, 1H), 4.26 - 4.47 (m, 1H), 3.97 - 4.18 (m, 2H), 3.51 -3.58 (m, 2H), 3.30 - 3.38 (m, 1H),2.66 -2.85 (m, 1H), 2.27 - 2.36 (m, 2H), 2.10 - 2.13 (m, 1H), 1.71 - 2.07 (m, 5H), 1.46 - 1.68 (m, 4H), 1.31 - 1.39 (m, 2 H), 1.39 (s, 9H), 1.16 (s, 1H).	573.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
217	N-(2-(4-((1s,4s)-4-(5-(tert-butyl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.89 - 8.98 (m, 1H), 8.52 - 8.53 (m, 1H), 8.22 (s, 1H), 8.17 - 8.22 (m, 1H) 7.91 - 7.93 (d, **J** = 8Hz, 1H), 7.72 - 7.78 (m, 2H), 7.58 - 7.56 (d, **J** = 8Hz, 1H), 4.93 (s, 1H), 4.26 - 4.47 (m, 1H), 4.10 - 4.19 (m, 1H), 3.95 -4.09 (m, 2H), 3.61 - 3.68 (m, 1H), 3.49 - 3.56 (m, 1H), 3.40 - 3.51 (m, 1H), 2.89 - 2.99 (m, 1H), 2.11 - 2.17 (m, 1H), 1.90 - 2.07 (m, 3H), 1.80 - 1.88 (m, 2H), 1.71 - 1.77 (m, 2H), 1.64 - 1.67 (m, 2H), 1.52 - 1.61 (m, 2H), 1.46 - 1.51 (m, 1 H), 1.32 (s, 9H).	573.5
218	N-(2-(4-((1r,4r)-4-(5-(6-azaspiro[2.5]octan-6-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88-8.97 (m, 1H), 8.21 (s, 2H), 8.16-8.18 (d, J=8Hz, 1H), 7.91-7.93 (d, J=7.6Hz, 1H), 7.72-7.75 (t, J=8Hz, 1H), 7.40-7.42 (d, J=8.8HZ, 1H). 7.32-7.35 (m, 1H), 4.76 (s, 1H), 4.25-4.46 (m, 1H), 3.96-4.17 (m, 1H), 3.50-3.56 (m, 2H),3.36-3.39 (m, 2H), 3.17-3.24 (m, 4H), 2.67-2.84 (m, 1H), 2.28-2.33 (m, 4H), 2.07-2.11 (m, 1H), 1.62-1.92 (m, 5H), 1.44-1.52 (m, 8H), 0.33 (s, 4H).	626.4
219	N-(2-(4-((1s,4s)-4-(5-(6-azaspiro[2.5]octan-6-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88-8.97 (m, 1H), 8.21 (s, 2H), 8.16-8.18 (d, J=8Hz, 1H), 7.91-7.93 (d, J=7.6Hz, 1H), 7.72-7.75 (t, J=8Hz, 1H), 7.40-7.42 (d, J=8.8HZ, 1H). 7.32-7.35 (m, 1H), 4.76 (s, 1H), 4.25-4.46 (m, 1H), 3.96-4.17 (m, 1H), 3.50-3.56 (m, 2H),3.36-3.39 (m, 2H), 3.17-3.24 (m, 4H), 2.67-2.84 (m, 1H), 2.28-2.33 (m, 4H), 2.07-2.11 (m, 1H), 1.62-1.92 (m, 5H), 1.44-1.52 (m, 8H), 0.33 (s, 4H).	626.4

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
220	N-(2-(4-((1r,4r)-4-(5-(4-acetylpiperazin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.89 (m, 1 H), 8.22-8.14(m, 3 H), 7.92 (d ,**J** =7.6 Hz,1 H), 7.74 (d, **J** =8 Hz, 1 H), 7.73 (t, **J** =8 Hz, 1 H), 7.45 (d, **J** =8.8 Hz, 1 H), 7.36-7.34(m,1H), 4.78(s, 1 H), 4.28-4.27 (m, 1 H), 4.15-3.96 (m, 2 H) 4.04-3.97(m, 1 H)3.58-3.49 (m, 6 H), 3.41-3.37 (m, 1 H), 3.20-3.11 (m, 4 H), 2.84-2.66 (m, 1 H), 2.12-2.08(m, 3 H), 1.87-1.64 (m, 4 H), 1.66-1.15(m, 9 H).	643.6
221	N-(2-(4-((1s,4s)-4-(5-(4-acetylpiperazin-1-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97-8.89 (m, 1 H), 8.22-8.17(m, 3 H), 7.92 (d, *J* =8 Hz,1 H), 7.74 (t, *J* =7.6 Hz, 1 H), 7.73 (t, *J* =8 Hz, 1 H), 7.49 (d, *J* =8.8 Hz, 1 H), 7.36-7.34 (m,1H), 4.85(s, 1 H), 4.84-4.28 (m, 1 H), 4.02-3.98 (m, 2 H) 4.04-3.97(m, 1 H),3.67-3.39 (m, 7 H), 3.24-3.18 (m, 4 H), 2.98-2.90 (m, 1 H), 2.14-1.48(m, 16 H).	643.6
226	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-methoxy-6-methylpyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.88 (m, 1H), 8.21-8.16 (m, 2H), 7.93-7.91 (d, *J*=8Hz, 1H), 7.75-7.71 (t, *J*=8Hz, 1H), 7.38-7.36 (d, *J*=8Hz, 1H), 7.09-7.07 (d, *J*=8Hz, 1H), 4.79(s, 1H), 4.45-4.28 (m, 1H), 4.11-3.99 (m, 3H), 3.79(s, 3H), 3.58-3.50 (m, 2H), 3.41-3.36 (m, 1H), 2.85-2.66(m, 1H), 2.42-2.27(m, 5H), 2.11-2.07(m, 1H),1.97-1.80(m, 5H), 1.74-1.65(m, 3H), 1.64-1.53(m, 2H)	561.2

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
227	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-methoxy-6-methylpyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.89(m, 1H), 8.21-8.17(m, 2H), 7.93-7.91(d, *J*=8Hz, 1H), 7.76-7.72(t, *J*=8Hz, 1H), 7.43-7.40(d, *J*=8Hz, 1H), 7.30-7.28(d, *J*=8Hz, 1H), 4.85(s, 1H), 4.82-4.44(m, 1H), 4.27-4.01(m, 2H), 3.79(s, 3H), 3.69-3.64(m, 1H), 3.51-3.49(m, 1H), 3.41-3.36(m, 1H), 3.25-3.22(m, 2H), 3.02-2.90(m, 1H), 2.33(s, 3H), 2.27-2.24(m, 1H), 2.01-1.97(m, 4H), 1.86-1.81(m, 2H), 1.78-1.76(m, 2), 1.66-1.57(m, 3H).	561.2
236	(3S)-1-(6-((1r,4S)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpyrrolidine-3-carboxamide	8.92 (tt, *J* = 5.6 Hz, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 8.17 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 2.8 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.93-6.91 (m, 1H), 4.70 (s, 1H), 4.43-3.99 (m, 3H), 3.55-3.46 (m, 4H), 3.40-3.33 (m, 4H), 3.0 (s, 3H), 2.85 (s, 3H), 2.76 (br, 1H), 2.34-2.04 (m, 5H), 1.92-1.79 (m, 5H), 1.74-1.65 (m, 1H), 1.51-1.33 (m, 5H)	657.6
237	(3S)-1-(6-((1s,4R)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpyrrolidine-3-carboxamide	8.96-8.89 (m, 1H), 8.21-8.16 (m, 2H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.86-7.82 (m, 1H), 7.74 (t, *J* = 8Hz, 1H), 7.42-7.36 (m, 1H), 6.93-6.90 (m, 1H), 4.79-4.78 (m, 1H), 4.70-4.01 (m, 3H), 3.64-3.46 (m, 4H), 3.38-3.34 (m, 4H), 3.07 (s, 3H), 2.85 (s, 3H), 2.67-2.66 (m, 1H), 2.33-2.04 (m, 4H), 1.96-1.33 (m, 12H)	657.6

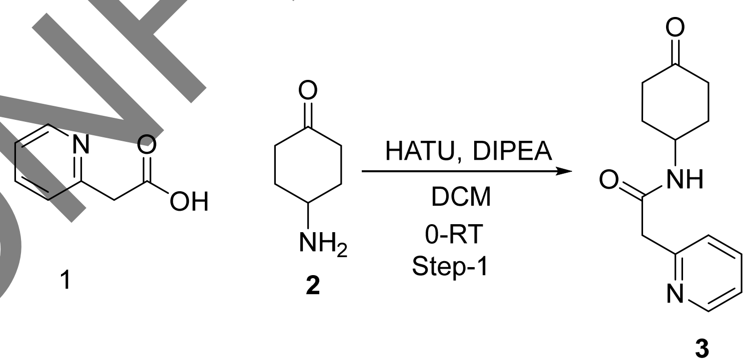
Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
240	(3R)-1-(6-((1r,4R)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpyrrolidine-3-carboxamide	8.97 - 8.89 (m, 1 H), 8.19 (t, *J* = 11.6 Hz, 3 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.86 (d, *J* = 2.8 Hz, 1 H), 7.74 (t, *J* = 8.0 Hz, 2 H), 4.70 (s, 1 H), 4.45 - 4.26 (m, 1H), 4.17 - 3.96 (m, 2 H), 3.62 - 3.46 (m, 4 H), 3.17 - 3.01 (m, 4 H), 2.90 - 2.67 (m, 5 H), 2.34 - 2.17 (m, 3 H), 2.09 - 1.63 (m, 7 H), 1.49 - 1.12 (m, 8 H).	657.6
241	(3R)-1-(6-((1s,4S)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpyrrolidine-3-carboxamide	8.97 - 8.89 (m, 1 H), 8.20 (t, *J* = 11.6 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 8.59 (m, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.42 - 7.36 (m, 1 H), 6.93 - 6.90 (m, 1 H), 4.79 (d, *J* = 2.8 Hz, 1 H), 4.70 (d, *J* = 2.0 Hz, 1 H), 4.70 - 4.28 (m, 1 H), 4.27 - 3.96 (m, 2 H), 366 - 3.32 (m, 7 H), 3.26 - 2.66 (m, 8 H), 2.33 - 2.06 (m, 5 H), 1.96 - 0.86 (m, 10 H)	657.6
242	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.88 (m, 1H), 8.21-8.16 (m, 2H), 8.04 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.14-7.11 (m, 1H), 4.70 (s, 1H). 4.56 (s, 1H), 4.45-3.96 (m, 5H), 3.77 (s, 1H), 3.57-3.50 (m, 2H), 3.39-3.37 (m, 1H), 2.84-2.77 (m, 1H), 2.48-2.47 (m, 2H), 2.33-2.25 (m, 3H), 2.10-2.07 (m, 1H), 1.96-1.83 (m, 8H), 1.76-1.33 (m, 8H)	642.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
243	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.89 (m, 1H), 8.22-8.17 (m, 2H), 8.01 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.14-7.11 (m, 1H), 4.78 (s, 1H), 4.55 (s, 1H), 4.46-3.95 (m, 5H), 3.77 (s, 1H), 3.66-3.40 (m, 3H), 3.24-3.22 (m, 1H), 2.98-2.90 (m, 1H), 2.49-2.48 (m, 2H), 2.33-2.25 (m, 2H), 2.14-2.07 (m, 1H), 1.95-1.86 (m, 8H), 1.78-1.49 (m, 8H)	624.6
244	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyrazin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.88 (m, 1 H), 8.28-8.27 (m, 1 H), 8.22 (d ,*J* =7.6 Hz,2 H), 8.17 (d,*J* =8 Hz, 1 H), 7.92 (t, *J* =7.6 Hz, 1 H), 7.73 (d,*J* =8 Hz, 1 H), 4.78 (s, 1 H), 4.71-4.69 (m, 1 H), 4.43-4.12 (m, 1 H) 4.11-3.95 (m, 4 H), 3.73 -3.68(m, 1 H), 3.57-3.50(m, 3 H), 3.16-3.09 (m, 2 H), 2.50-2.27 (m, 4 H), 2.10-1.74(m, 7 H), 1.48-1.32 (m, 7 H).	617.6
245	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyrazin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-8.89 (m, 1 H), 8.29 (s, 1 H), 8.19 (t ,**J** =10.8 Hz,3 H), 7.92 (d, **J** =7.6 Hz, 1 H), 7.74 (t, **J** =8 Hz, 1 H), 4.85-4.84 (m, 1 H), 4.70-4.69 (m,1 H), 4.28-4.10 (m, 1 H) 4.02-3.95 (m, 4 H), 3.71 -3.41 (m, 4 H), 3.31-3.08 (m, 3 H), 2.90-2.67-2.50 (m, 1 H), 1.92-1.90 (m, 1 H), 1.89-1.62(m, 12 H), 1.50-1.38 (m, 3 H).	617.6
250	N-(2-(4-((1r,4r)-4-(3-fluoro-5-(2-hydroxypropan-2-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1H), 8.45 (s, 1H), 8.22 - 8.17 (m, 2H), 7.93 - 7.91 (m, 1H), 7.76-7.72 (m, 1H), 7.68 - 7.67 (m, 0.5 H), 7.65 - 7.64 (m, 0.5H), 5.30 (s, 1H), 5.12 (s, 1H), 4.46 - 4.44 (m, 1H), 4.38 - 4.27 (m, 1H), 4.01 - 3.95 (m, 1H), 3.70 - 3.60 (m, 1H), 3.59 - 3.40 (m, 2H), 3.39 - 3.30 (m, 1H), 3.05-2.90 (m, 1H), 2.45 - 2.40 (m, 2H), 2.10 - 2.20(m, 1H), 1.98 - 1.90 (m, 2H), 1.85 - 1.68 (m, 7H), 1.59 - 1.48 (m, 7H).	**593.5**

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
251	N-(2-(4-((1s,4s)-4-(3-fluoro-5-(2-hydroxypropan-2-yl)pyridin-2-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.99 - 8.89 (m, 1H), 8.44 (s, 1H), 8.22 - 8.18 (m, 2H), 7.94 - 7.91 (m, 1H), 7.76-7.72 (m, 1H), 7.68 - 7.66 (m, 0.5 H), 7.65 - 7.64 (m, 0.5H), 5.30 (s, 1H), 5.12 (s, 1H), 4.47 - 4.45 (m, 1H), 4.39 - 4.28 (m, 1H), 4.01 - 3.95 (m, 1H), 3.71 - 3.60 (m, 1H), 3.59 - 3.40 (m, 2H), 3.40 - 3.30 (m, 1H), 3.05-2.90 (m, 1H), 2.45 - 2.40 (m, 2H), 2.10 - 2.20(m, 1H), 1.98 - 1.90 (m, 2H), 1.85 - 1.68 (m, 7H), 1.57 - 1.48 (m, 7H).	**593.5**
254	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxypentan-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90-8.99 (m, 1 H), 8.48 (s, 1 H), 8.16-8.21 (m, 2 H), 7.92 (d, J= 7.6 Hz, 1 H), 7.70- 7.76 (m, 2 H), 7.53 (d, J= 8.4 Hz, 1 H), 4.91 (s, 1 H), 4.67 (s, 1 H), 4.17- 4.47 (m, 1 H), 4.02- 4.16 (m, 2 H), 3.52- 3.58 (m, 2 H), 3.50 (s, 1 H), 2.67- 2.84 (m, 1 H), 2.27- 2.36 (m, 4 H), 1.85- 1.94 (m, 3 H), 1.68- 1.81 (m, 5 H), 1.56- 1.64 (m, 3 H), 1.35- 1.40 (m, 3 H), 0.65 (t, J= 7.2 Hz, 6 H).	603.6
255	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxypentan-3-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90-8.99 (m, 1 H), 8.48 (s, 1 H), 8.18-8.22 (m, 2 H), 7.93 (d, J= 7.6 Hz, 1 H), 7.70- 7.77 (m, 2 H), 7.58 (d, J= 8.4 Hz, 1 H), 4.95 (s, 1 H), 4.67 (s, 1 H), 4.27- 4.50 (m, 1 H), 4.09- 4.12 (m, 1 H), 3.92- 4.05 (m, 1 H), 3.61- 3.73 (m, 1 H), 3.42- 3.59 (m, 2 H), 3.22 (s, 1 H), 2.89- 3.03 (m, 1 H), 2.12- 2.19 (m, 1 H), 1.89- 2.05 (m, 3 H), 1.80- 1.91 (m, 2 H), 1.57- 1.79 (m, 10 H), 1.49- 1.53 (m, 1 H), 0.66 (t, J= 7.2 Hz, 6 H).	603.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
256	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-methylthiazol-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.04 (d, *J* = 2 Hz, 1 H), 8.98 - 8.88 (m, 1 H), 8.26 - 8.16 (m, 3 H), 8.03 (s, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.76 - 7.67 (m, 2 H), 5.02 (s, 1 H), 4.47 - 4.28 (m, 1 H), 4.13 - 3.97 (m, 2 H), 3.58 - 3.51 (m, 2 H), 3.42 - 3.33 (m, 1 H), 2.85 - 2.56 (m, 6 H), 2.50 - 2.32 (m, 2 H), 2.14 - 2.11 (m, 1 H), 1.95 - 1.43 (m, 9 H).	614.5
257	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-methylthiazol-4-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	9.02 (d, *J* = 2 Hz, 1 H), 9.00 - 8.91 (m, 1 H), 8.26 - 8.17 (m, 3 H), 8.03 (s, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.76 - 7.68 (m, 2 H), 5.05 (s, 1 H), 4.47 - 4.20 (m, 3 H), 4.18 - 3.32 (m, 3 H), 3.25 - 2.73 (m, 2 H), 2.67 (s, 3 H), 2.27 - 1.51 (m, 13 H).	614.5

Procedure 67: Synthesis of N-(4-oxocyclohexyl)-2-(pyridin-2-yl) acetamide

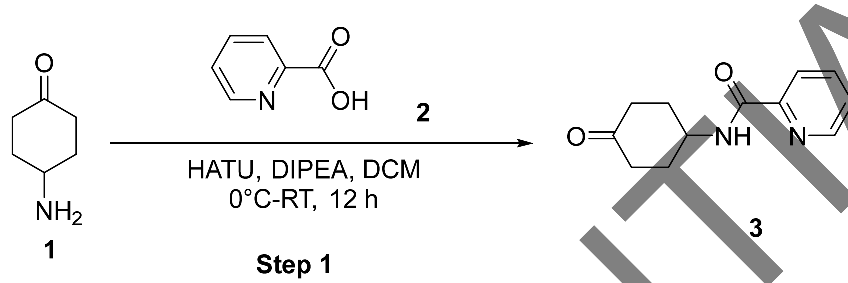


Step-1: Synthesis of N-(4-oxocyclohexyl)-2-(pyridin-2-yl) acetamide

[0523] To a stirred solution of 2-(pyridin-2-yl)acetic acid (0.3 g, 1 *eq,* 2.19 mmol), 4-aminocyclohexan-1-one (394 mg, 1.2 eq., 2.63 mmol) in DCM (10 mL) at room temperature under nitrogen atmosphere to the reaction mixture ethylbis(propan-2-yl)amine (1.91 mL, 5 *eq*., 10.9 mmol) was added and stirred for 5 minutes then HATU (915 mg, 1.1 *eq*., 2.41 mmol) was added and the stirring was continued 12 hrs, the progress of the reaction was monitored by TLC and LCMS. After completion of the reaction the mixture was quenched with sat sodium bi carbonate and extracted with ethyl acetate washed with brine solution, dried over by sodium sulphate the combined organic layers were concentrated under reduced pressure to get crude product. The crude product was purified with 10% MeOH in DCM desired product of N-(4-oxocyclohexyl)-2-(pyridin-2-yl)acetamide (170 mg, 33 %).

[0524] LC-MS (ES) m/z: 233.2 $[M+H]^+$

Procedure 68: Synthesis of N-(4-oxocyclohexyl)picolinamide

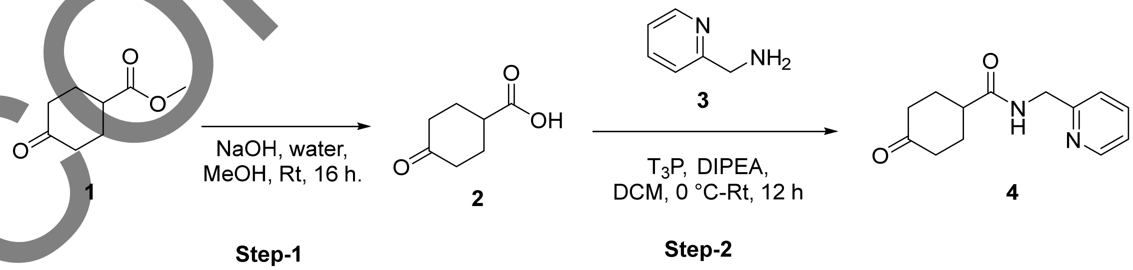


Step 1: Preparation of N-(4-oxocyclohexyl)pyridine-2-carboxamide

[0525] To a stirred solution of pyridine-2-carboxylic acid (326 mg, 2.65 mmol)in DCM (15 mL) were added HATU (101 mg, 1 *eq* , 265 μmol) and ethylbis(propan-2-yl)amine (1.03 g, 3 *eq*., 7.95 mmol) followed by the addition of 4-aminocyclohexan-1-one (0.3 g, 2.65 mmol) at 0°C. Stirred the reaction mixture at rt for 12 hrs. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (5 mL) and extracted with DCM (2 x 20 mL) concentrated in vacuo to get the crude material. The crude material was purified by flash column chromatography using 30% ethylacetate and hexane as an eluent to afford as N-(4-oxocyclohexyl)pyridine-2-carboxamide (0.3 g, 51 % yield).

[0526] LCMS (ES) m/z: 219.2 $[M+H]^+$

Procedure 69: Synthesis of 4-oxo-N-(pyridin-2-ylmethyl)cyclohexane-1-carboxamide



Step 1: Synthesis of 4-oxocyclohexane-1-carboxylic acid

[0527] To the solution of the methyl 4-oxocyclohexane-1-carboxylate (1 g, 6.4 mmol) in methanol (10 mL, 247 mmol) was added 4N sodium hydroxide (1.02 g, 4 eq., 25.6 mmol). solution in water (5 mL, 278 mmol). The reaction mixture was stirred at room temperature overnight. Once the reaction was completed, the solvents were evaporated in vacuum. The residue was extracted with ether once. The aqueous layer was acidified to pH of 1 with 6N HCl and extracted with EtOAc (3 X 70 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo to afford 4-oxocyclohexane-1-carboxylic acid (850 mg, Yield: 93 %).

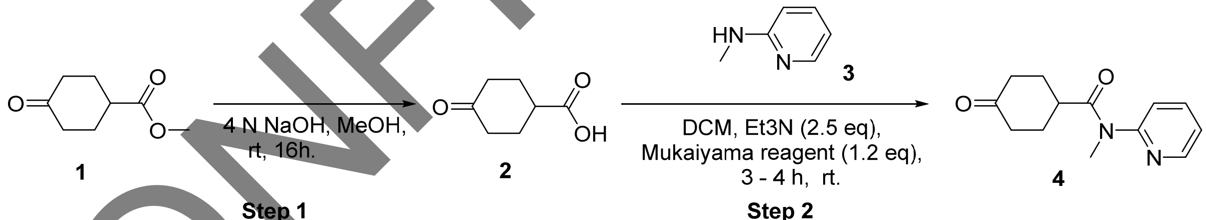
[0528] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.76- 2.92 (m, 1 H), 2.46- 2.59 (m, 2 H), 2.32- 2.44 (m, 2 H), 2.19- 2.31 (m, 2 H), 1.98- 2.14 (m, 2 H).

Step 2: Synthesis of 4-oxo-N-[(pyridin-2-yl)methyl]cyclohexane-1-carboxamide:

[0529] To a stirred solution of 4-oxocyclohexane-1-carboxylic acid (158 mg, 1.11 mmol) in DCM (3.0 mL) were added T_3P (569 µL, 2 eq., 2.22 mmol) and ethylbis(propan-2-yl)amine (574 µL, 3 eq., 3.33 mmol) followed by the addition of 1-(pyridin-3-yl)methanamine (120 mg, 1.11 mmol) at 0 °C. Stirred the reaction mixture at rt for 12 hours. The progress of the reaction mixture was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (15 mL) and extracted with DCM (2x 20 mL). Combined organic extracts were washed with water, brine and concentrated under reduced pressure to get the crude product. The crude material was loaded in silica gel column MPLC using 2-4% MeOH in DCM as an eluent to afford 4-oxo-N-[(pyridin-2-yl)methyl]cyclohexane-1-carboxamide (100 mg, 39 %).

[0530] LCMS (ES) m/z: 233.1 $[M+H]^+$

Procedure 70: Synthesis of N-methyl-4-oxo-N-(pyridin-2-yl)cyclohexane-1-carboxamide



Step 1: Synthesis of 4-oxocyclohexane-1-carboxylic acid

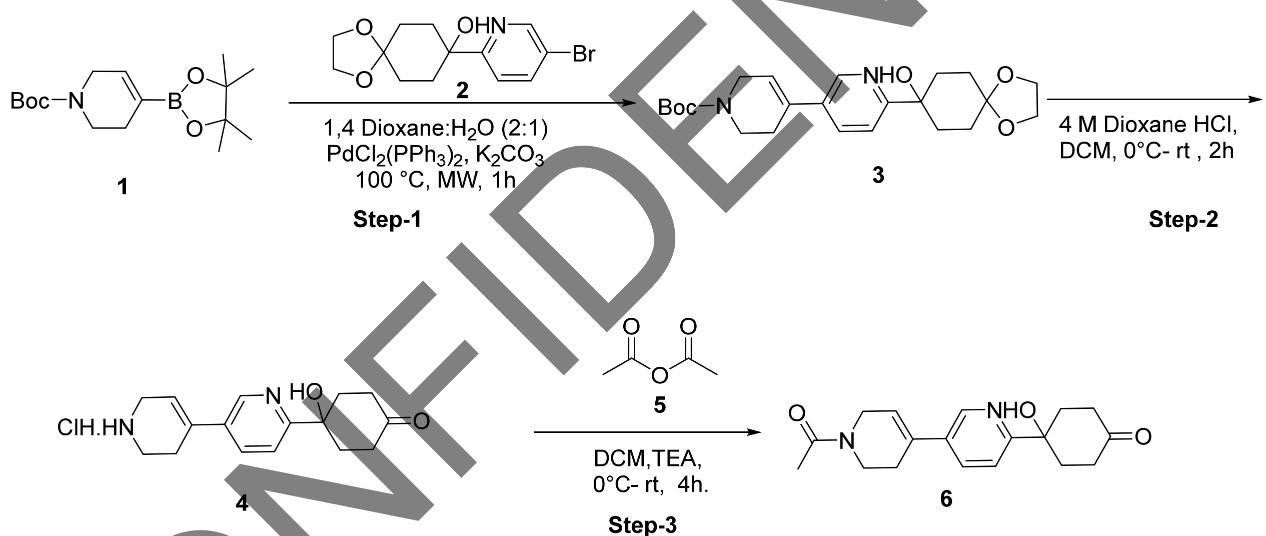
[0531] To the solution of methyl 4-oxocyclohexane-1-carboxylate (1 g, 6.4 mmol) in methanol (10 mL, 247 mmol) was added 4N sodium hydroxide aqueous solution (10 mL, 5 eq., 32 mmol). The reaction mixture was stirred at room temperature overnight. The progress of the reaction was monitored by TLC. The solvents were evaporated in vacuum. The residue was extracted with ether once. The aqueous layer was acidified to pH is 1 with 6N HCl and extracted with EtOAc three times. T he combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuum. The product was obtained as a yellow oil 4-oxocyclohexane-1-carboxylic acid (840 mg, 92 %). The crude material was directly taken for the next step.

Step 2: Synthesis of N-methyl-4-oxo-N-(pyridin-2-yl)cyclohexane-1-carboxamide

[0532] To a stirred solution of 4-oxocyclohexane-1-carboxylic acid (250 mg, 1.2 eq., 1.76 mmol) in dichloromethane (12.5 mL, 195 mmol) was added with triethylamine (0.005 mL, 2.5 eq., 3.66 mmol) followed by N-methylpyridin-2-amine (158 mg, 1.47 mmol) and 2-chloro-1-methylpyridin-1-ium iodide (449 mg, 1.2 eq., 1.76 mmol) and allowed to stir for 3-4 h at room temperature. The progress of the reaction monitored by TLC and LCMS. The reaction mixture is diluted using (15 mL) water and washed with (15mL x 3) ethyl acetate, organic layer is dried with using sodium sulphate and concentrated using rotavapor, to get the crude product, which was then purified using column chromatography using 5-10% methanol in DCM as eluents to afford N-methyl-4-oxo-N-(pyridin-2-yl)cyclohexane-1-carboxamide (110 mg, 32 %).

[0533] LCMS (ES) m/z: 233.0 $[M+H]^+$

Procedure 71: Synthesis of 4-(1'-acetyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)-4-hydroxycyclohexan-1-one



Step 1: Synthesis of tert-butyl 6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate

[0534] To a stirred solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (0.5 g, 1.62 mmol) and 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (508 mg, 1.62 mmol) in 1,4-dioxane (8 mL) and water (4 mL) at room temperature purged with nitrogen for 10 min further dipotassium carbonate (670 mg, 4.85 mmol) and palladium(2+) bis(triphenylphosphane) dichloride (113 mg, 0.16 mmol) and again purged with nitrogen for 5 min and stirred for 1h at 100 °C in microwave . After the completion of the reaction, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over sodium sulphate and filtered and concentrated under reduced pressure to get the crude compound. The crude material was purified by flash column chromatography using 30-35% of EtOAc:Hex to afford title compound (650 mg, 96%).

[0535] LC-MS (ES) m/z: 417.6 $[M+H]^+$

Step 2: 4-hydroxy-4-(1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)cyclohexan-1-one hydrochloride

[0536] To a stirred solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-1'-yl)ethan-1-one (275 mg, 0.76 mmol) in THF (5 mL) was added 4N HCl in water (10 mL), the reaction mixture was stirred for 4h at RT. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to remove solvent and the reaction mixture was neutralized with sodium bicarbonate (25 mL) and extracted using ethyl acetate (2 x 25 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to get crude compound (200 mg, 83%).

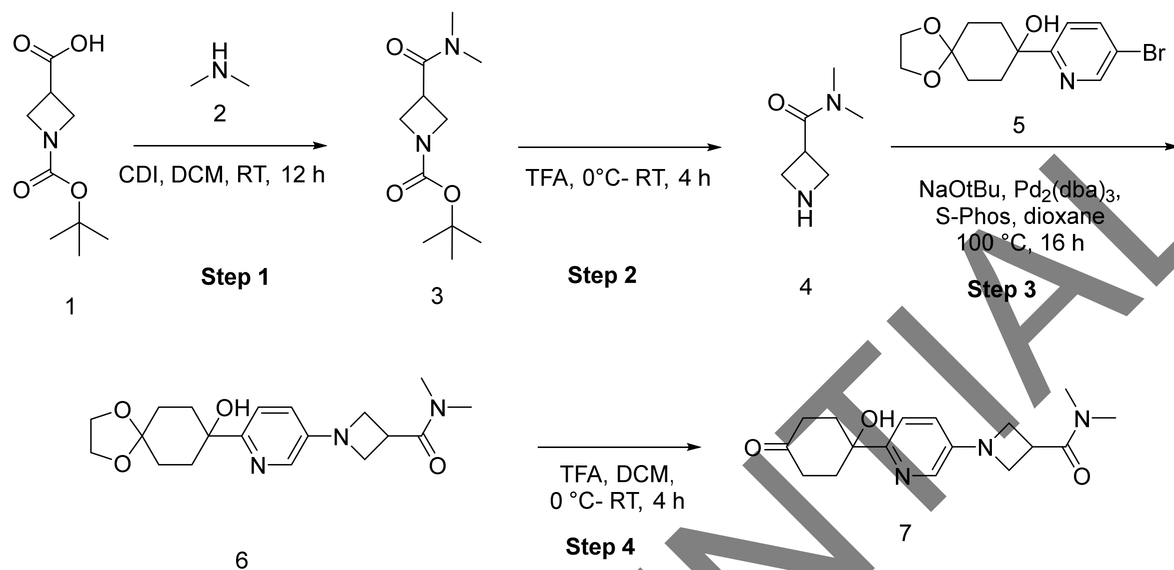
[0537] LC-MS (ES) m/z: 273.1 $[M+H]^+$

Step 3: Synthesis of 4-(1'-acetyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)-4-hydroxycyclohexan-1-one

[0538] To a stirred solution of 4-hydroxy-4-(1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)cyclohexan-1-one hydrochloride (250 mg, 0.91 mmol) in DCM (5 mL) was added with TEA (0.25 mL, 1.84 mmol) and stirred for 2 min. To this reaction mixture then added acetic anhydride (0.1 mL, 1.1 mmol) at cold condition and stirred for 4 h at room temperature. The progress of the reaction monitored by TLC and LCMS. After the completion of the reaction, reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated under reduced pressure to get the crude compound (275 mg, crude).

[0539] LC-MS (ES) m/z: 315.2 $[M+H]^+$

Procedure 72: Synthesis of 1-(6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide



Step 1: Synthesis of tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate:

[0540] To a stirred solution of 1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (2 g, 9.94 mmol) in DCM (20.0 mL) was added CDI (3.22 g, 2 eq., 19.9 mmol) and the reaction mixture was stirred at room temperature for 1 h, followed by the addition of dimethylamine (4.48 g, 10 eq., 99.4 mmol) at 0 °C. The reaction mixture was stirred at rt for 12 hours. The progress of the reaction mixture was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (40 mL) and extracted with DCM (2x 35 mL) concentrated in vacuo to get the crude. The crude was loaded in silica gel column MPLC using 2-4% MeOH in DCM as an eluent to afford tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate (0.8 g, 35 %).

[0541] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.03- 4.16 (m, 4 H), 3.43- 3.51 (m, 1 H), 2.97 (s, 3 H), 2.88 (s, 3 H), 1.46 (s, 9 H).

Step 2: Synthesis of N,N-dimethylazetidine-3-carboxamide:

[0542] A solution of tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate (0.5 g, 2.19 mmol) in trifluoroacetic acid (5 mL) was stirred at room temperature for 1 h and concentrated in vacuo to get the crude of title compound N,N-dimethylazetidine-3-carboxamide (0.6 g, 4.68 mmol).

[0543] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.00- 4.09 (m, 4 H), 3.83- 3.94 (m, 1 H), 2.91 (s, 3 H), 2.83 (s, 3 H).

Step 3: Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide.

[0544] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.2 g, 0.7 eq., 3.82 mmol) and N,N-dimethylazetidine-3-carboxamide (0.7 g, 5.46 mmol) in dioxane (8.0 mL) was added sodium 2-methylpropan-2-olate (1.57 g, 3 eq., 16.4 mmol). The reaction mixture was purged with argon for 15 min and then added Sphos (673 mg, 0.3 eq., 1.64 mmol) and tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.5 g, 0.1 eq., 546 µmol). The reaction mixture was stirred at 100°C for 16 h. After the completion of the reaction, reaction mixture was quenched with water (40 mL) extracted with ethyl acetate (2 x 35 mL), Combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude. The crude was purified by flash column MPLC eluted on 2.5 % MeOH - DCM to afford 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (0.8 g, Yield: 40 %).

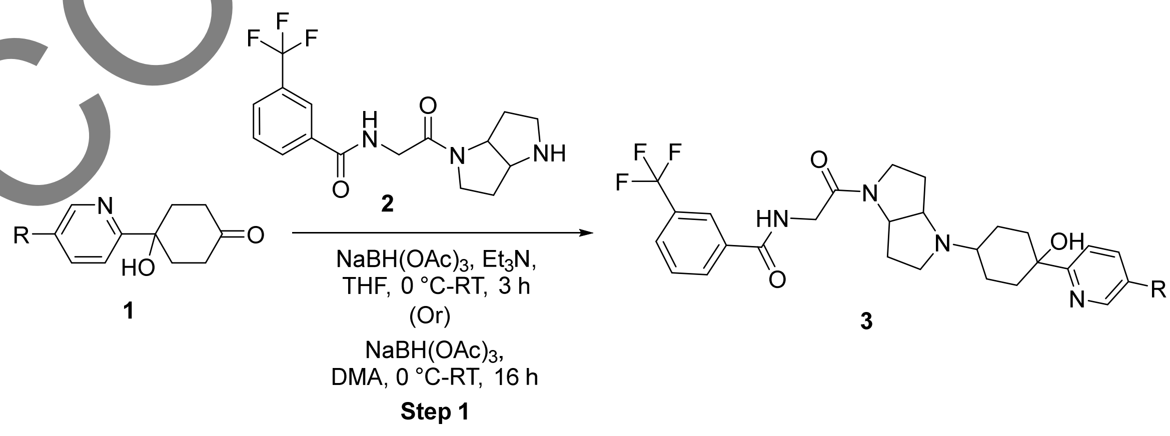
[0545] LC-MS (ES) m/z: 362.1 $[M+H]^+$

Step 4: Synthesis of 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylazetidine-3-carboxamide.

[0546] A solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (350 mg, 968 µmol) in dichloromethane (4 mL, 62.5 mmol) was added trifluoroacetic acid (1 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h. Once the reaction was completed, reaction mixture was concentrated under reduced pressure to get the crude of title compound 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylazetidine-3-carboxamide (450 mg, crude).

[0547] LC-MS (ES) m/z: 318.1 $[M+H]^+$

Procedure 73: Compound synthesized using Procedure 67 to Procedure 72 are converted into corresponding final compound using below general scheme.



Step-1: General procedure for reductive amination

[0548] To a stirred solution of N-(2-(hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (**3**) (20 mmol) in THF (10 mL) at 0 °C were added corresponding keto compound (Intermediate **1**) and triethylamine (100 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then sodium triacetoxy borohydride (20 mmol) was added and stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aq sodium bicarbonate solution at RT and diluted with water (10 mL). The aqueous layer was extracted using ethyl acetate (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to get the crude product. The crude compound was further purified using preparative TLC using (1 to 10% methanolic ammonia in DCM or in ethylacetate) to afford non polar and polar isomer.

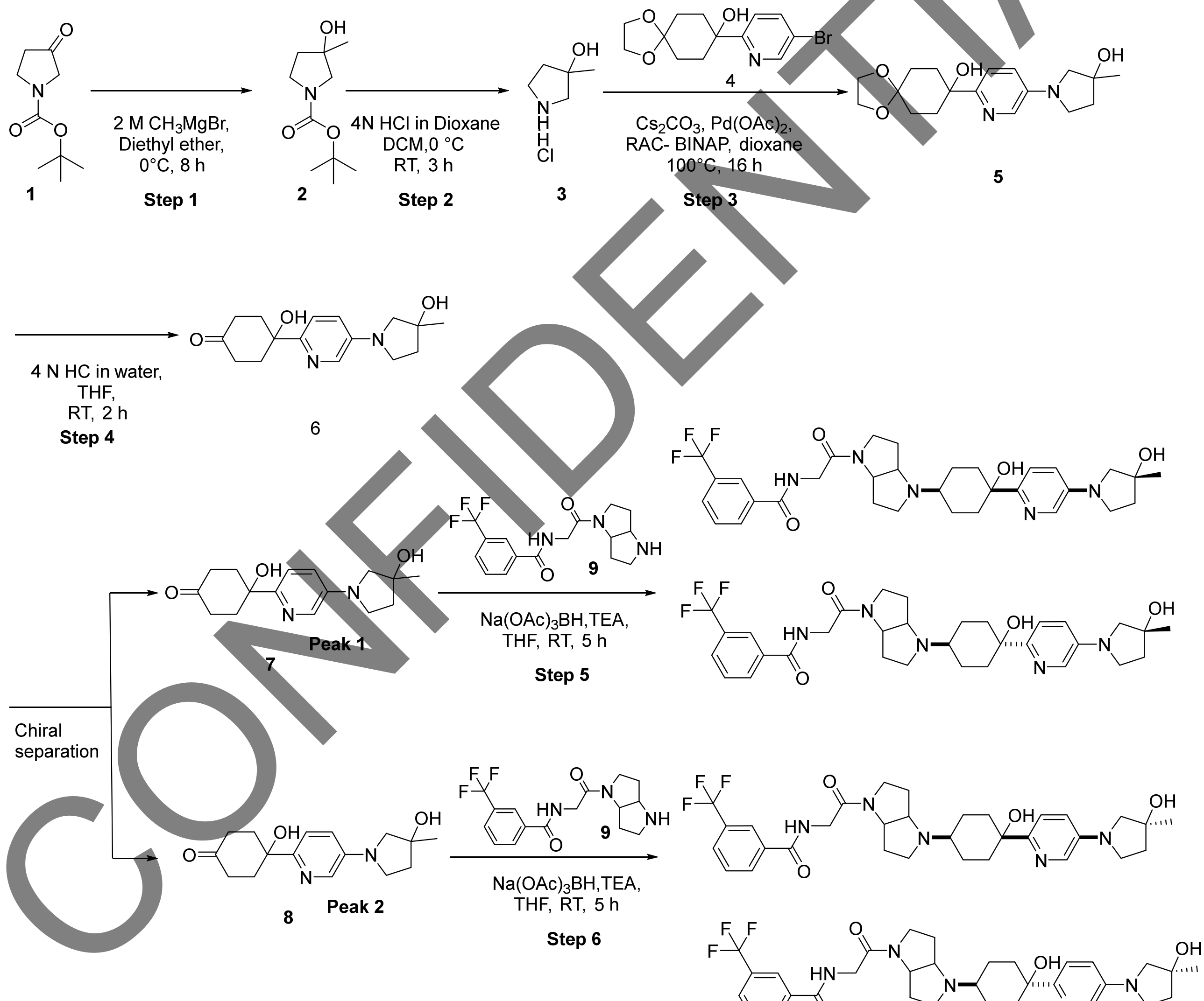
Ex.	**IUPAC name**	**1H NMR (400 MHz, DMSO-d_6) δ ppm**	**LC-MS (m/z) [M+H]$^+$**
222	N-((1s,4s)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)picolinamide	8.99-8.90 (m, 1 H), 8.65-8.64 (m, 1 H), 8.33 (d, *J* = 8 Hz,1 H), 8.19 (t ,*J* =11.6 Hz, 2 H), 8.04-8.01 (m, 2 H), 7.92 (d, *J*= 8 Hz, 1 H) ,7.74 (t, *J* =8 Hz, 1 H),7.62-7.59 (m, 1 H), 4.32-4.17 (m, 1 H) , 4.14-3.97 (m, 3 H), 3.60-3.41 (m, 3 H), 2.93-2.80 (m, 1 H), 2.53-2.52 (m, 2 H), 2.33-2.12 (m, 1 H), 1.96-1.50 (m, 11 H).	544.5
223	N-((1r,4r)-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)picolinamide	8.98-8.89 (m, 1 H), 8.63 (d, *J* = 4.4 Hz, 1 H), 8.45 (d, *J* = 8.4 Hz,1 H), 8.19 (t ,*J* =12 Hz, 2 H), 8.04-91 (m, 3 H), 7.74 (t, *J*= 7.6 Hz, 1 H),7.61-7.57 (m, 1 H), 4.32-4.15 (m, 1 H) , 4.13-4.10(m, 1 H), 4.02-3.94 (m, 1 H),3.77-3.37 (m, 4 H), 3.27-3.20 (m, 1 H), 2.89-2.85 (m ,1 H), 2.68-2.12 (m, 2 H), 2.11-1.78 (m, 10 H),1.77-1.50(m, 1 H).	544.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
228	N-(2-oxo-2-(4-((1s,4s)-4-((pyridin-2-ylmethyl)carbamoyl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.91-8.98 (m, 1 H), 8.43-8.45 (m, 2 H) , 8.28 (bs, 1 H), 8.16-8.21 (m, 2 H), 7.92 (d, J= 8.0 Hz, 1 H), 7.74 (t, J= 7.6 Hz, 1 H), 7.62 (d, J=8.4 Hz, 1 H), 7.32- 7.35 (m, 1 H), 4.44- 4.46 (m, 1 H), 4.274 (d, J=5.6 Hz, 2 H), 4.09- 4.17 (m, 1 H), 3.97-4.01 (m, 1 H), 3.38-3.57 (m, 3 H), 2.82-2.92 (m, 1 H), 2.45 (s, 2 H), 2.30 -2.32 (m, 1 H), 2.07-2.23 (m, 1 H), 1.86- 1.90 (m, 3 H), 1.74- 1.75 (m, 3 H), 1.48-1.50 (m, 4 H), 1.33 (s, 1 H).	558.5
229	N-(2-oxo-2-(4-((1r,4r)-4-((pyridin-2-ylmethyl)carbamoyl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.90-8.98 (m, 1 H), 8.43-8.44 (dd, ,J= 6.0 Hz, 1.2 Hz, 2 H) , 8.30- 8.32 (m, 1 H), 8.16-8.21 (m, 2 H), 7.92 (d, J= 8.0 Hz, 1 H), 7.74 (t, J= 7.6 Hz, 1 H), 7.61 (d, J=7.6 Hz, 1 H), 7.32- 7.35 (m, 1 H), 4.25 (s, 2 H), 4.08- 4.19 (m, 1 H), 3.94- 4.15 (m, 1 H), 3.59-3.72 (m, 1 H), 3.42- 3.57 (m, 1 H), 3.09- 3.28 (m, 1 H), 2.79- 3.01 (m, 1 H), 2.23- 2.42 (m, 2 H), 2.01- 2.19 (m, 2 H), 1.72- 1.99 (m, 6 H), 1.54-1.70 (m, 1 H), 1.38-1.50 (m, 3 H), 1.12- 1.36 (s, 2 H).	558.5
230	N-(2-oxo-2-(4-((1s,4s)-4-(2-(pyridin-2-yl)acetamido)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.91-8.97 (m, 1H), 8.46-8.47 (d, J=4.8Hz, 1H), 8.16-8.21 (m, 2H), 8.02-8.04 (M, 1H), 7.91-7.93 (d, J=7.6 Hz, 1H), 7.69-7.79 (m, 2H), 7.30-7.32 (d, J=8 Hz, 1H), 7.21-7.24 (m,1H), 4.27-4.46 (m, 1H), 4.08-4.18 (m, 1H), 3.97-4.04 (m, 1H), 3.75 (bs, 1H), 3.42-3.62 (m, 5H), 2.81-2.90 (m, 1H), 2.38 (bs, 1H), 2.12-2.31 (m, 2H), 1.75-1.92 (m, 2H), 1.48-1.71(m, 9H).	558.5
231	N-(2-oxo-2-(4-((1r,4r)-4-(2-(pyridin-2-yl)acetamido)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)ethyl)-3-(trifluoromethyl)benzamide	8.91-8.97 (m, 1H), 8.46-8.47 (d, J=4.8Hz, 1H), 8.16-8.21 (m, 2H), 8.02-8.04 (M, 1H), 7.91-7.93 (d, J=7.6 Hz, 1H), 7.69-7.79 (m, 2H), 7.30-7.32 (d, J=8 Hz, 1H), 7.21-7.24 (m,1H), 4.27-4.46 (m, 1H), 4.08-4.18 (m, 1H), 3.97-4.04 (m, 1H), 3.75 (bs, 1H), 3.42-3.62 (m, 5H), 2.81-2.90 (m, 1H), 2.38 (bs, 1H), 2.12-2.31 (m, 2H), 1.75-1.92 (m, 2H), 1.48-1.71(m, 9H).	558.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
232	N-(2-(4-((1s,4s)-4-(methyl(pyridin-2-yl)carbamoyl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88 - 8.98 (m, 1H), 8.47 - 8.49 (m, 1H), 8.16 - 8.21 (m, 2H), 7.87 - 7.39 (m, 2H), 7.74 (t, **J** = 3.0 Hz, 1H), 7.44-7.76 (d, **J** = 8Hz, 1H), 7.31 - 7.34 (m, 1H), 4.27 - 4.46 (m, 1H), 3.97 - 4.08 (m, 1H), 4.12 - 4.14 (m, 1H), 3.50 -3.58 (m, 2H), 3.34 - 3.41 (m, 1H), 3.22 (s, 3), 2.66 - 2.81 (m, 1H), 1.66 -1.92 (m, 7H), 1.44 - 1.66 (m, 1H), 1.22 - 1.42 (m, 6H), 0.81 - 0.92 (m, 1H)	558.5
233	N-(2-(4-((1r,4r)-4-(methyl(pyridin-2-yl)carbamoyl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.88 - 8.98 (m, 1H), 8.47 - 8.49 (m, 1H), 8.16 - 8.21 (m, 2H), 7.87 - 7.39 (m, 2H), 7.74 (t, **J** = 3.0 Hz, 1H), 7.44-7.76 (d, **J** = 8Hz, 1H), 7.31 - 7.34 (m, 1H), 4.27 - 4.46 (m, 1H), 3.97 - 4.08 (m, 1H), 4.12 - 4.14 (m, 1H), 3.50 -3.58 (m, 2H), 3.34 - 3.41 (m, 1H), 3.22 (s, 3), 2.66 - 2.81 (m, 1H), 1.66 -1.92 (m, 7H), 1.44 - 1.66 (m, 1H), 1.22 - 1.42 (m, 6H), 0.81 - 0.92 (m, 1H)	558.5
234	N-(2-(4-((1r,4r)-4-(1'-acetyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98 - 8.89 (m, 1 H), 8.59 (d, *J* = 5.6 Hz, 1 H), 8.20 (t, *J* = 11.6 Hz, 2 H), 7.925 (t, *J* = 8.0 Hz, 1 H), 7.83 - 7.80 (m, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 6.25 (s, 1 H), 4.96 (s, 1 H), 4.47 - 4.29 (m, 1 H), 4.17 - 4.09 (m, 3 H), 4.07 - 3.98 (m, 1 H), 3.68 - 3.64 (m, 2 H), 3.62 - 3.50 (m, 2 H), 3.41 - 3.35 (m, 1 H), 2.84 - 2.78 (m, 1 H), 2.66 - 2.57 (m, 2 H), 2.37 - 2.32 (m, 3 H), 2.12 - 2.07 (m, 4 H), 1.90 - 1.74 (m, 4 H), 1.57 - 1.39 (m, 3 H), 1.33 - 1.29 (m, 2 H), 1.29 - 1.25 (m, 1 H).	640.5
235	N-(2-(4-((1s,4s)-4-(1'-acetyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)-4-hydroxycyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97 - 8.91 (m, 1 H), 8.56 (d, *J* = 4.4 Hz, 1 H), 8.20 (t, *J* = 11.6 Hz, 2 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.82 - 7.72 (m, 2 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 6.24 (s, 1 H), 5.0 (s, 1 H), 4.46 - 4.19 (m, 1 H), 4.13 (d, *J* = 11.6 Hz, 3 H), 4.01 - 3.97 (m, 1 H), 3.66 - 3.63 (m, 3 H), 3.56 - 3.41 (m, 2 H), 2.99 - 2.91 (m, 1 H), 2.67 - 2.66 (m, 2 H), 2.33 - 2.32 (m, 1 H), 2.14 - 2.04 (m, 4 H), 2.00 - 1.97 (m, 3 H), 1.83 - 1.51 (m, 9 H), 1.29 - 1.23 (m, 1 H).	640.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
238	1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide	8.88-8.97 (m, 1 H), 8.21 (s, 1 H), 8.17 (d, J=8.0 Hz, 1 H), 7.92 (d, J=7.6 Hz, 1 H), 7.73 (t, J=7.6 Hz, 2 H), 7.39 (d, J=8.8 Hz, 1 H), 6.84- 6.87 (m, 1 H), 4.74 (s, 1 H), 4.22-4.50 (m, 1 H), 3.95-4.15 (m, 4 H), 3.82-3.93 (m, 3 H), 3.48-3.63 (m, 2 H), 3.43 (s, 1 H), 2.89 (s, 3 H), 2.84 (s, 3 H), 2.76 (s, 1 H), 2.32- 2.33 (m, 4 H), 2.10 (s, 1 H), 1.82-1.95 (m, 3 H), 1.76 (s, 1H), 1.71- 1.75 (m, 3 H), 1.37-1.63 (m, 2 H).	643.6
239	1-(6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide	8.91-8.97 (m, 1H), 8.46-8.47 (d, J=4.8Hz, 1H), 8.16-8.21 (m, 2H), 8.02-8.04 (M, 1H), 7.91-7.93 (d, J=7.6 Hz, 1H), 7.69-7.79 (m, 2H), 7.30-7.32 (d, J=8 Hz, 1H), 7.21-7.24 (m,1H), 4.27-4.46 (m, 1H), 4.08-4.18 (m, 1H), 3.97-4.04 (m, 1H), 3.75 (bs, 1H), 3.42-3.62 (m, 5H), 2.81-2.90 (m, 1H), 2.38 (bs, 1H), 2.12-2.31 (m, 2H), 1.75-1.92 (m, 2H), 1.48-1.71(m, 9H).	643.6

Procedure 75: Synthesis of N-(2-(4-((1R,4r)-4-hydroxy-4-(5-((R)-3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide, N-(2-(4-((1S,4s)-4-hydroxy-4-(5-((R)-3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide, N-(2-(4-((1S,4r)-4-hydroxy-4-(5-((S)-3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide, and N-(2-(4-((1R,4s)-4-hydroxy-4-(5-((S)-3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (246, 247, 248, and 249).



Step-1: Preparation of tert-butyl 3-hydroxy-3-methylpyrrolidine-1-carboxylate.

[0549] To a stirred solution of tert-butyl 4-oxopiperidine-1-carboxylate (10 g, 54 mmol, 1 eq) in diethyl ether (150 mL) at 0°C was added methyl magnesium bromide (36 mL, 108 mmol, 2 eq). After 8 h, reaction mixture was quenched with NH_4Cl (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 35% of EtOAc:Heptane to afford tert-butyl 3-hydroxy-3-methylpyrrolidine-1-carboxylate (7 g, 64 % yield).

[0550] LC - MS (m/z) = 146.1 $[M - 56]^-$

Step-2: Preparation of 3-methylpyrrolidin-3-ol hydrochloride.

[0551] To a stirred solution of tert-butyl 3-hydroxy-3-methylpyrrolidine-1-carboxylate (7 g, 1eq, 34.8 mmol) in DCM (100 mL), 4N HCl in 1,4-dioxane (15 mL) was added dropwise to the reaction solution at 0 °C for 3 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure to get crude compound. The crude material was triturated with n-pentane and diethyl ether combination, decant the solvent and dried to afford 3-methylpyrrolidin-3-ol hydrochloride (4.7 g, 98 %).

[0552] LC-MS (m/z) = 102.2 $[M+H]^+$

Step-3: Preparation of 1-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-3-methylpyrrolidin-3-ol.

[0553] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (4.7 g, 4.77 mmol, 1 eq) and 3-methylpyrrolidin-3-ol hydrochloride (1.31 g, 9.55 mmol, 2 eq) in dioxane (50 mL), were added cesium carbonate (9.67 g, 14.3 mmol, 3 eq). The reaction mixture was purged with argon for 15 min and then added RAC-BINAP (1 g, 0.95 mmol, 0.2 eq) and $Pd(OAc)_2$ (0.5 g, 0.47 mmol, 0.1 eq). The reaction mixture was stirred at 100°C for 16 h. After the completion of the reaction, reaction mixture was quenched with water (100 mL) extracted with ethyl acetate (2 x 100 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 60-64% of EtOAc : Heptane to afford 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-3-methylpyrrolidin-3-ol (3 g, 60 %).

Step-4: Preparation of 4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexan-1-one.

[0554] To a stirred solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-3-methylpyrrolidin-3-ol (3 g, 1 eq, 8.97 mmol,) in THF (30 mL) was added 4N HCl (9 mL in 21 mL water) in water drop wise under cooling condition. Then the reaction mixture was stirred at room temperature for 8 h, reaction progress was checked by TLC monitoring. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to get the aqueous residue, obtained crude was basified with solid $NaHCO_3$ to pH 8~9., then the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product. which was purified by prep. peak 1 and peak 2 collected and concentrated to afford 4-hydroxy-4-[5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl]cyclohexan-1-one (0.7 g, 26 % peak 1) and (0.7 g, 26 % yield, peak 2).

[0555] LC - MS (m/z) = 291.2 $[M + H]^+$.

[0556] Analytical Conditions: Column: CHIRALPAK IA (250 mm X 30 mm X 5 mic); Mobile phase: n Hexane: IPA in 0.1 DEA (50:50); Flow rate: 40 mL/min.

Step-5: Synthesis of N-(2-(4-(4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide (246 and 247, Peak 1).

[0557] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (0.5 g, 1 eq, 1.46 mmol) in THF (15 mL) were added 4-hydroxy-4-[5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl]cyclohexan-1-one (0.51 g, 1.2 eq, 1.76 mmol,) and at 0 °C triethylamine (1.24 mL, 8.79 mmol, 6 eq). The reaction mixture was stirred at rt for 0.5 h and then cooled to 0 °C, sodium bis(acetyloxy)boranuidyl acetate (0.62 g, 2 eq, 2.93 mmol) was added and stirred at room temperature for 5 h. The progress of the reaction mixture was checked by TLC monitoring, after completion of the reaction, The reaction mixture was evaporated under reduced pressure, extracted with DCM (2 x 50 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product. The crude was purified by column chromatography eluted on 75 % THF in heptane, non-polar and polar isomers concentrated to afford N-[2-(4-{4-hydroxy-4-[5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl]cyclohexyl}-octahydropyrrolo[3,2-b]pyrrol-1-yl)-2-oxoethyl]-3-(trifluoromethyl)benzamide: non polar isomer 246 (0.045 g) and polar isomer 247 (0.09).

[0558] Similarly, peak 2 obtained at step-4 of Procedure 75 was converted to corresponding final compounds 248 and 249 using Step 5 in Procedure 75.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
246	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97 - 8.89 (m, 1 H), 8.20 (t, *J* = 11.6 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.79 - 7.72 (m, 2 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 6.85 - 6.83 (m, 1 H), 4.78 (d, *J* = 2.8 Hz, 2 H), 4.45 - 4.25 (m, 1 H), 4.19 - 3.95 (m, 2 H), 3.68 - 3.37 (m, 4 H), 3.24 - 2.66 (m, 3 H), 2.33 - 2.12 (m, 4 H), 1.95 - 1.47 (m, 13 H), 1.34 (s, 3 H).	616.5
247	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97 - 8.89 (m, 1 H), 8.22 (s, 1H), 8.19-8.17 (d, *J* = 8 Hz,1 H), 7.93 - 7.91 (d, *J* = 8 Hz , 1 H), 7.78-7.72(m, 2H), 7.40-7.38(d, *J* = 8 Hz, 1H), 6.87-6.83(m, 1H), 4.78 (m, 2 H), 4.40 - 4.28(m, 1 H), 4.22-3.90 (m, 2 H), 3.70 - 3.50 (m, 2 H), 3.50=3.40(m, 2 H), 3.24-3.18 (m, 2H), 3.10-2.85(m, 1H),2.35-2.32 (m, 3 H), 2.18-2.12(m, 2H), 1.95-1.89 (m, 6 H), 1.80-1.60(m, 4H), 1.60-1.50(m, 3H), 1.40-1.30(m, 3H)	616.5
248	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.96 - 8.89 (m, 1 H), 8.21 (s, 1H), 8.18-8.16 (d, *J* = 8 Hz,1 H), 7.93 - 7.91 (d, *J* = 8 Hz , 1 H), 7.79(m, 1H), 7.75-7.72 (t, *J* = 8 Hz, 1 H), 7.36-7.34(d, *J* = 8 Hz, 1H), 6.87-6.83(m, 1H), 4.78 (s, 1 H), 4.69 (s, 1H), 4.13 - 4.11 (m, 1 H), 4.07-3.97 (m, 2 H), 3.55 - 3.52 (m, 2 H), 3.40-3.3-36(m, 2 H), 3.21-3.15 (m, 6 H), 2.67-2.66 (m, 1 H), 2.52(m, 2H), 2.40-2.33 (m, 2 H), 1.94-1.82(m, 5H), 1.50-1.49(m, 2H), 1.41-1.39(m, 5H)	616.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
249	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-3-methylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.97 - 8.89 (m, 1 H), 8.22 (s, 1H), 8.19-8.17 (d, *J* = 8 Hz,1 H), 7.93 - 7.91 (d, *J* = 8 Hz , 1 H), 7.78-7.72(m, 2H), 7.40-7.38(d, *J* = 8 Hz, 1H), 6.87-6.83(m, 1H), 4.78 (m, 2 H), 4.40 - 4.28(m, 1 H), 4.22-3.90 (m, 2 H), 3.70 - 3.50 (m, 2 H), 3.50=3.40(m, 2 H), 3.24-3.18 (m, 2H), 3.10-2.85(m, 1H),2.35-2.32 (m, 3 H), 2.18-2.12(m, 2H), 1.95-1.89 (m, 6 H), 1.80-1.60(m, 4H), 1.60-1.50(m, 3H), 1.40-1.30(m, 3H)	616.5

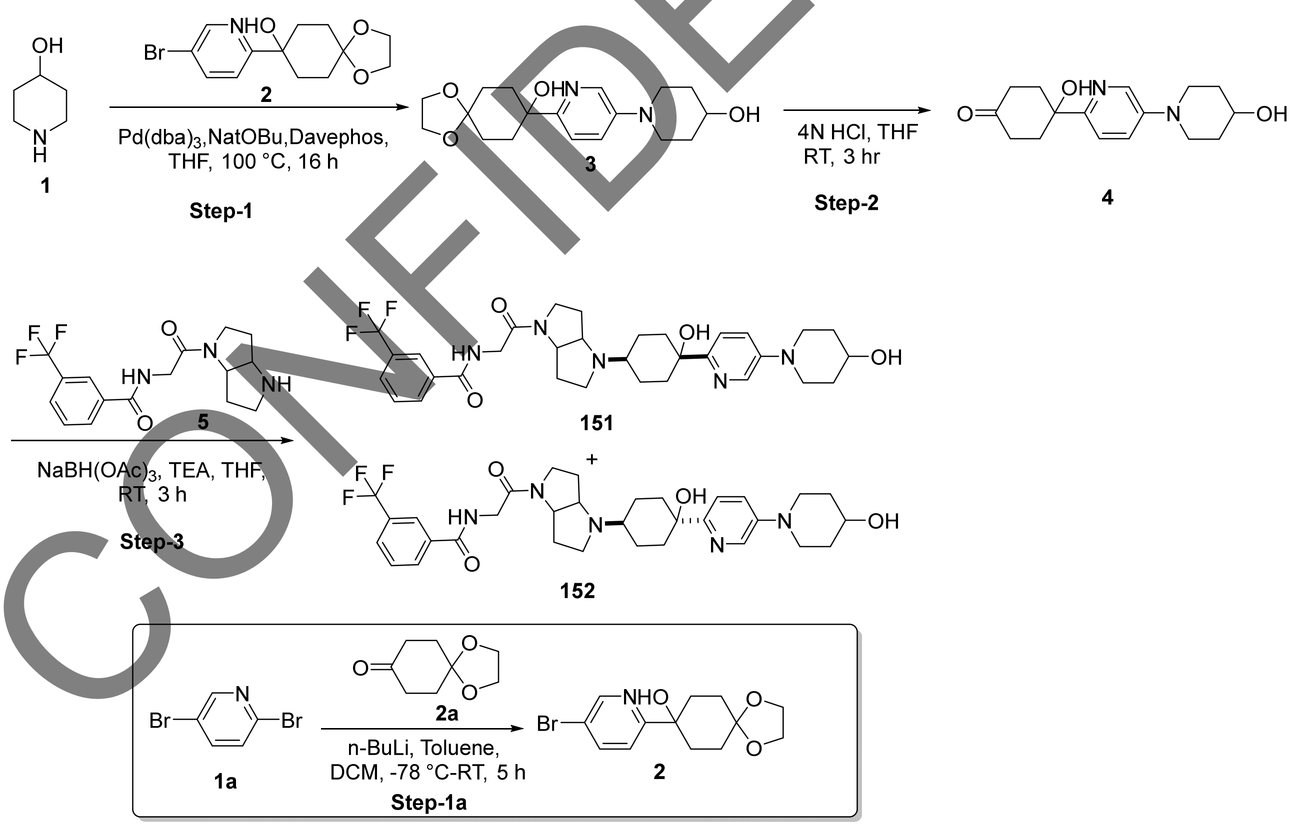
[0559] The compounds below were synthesized using experimental protocol of Procedure 75.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
260	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-3-isopropylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.89 - 8.99 (m, 1H), 8.21 (s, 1H), 8.16 - 8.18 (d, *J* = 8 Hz, 1H), 7.91 – 7.93 (d, J = 8 Hz, 1H), 7.81 (s, 1H), 7.74 (t, **J** = 3.0 Hz, 1H), 7.34 - 7.36 (d, *J* = 8 Hz, 1H), 6.85 – 6.88 (m, 1H), 4.70 (m, 1H), 4.27 – 4.45 (m, 2H), 3.97 - 4.26 (m, 2H), 3.53 – 3.55 (m, 2H), 3.32 – 3.37 (m, 2H), 3.13 – 3.24 (m, 2H), 2.49 – 2.67 (m, 2H), 2.27 – 2.40 (m, 3H), 1.73 – 1.89 (m, 8H), 1.37 – 1.69 (m, 6H), 0.92- 0.95 (m, 6H)	644.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
261	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-3-isopropylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90 - 8.98 (m, 1 H), 8.22 (s, 1H), 8.17 – 8.19 (d, **J** = 8Hz, 1H), 7.92 – 7.94 (d, **J** = 8Hz, 1H), 7.72 7.78 (m, 2H), 7.38 – 7.41 (m, 1H), 6.85 – 6.88 (m, 1H), 4.80 (m, 1H), 4.25 – 4.47 (m, 2H), 3.99 – 4.19 (m, 2H), 3.48 – 3.69 (m, 2H), 3.32 – 3.46, (m, 2H), 3.12 – 3.24 (m, 3H), 2.90 – 2.99 (m, 1H), 2.07 - 2.32 (m, 1H), 1.78 – 1.95 (m, 7H), 1.63 -1.78 (m, 5H), 1.46 – 1.57 (m, 3H), 0.91 – 0.95 (m, 6H).	644.6
262	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(3-hydroxy-3-isopropylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.98-9.88 (m, 1H), 8.21-8.16 (m, 2H), 7.91 – 7.93 (d, J = 7.6 Hz, 1H), 7.81 (m, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.33 -7.36 (d, J = 8.8 Hz, 1H), 6.88-6.85 (m, 1H), 4.69 (m, 1H), 4.43 (s, 1H), 4.13-3.97 (m, 2H), 3.55-3.53 (m, 2H), 3.39-3.35 (m, 3H), 3.24-3.22 (m, 1H), 3.17-3.13 (m, 1H), 2.83-2.76 (m, 1H), 2.45-2.40 (m, 2H), 2.32-2.29 (m, 2H), 2.10-2.07 (m, 1H), 1.89-1.62 (m, 7H), 1.64-1.62 (m, 1H), 1.50-1.49 (m, 2H), 1.39-1.37 (m, 2H), 1.25-1.23 (m, 1H), 0.95-0.92 (m, 6H).	644.6

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
263	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(3-hydroxy-3-isopropylpyrrolidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide	8.90 – 9.02 (m, 1 H), 8.27 (s, 1H), 8.18 – 8.26 (d, **J** = 8Hz, 1H), 7.92 – 7.94 (d, **J** = 8Hz, 1H), 7.72 7.78 (m, 2H), 7.37 – 7.85 (m, 2H), 7.39 – 7.41 (d, **J** = 8Hz, 1H), 6.86 – 6.88 (m, 1H), 4.79 – 4.80 (m, 1H), 3.95 - 4.19 (m, 2H), 3.48 – 3.69 (m, 2H), 3.32 – 3.46, (m, 2H), 3.12 – 3.24 (m, 3H), 2.90 – 2.99 (m, 1H), 2.07 - 2.32 (m, 1H), 1.79 – 1.96 (m, 6H), 1.63 -1.82 (m, 5H), 1.49 – 1.61 (m, 3H), 0.93 – 0.96 (m, 6H).	644.6

[0560] The synthesis of compounds 151 and 152 is below.



[0561] Synthesis of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (2):

[0562] To a solution of 2,5-dibromopyridine (10 g, 42.2 mmol) in toluene (120 mL) at -78 °C, n-BuLi (1.6 M, 26 mL, 40.3 mmol, 1.2 eq) was added dropwise. After being stirred at –78 °C for 2.5 hours, a solution of 1,4-dioxaspiro[4.5]decan-8-one (6.59 g, 42.2 mmol) in toluene (20 mL) was added into the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. The reaction mixture was poured into aqueous NH_4Cl (300 mL) and extracted with EtOAc (500 mL x 2). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting solid purified by using combiflash and eluent used as 0 – 15 % ethyl acetate/n-hexane to afford 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (8 g, 56.1%). LCMS (ES) m/z: 316.1 $[M+H]^+$

[0563] Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidin-4-ol (3):

[0564] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.1 g, 3.46 mmol, 1 eq) in THF (12 mL) were added sodium *tert*-butoxide (665 mg, 6.92 mmol, 3 eq) and piperidin-4-ol (350 mg, 3.46 mmol, 1 eq). The reaction mixture was purged with N_2 for 15 min and then Davephos (410 mg, 1.04 mmol, 0.2 eq) and Pd2(dba)3 (634 mg, 0.692 mmol, 0.1 eq) was added. After that reaction mixture was stirred at 100 °C for 16 h, after reaction mixture was quenched with water (5 mL) extracted with ethyl acetate (2 x 5 mL). The combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product (210 mg, 14%). LC-MS (ES) m/z: 335.2 $[M+H]^+$

[0565] Synthesis of 4-hydroxy-4-[5-(4-hydroxypiperidin-1-yl)pyridin-2-yl]cyclohexan-1-one (4):

[0566] A stirred solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidin-4-ol (210 mg, 1.75 mmol, 1eq) in THF (5 mL), 4N HCl in water (5 mL) was added dropwise to the reaction solution at 0 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under reduced pressure and neutralized with NaHCO3 and extracted with EtOAc. The organic layer was dried over Na2SO4 and concentrated under reduced pressure to get 4-hydroxy-4-[5-(4-hydroxypiperidin-1-yl)pyridin-2-yl]cyclohexan-1-one (180 mg, crude). LC-MS (ES) m/z: 291 $[M+H]^+$

[0567] Synthesis of N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide:

[0568] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide hydrochloride (235 mg, 0.62 mL, 1 eq) in THF (5 mL) were added triethylamine (0.5 mL, 0.873 mmol, 6 eq) and 4-hydroxy-4-[5-(4-hydroxypiperidin-1-yl)pyridin-2-yl]cyclohexan-1-one (180 mg, 0.62 mmol, 1 eq). The reaction mixture was stirred at rt for 0.5 h and then sodium triacetoxy borohydride (260 mg,1.24 mmol, 2 eq) was added and stirred at room temperature for 3 h. Progress of the reaction was checked by TLC monitoring. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ solution, extracted with ethyl acetate (2 x 5 mL), combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product which was purified first with Prep. HPLC and then with Prep. TLC (8 % Methanolic ammonia in EtOAc) to afford the two isomers of the N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide **(151)** (12 mg, 3%) and N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-3-(trifluoromethyl)benzamide **(152)** (35 mg, 9%).

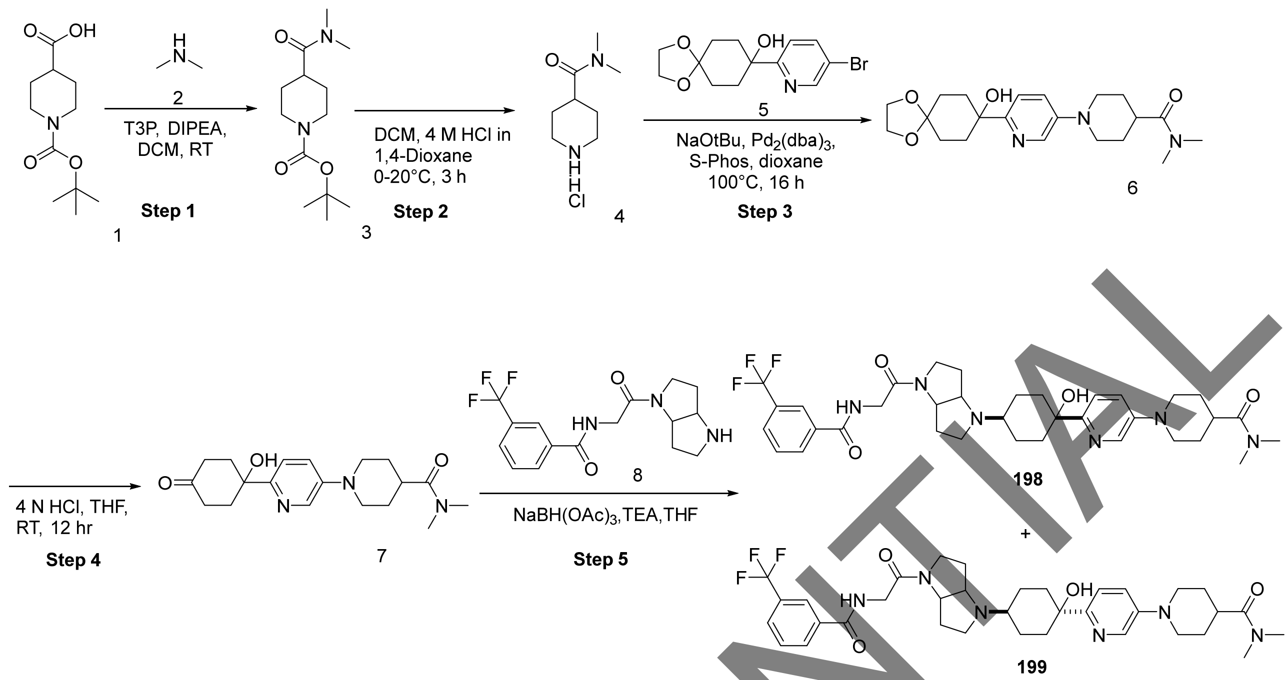
[0569] Analytical data for Example 151: LC-MS (ES) m/z: 616.4 $[M+H]^+$

[0570] 1H NMR (400 MHz, DMSO d6) δ ppm: 8.996 - 8.88 (m, 1 H), 8.22 - 8.17 (m, 3 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.30 (m, 1 H), 4.76 (s,1 H), 4.67 (d, *J* = 4.4 Hz, 1 H), 4.47 - 4.28 (m, 1 H), 4.18 - 4.04 (m, 1 H), 4.03 - 3.99 (m, 1 H), 3.67 - 3.6 (m, 2 H), 3.57 - 3.53 (m, 3 H), 3.41 - 3.4 (m, 2 H), 2.91 - 2.84 (m, 2 H), 2.72 - 2.8 (m, 1 H), 2.34 - 2.25 (m, 2 H), 2.14 - 2.08 (m, 1 H), 1.91 - 1.75 (m, 6 H), 1.54 - 1.52 (m, 1 H), 1.51 - 1.46 (m, 4 H), 1.44 - 1.38 (m, 2 H).

[0571] Analytical data for Example 152: LC-MS (ES) m/z: 616.4 $[M+H]^+$

[0572] 1H NMR (400 MHz, DMSO d6) δ ppm: 8.98 - 8.89 (m, 1 H), 8.23 (s, 1 H), 8.19 (d, *J* = 7.2 Hz, 2 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 15.6 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.33 - 7.3 (m, 1 H), 4.81 (s, 1 H), 4.66 (d, *J* = 4.4 Hz, 1 H), 4.47 - 4.28 (m, 1 H), 4.19 - 4.11 (m, 1 H), 4.03 - 3.96 (m, 1 H), 3.67 - 3.6 (m, 2 H), 3.56 - 3.52 (m, 3 H), 3.42 - 3.4 (m, 1 H), 3.25 - 3.23 (m, 1 H), 2.99 - 2.83 (m, 3 H), 2.15 - 2.08 (m, 1 H), 1.97 - 1.91 (m, 2 H), 1.89 - 1.80 (m, 4 H), 1.76 - 1.56 (m, 2 H), 1.52 - 1.51 (m, 2 H), 1.5 - 1.46 (m, 4 H).

[0573] The synthesis of compounds 198 and 199 is below.



[0574] Step 1: Synthesis of tert-butyl 4-(dimethylcarbamoyl)piperidine-1-carboxylate (3)

[0575] To a stirred solution of 1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid (3 g, 13.1 mmol) in DCM (30 mL) were added T3P (17 mL, 13.1 mmol) and DIPEA (7 mL, 13.1 mmol) followed by the addition of dimethylamine (6.5 mL, 13.1 mmol) at 0°C. Stirred the reaction mixture at rt for 12 h. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water (5 mL) and extracted with DCM (2x20 mL) concentrated in vacuo to get the crude. The crude material was purified by flash column chromatography using 10% MeOH/DCM to afford mixture (2.2 g). This mixture was quenched with NaHCO3 (20 mL) and extracted with ethyl acetate (2 x 100 mL) to get the title compound (1 g, 30%).

[0576] 1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.16 – 4.12 (m, 2 H), 3.07 (s, 3 H), 2.96 (m, 3 H), 2.77 – 2.69 (m, 2 H), 1.74 – 1.70 (m, 4 H), 1.27 (s, 9 H).

[0577] Step 2: Synthesis of N,N-dimethylpiperidine-4-carboxamide hydrochloride (4)

[0578] To a stirred solution of tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (1 g, 3.9 mmol) in DCM (15 mL) at 0°C was added 4 M HCl in Dioxane (3 mL, 11.7 mmol) and stirred for 3 h. Then reaction mixture was evaporated under reduced pressure to get the crude (725 mg, 96%) as HCl salt. Crude was taken for next step without any purification.

[0579] 1H NMR (400 MHz, DMSO d6) δ ppm: 9.14 (bs, 1 H), 8.72 (bs, 1 H), 3.24 (d, J = 12.0 Hz, 2 H), 2.98 (s, 3 H), 2.96 – 2.89 (m, 2 H), 2.85 (s, 3 H), 1.76 – 1.67 (m, 4 H).

[0580] Step 3: Synthesis of 1-(6-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide (6)

[0581] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (978 mg, 3.11 mmol) and 4-methylpiperidin-4-ol hydrochloride (600 mg, 3.11 mmol) in dioxane (20 mL) were added NaOtBu (898 mg, 3.11 mmol). The reaction mixture was purged with argon for 15 min and then added S-Phos (384 mg, 3.11 mmol) and Pd2(dba)3 (15 mg, 0.07 mmol). The reaction mixture was stirred at 100°C for 16 h. After the completion of the reaction, reaction mixture was quenched with water (25 mL) extracted with ethyl acetate (2 x 200 mL), combined organic layer were dried with anhydrous Na2SO4, filtered and concentrated under reduced pressure to get the crude. The crude material was purified by flash column chromatography using 7-8% MeOH/DCM to afford the title compound (260 mg, 21%).

[0582] LCMS (ES) m/z: 390.1 $[M+H]^+$

[0583] Step 4: Synthesis of 1-(6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide (7)

[0584] To a stirred solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide (300 mg, 0.77 mmol) in THF (7 mL) was added 4N HCl in water (10 mL), the reaction mixture was stirred for 12 h at RT. The progress of the reaction mixture was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to remove solvent and the reaction mixture was neutralized with sodium bicarbonate (25 mL) and extracted using ethyl acetate (2x100 mL). The combined organic layer was dried over Na2SO4, filtered and concentrated under vacuum to get crude compound (180 mg, 68%).

[0585] LC-MS (ES) m/z: 346.2 $[M+H]^+$

[0586] Step 5: 1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide

[0587] To a stirred solution of 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylpiperidine-4-carboxamide (60 mg, 0.17 mmol) in THF (6 mL) was added N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (60 mg, 0.17 mmol) and TEA (0.07 mL, 0.17 mmol). After 30 min, reaction mixture was cooled to 0°C and added Sodium triacetoxy borohydride(75 mg, 0.17 mmol) and stirred at room temperature for 4 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (5 mL). Aqueous layer was extracted with Ethylacetate (2 x 50 mL), combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude product. The crude product was purified by Cyclo-graph using 5% methanolic ammonia with DCM to afford the isomers i.e. non polar isomer 1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-

yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide (198) (0.009 g, 8%) and polar isomer 1-(6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylpiperidine-4-carboxamide (199) (0.014 g, 12%).

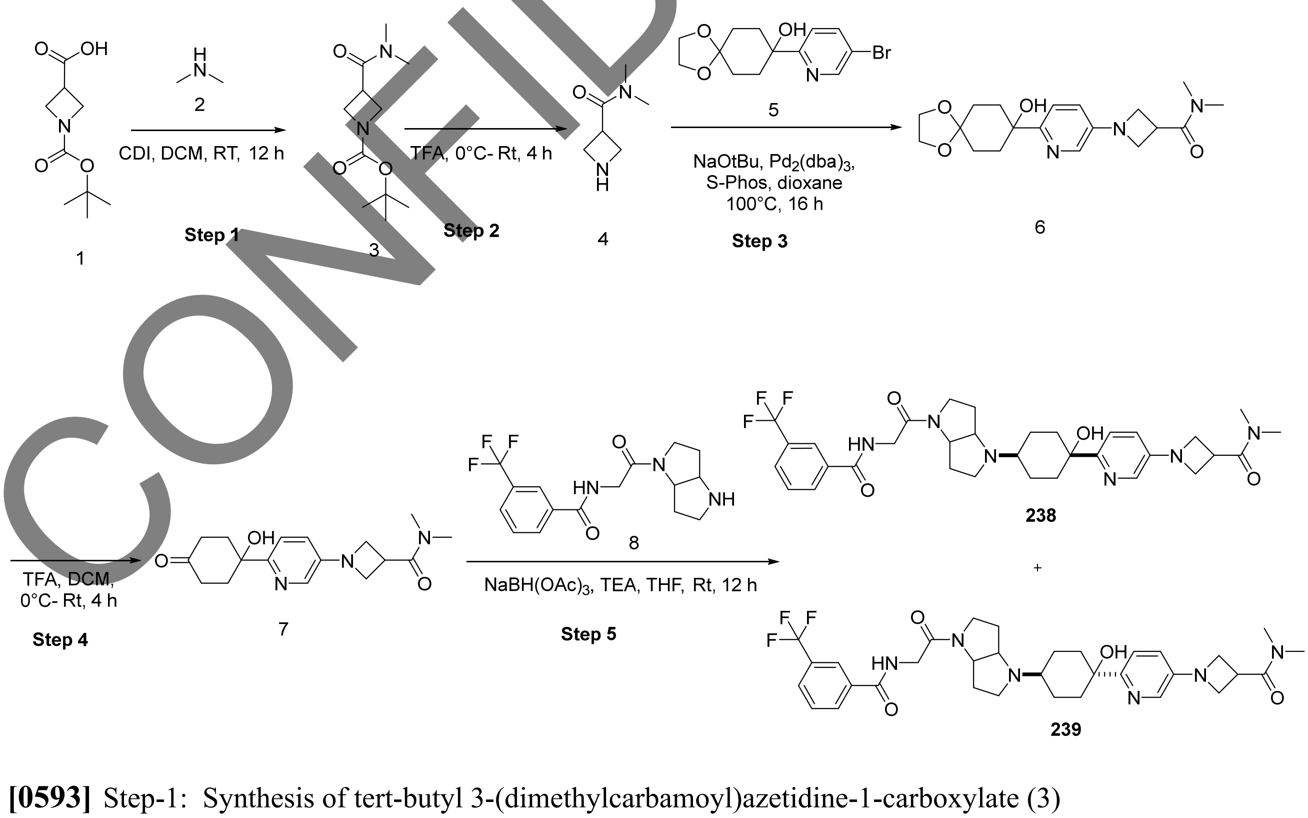
[0588] Example 198: LC-MS (ES) m/z: 671.4 $[M+H]^+$

[0589] 1H NMR (400 MHz, DMSO d6) δ ppm: 8.96-8.90 (m, 1 H), 8.21-8.16 (m, 3 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.76 (s, 1 H), 4.46 - 4.27 (m, 1 H), 4.15 - 3.97 (m, 2 H), 3.74 (d, J = 12.0 Hz, 2 H), 3.56 - 3.50 (m, 2 H), 3.41 - 3.36 (m, 1 H), 3.04 (s, 3 H), 2.81 - 2.66 (m, 5 H), 2.50 - 2.24 (m, 5 H), 2.11 - 2.07 (m, 1 H), 1.92 - 1.83 (m, 5 H), 1.78 - 1.58 (m, 4 H), 1.52 - 1.40 (m, 2 H), 1.40 - 1.38 (m, 2 H). SOR: $[\alpha]_D^{25}$ +0.009. MP: 58.2 °C.

[0590] Example 199: LC-MS (ES) m/z: 671.4 $[M+H]^+$

[0591] 1H NMR (400 MHz, DMSO d6) δ ppm: 8.95-8.88 (m, 1 H), 8.21-8.17 (m, 3 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.33-7.30 (m, 1 H), 4.81 (d, *J* = 8.0 Hz, 1 H), 4.27 - 4.10 (m, 1 H), 4.02 - 3.96 (m, 2 H), 3.73 (d, *J* = 16.0 Hz, 2 H), 3.63 - 3.41 (m, 3 H), 3.41 - 3.29 (m, 1 H), 3.04 - 2.90 (m, 4 H), 2.81 - 2.73 (m, 6 H), 2.33 - 2.32 (m, 1 H), 2.13 - 1.79 (m, 5 H), 1.75 - 1.51 (m, 11 H). SOR: $[\alpha]_D^{25}$ 0.002. MP: 96.8 °C.

[0592] The synthesis of compounds 238 and 239 is below.



[0593] Step-1: Synthesis of tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate (3)

[0594] To a stirred solution of 1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (2 g, 9.94 mmol) in DCM (20.0 mL) was added CDI (3.22 g, 2 eq., 19.9 mmol) and the reaction mixture was stirred at room temperature for 1 h, followed by the addition of dimethylamine (4.48 g, 10 eq., 99.4 mmol) at 0 °C. and continued stirring the reaction mixture at rt for 12 hours. The progress of the reaction mixture was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with water (40 mL) and extracted with DCM (2x 35 mL) concentrated in vacuo to get the crude product. Crude was loaded in silica gel column MPLC using 2-4% MeOH in DCM as an eluent to afford tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate (0.8 g, 35.0%).

[0595] **1H NMR** (400 MHz, CDCl3) δ ppm: 4.03- 4.16 (m, 4 H), 3.43- 3.51 (m, 1 H), 2.97 (s, 3 H), 2.88 (s, 3 H), 1.46 (s, 9 H).

[0596] Step 2: Synthesis of N,N-dimethylazetidine-3-carboxamide (4)

[0597] A solution of tert-butyl 3-(dimethylcarbamoyl)azetidine-1-carboxylate (0.5 g, 2.19 mmol) in trifluoroacetic acid (5 mL) was stirred at room temperature for 1 h and concentrated in vacuo to get the crude of title compound N,N-dimethylazetidine-3-carboxamide (0.6 g, 4.68 mmol).

[0598] 1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.00- 4.09 (m, 4 H), 3.83- 3.94 (m, 1 H), 2.91 (s, 3 H), 2.83 (s, 3 H).

[0599] Step 3: Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (6)

[0600] To a stirred solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.2 g, 0.7 eq., 3.82 mmol) and N,N-dimethylazetidine-3-carboxamide (0.7 g, 5.46 mmol) in dioxane (8.0 mL) was added sodium 2-methylpropan-2-olate (1.57 g, 3 eq., 16.4 mmol). The reaction mixture was purged with argon for 15 min and then added s phos (673 mg, 0.3 eq., 1.64 mmol) and tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (0.5 g, 0.1 eq., 546 µmol). The reaction mixture was stirred at 100°C for 16 h. After the completion of the reaction, reaction mixture was quenched with water (40 mL) extracted with ethyl acetate (2 x 35 mL), Combined organic layer were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude. The crude was purified by flash column MPLC eluted on 2.5 % MeOH - DCM to afford 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (0.8 g, 40.53%). LCMS (ES) m/z: 362.1 $[M + H]^+$

[0601] Step 4: Synthesis of 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylazetidine-3-carboxamide (7)

[0602] A solution of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (350 mg, 968 µmol) in dichloromethane (4 mL, 62.5 mmol) was added trifluoroacetic acid (1 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h. Once the reaction was completed, reaction mixture was concentrated under reduced pressure to get the crude of title compound 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylazetidine-3-carboxamide (450 mg, crude).

[0603] LCMS ES (m/z): 318.1 $[M+H]^+$

[0604] Step 5: Synthesis of 1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (238 and 239):

[0605] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (170 mg, 498 µmol) and 1-[6-(1-hydroxy-4-oxocyclohexyl)pyridin-3-yl]-N,N-dimethylazetidine-3-carboxamide (174 mg, 1.1 eq., 548 µmol) in THF (2 mL) was added triethylamine (135 µL, 2 eq., 996 µmol). The reaction mixture was stirred at rt for 0.5 h and then cooled to 0 °C, Sodium triacetoxy borohydride (209 mg, 2 eq., 996 µmol) was added and stirred at room temperature for another 3 h. Progress of the reaction was monitored by TLC and LCMS data. Once the reaction was completed, the reaction mixture was quenched with water and extracted with 5% MeOH in DCM (2 x 15 mL), combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product. which was purified by flash column MPLC using 2-3% MeOH in DCM as an eluent to get geometrical isomer (i.e non polar from TLC) 1-(6-((1r,4r)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide **(238)** (8 mg, 2.5%) and 1-(6-((1s,4s)-1-hydroxy-4-(4-((3-(trifluoromethyl)benzoyl)glycyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)cyclohexyl)pyridin-3-yl)-N,N-dimethylazetidine-3-carboxamide (**239**) (50 mg, 15.6%) (i.e, Polar isomer).

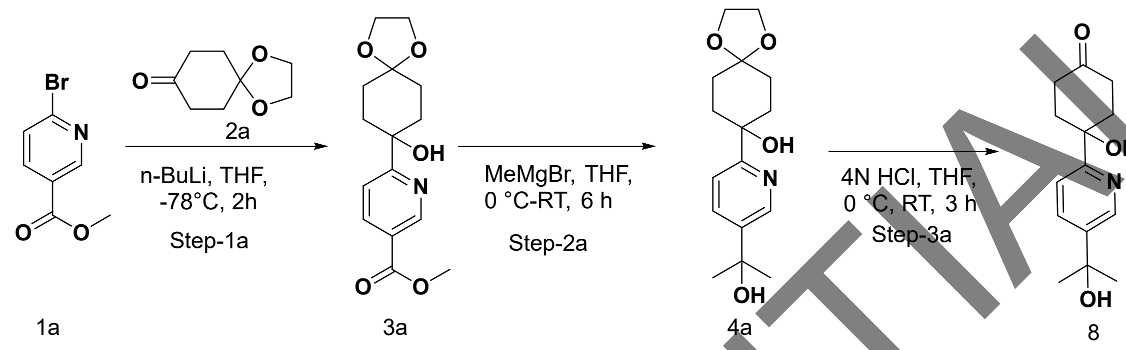
[0606] Example 238: LCMS ES (m/z): 643.6 $[M+H]^+$

[0607] ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm; 8.88-8.97 (m, 1 H), 8.21 (s, 1 H), 8.17 (d, J=8.0 Hz, 1 H), 7.92 (d, J=7.6 Hz, 1 H), 7.73 (t, J=7.6 Hz, 2 H), 7.39 (d, J=8.8 Hz, 1 H), 6.84- 6.87 (m, 1 H), 4.74 (s, 1 H), 4.22-4.50 (m, 1 H), 3.95-4.15 (m, 4 H), 3.82-3.93 (m, 3 H), 3.48-3.63 (m, 2 H), 3.43 (s, 1 H), 2.89 (s, 3 H), 2.84 (s, 3 H), 2.76 (s, 1 H), 2.32- 2.33 (m, 4 H), 2.10 (s, 1 H), 1.82- 1.95 (m, 3 H), 1.76 (s, 1H), 1.71- 1.75 (m, 3 H), 1.37- 1.63 (m, 2 H).

[0608] Example 239: LCMS: ES (m/z): 643.6 $[M+H]^+$.

[0609] ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm; 8.89-8.97 (m, 1 H), 8.19 (t, J=12.0 Hz, 2 H), 7.92 (d, J=7.6 Hz, 1 H), 7.73- 7.76 (m, 2 H), 7.38- 7.44 (m, 1 H), 6.84- 6.86 (m, 1 H), 4.85 (s, 1 H), 4.41- 4.49 (m, 1 H), 4.22- 4.32 (m, 1 H), 3.95- 4.12 (m, 4 H), 3.78- 3.92 (m, 3 H), 3.59- 3.62 (m, 1 H), 3.47- 3.55 (m, 1 H), 3.40 (s, 1 H), 3.22 (s, 1 H), 3.02 (s, 1 H), 2.92 (s, 3 H), 2.82 (s, 3 H), 2.25 (s, 1 H), 2.09-2.20 (m, 1 H), 1.77- 2.01 (m, 5 H), 1.42- 1.78 (m, 5 H).

Procedure 76: Synthesis of 8-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol



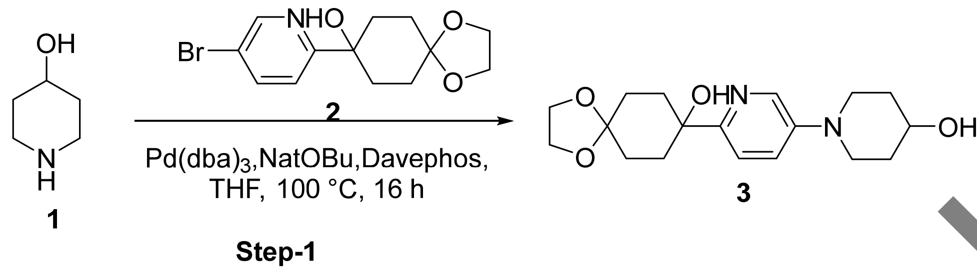
Step-1: 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol

[0610] To a solution of 2,5-dibromopyridine (40 g, 168.8 mmol, 1 *eq*) in anhydrous toluene (300 mL) at -78 °C, n-BuLi in hexane (1.6 M, 126.4 mL, 202.8 mmol, 1.2 *eq*) was added dropwise. After being stirred at –78 °C for 2.5 hours, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (26.4 g, 168.8 mmol, 1 *eq*) in toulene (40 mL) was added in to the reaction mixture. The resulting mixture was stirred for 1 hour at –78 °C and allowed to warm to room temperature slowly. After completion of the reaction, the reaction mixture was poured into aqueous $NaHCO_3$ (400 mL) and extracted with EtOAc (600 mL x 2). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under vacuum at rotavapor. The resulting product was purified by using combiflash using eluent of 0 - 15 % ethyl acetate/n-hexane to afford 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (34.3 g, 64 %). LCMS (ES) m/z: 316.1 $[M+H]^+$

Step-2: Synthesis of 8-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol:

[0611] After stirring a solution of methyl 6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridine-3-carboxylate (0.4 g, 1.36 mmol) in tetrahydrofuran (15 mL) at room temperature under nitrogen atmosphere, the reaction mixture was cooled 0°C and methylmagnesium bromide solution 3.0 M in diethyl ether 1.64 mL was added dropwise and stirred for 16 h at room temperature. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride 20 mL, extracted with ethyl acetate 2 X 20 mL, washed with brine solution, dried over by sodium sulphate, and the combined organic layers were concentrated under reduced pressure to get crude product. The crude product was purified by column chromatography using 40% ethyl acetate in hexane as eluent to afford 8-[5-(2-hydroxypropan-2-yl)pyridin-2-yl]-1,4-dioxaspiro[4.5]decan-8-ol (245 mg, 61.24% yield). LC-MS (ES) m/z : 294.2 $[M+H]^+$

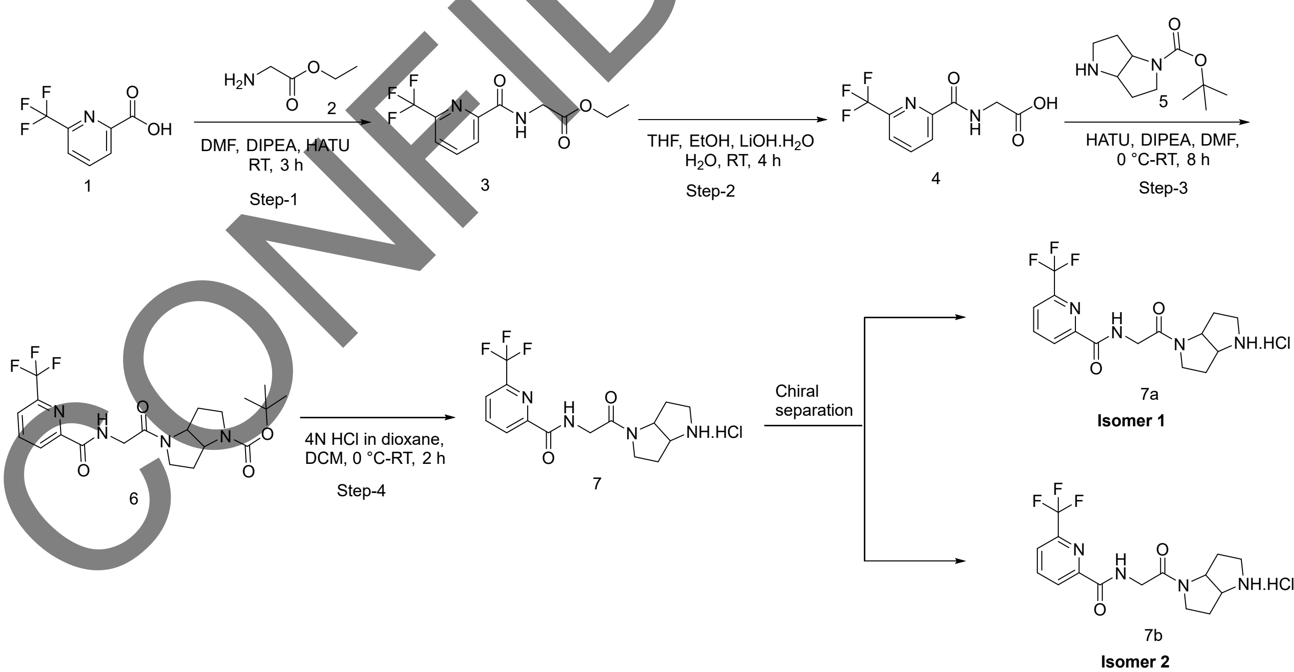
Procedure 77: Synthesis of 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidin-4-ol



Step-1: 1-(6-{8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl}pyridin-3-yl)piperidin-4-ol

[0612] To a stired solution of 8-(5-bromopyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.1 g, 3.46 mmol, 1 eq) in THF (12 ml) were added sodium 2-methylpropan-2-olate (665 mg, 6.92 mmol, 3 eq) and piperidin-4-ol (350 mg, 3.46 mmol, 1 eq). The reaction mixture was purged with N_2 for 15 min. Davephos (410 mg, 1.04 mmol, 0.2 eq) and Pd2(dba)3 (634 mg, 0.692 mmol, 0.1 eq) was added, and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (2 x 5 mL), the combined organic layers dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product (210 mg, 14.34% yield). LC-MS (ES) m/z : 335.1 $[M+H]^+$

Procedure 78: N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-6-(trifluoromethyl)pyridine-2-carboxamide hydrochloride (7)



Step-1: Ethyl 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetate (3):

[0613] To a stirred solution of 6-(trifluoromethyl)pyridine-2-carboxylic acid (2 g, 10.5 mmol, 1 eq) in DMF (15 ml) were added HATU (3.98 g, 10.5 mmol) , ethyl 2-aminoacetate hydrochloride (1.5 g, 10.5 mmol, 1 eq) and DIPEA (5.5 mL, 31.4 mmol, 3 eq) at 0 °C and resultant mixture was stirred at RT for 12 h. Progress of the reaction was monitored by TLC and LC-MS. The reaction mass was quenched with cold water (20 mL) and the aqueous layer was extracted with ethylacetate (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduce pressure to get the crude product which was further purified with flash column chromatography, and the compound was eluted with 30 - 35% of EA/Heptane to afford ethyl 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetate (2.4 g, 83.03 %). LC-MS (ES) m/z : 277.1 $[M+H]^+$.

Step-2: 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetic acid (4):

[0614] To a stirred solution of ethyl 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetate (2.4 g, 8.69 mmol) in tetrahydrofuran (15 mL), EtOH (10 mL) was added lithium(1+) hydroxide (624 mg, 3 eq., 26.1 mmol) in water (10 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction was evaporated under reduced pressure and acidified to pH~3 using dilute HCl to get a white precipitate which was filtered through buckner funnel to afford 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetic acid (1.9 g, 86.88 %). LCMS LC-MS (ES) m/z : 249.1 [M+H]+.

Step-3: *tert*-butyl 4-(2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetyl)-octahydropyrrolo[3,2-*b*]pyrrole-1-carboxylate (6):

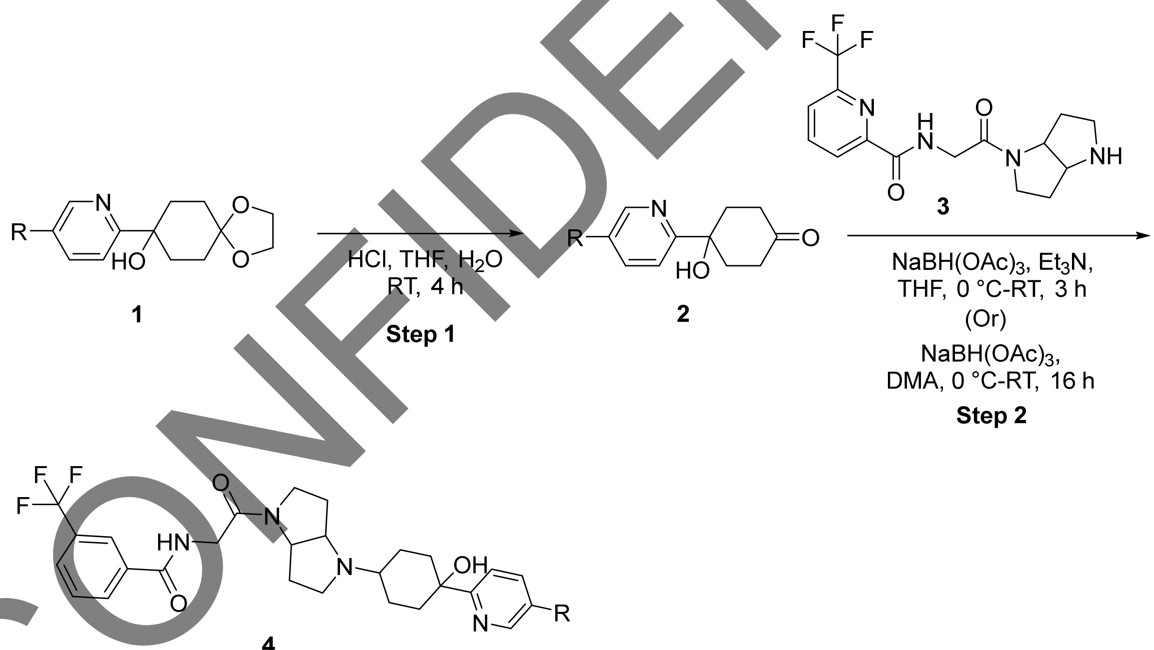
[0615] To a stirred solution of 2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetic acid (0.643 g, 2.59 mmol, 1.1 eq) in *N,N*-dimethylformamide (10 mL) was added HATU (896 mg, 2.36 mmol), tert-butyl octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (500 mg, 1 eq., 2.36 mmol) and DIPEA (1.26 mL, 3 eq., 7.07 mmol) at 0 °C. The resultant mixture was stirred at rt for 12 h. Progress of the reaction was monitored by TLC and LC-MS. The reaction mass was quenched with cold water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 * 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduce pressure to get the crude product, which was further purified with flash column chromatography (30-35% EtOAc in hexane) to afford *tert*-butyl 4-(2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetyl)-octahydropyrrolo[3,2-*b*]pyrrole-1-carboxylate (1.8 g, 47.98 %). LC-MS (ES) m/z : 443.1 [M+H]+

Step-4: *N*-(2-{octahydropyrrolo[3,2-*b*]pyrrol-1-yl}-2-oxoethyl)-6-(trifluoromethyl)pyridine-2-carboxamide hydrochloride (7):

[0616] To a stirred solution of tert-butyl 4-(2-{[6-(trifluoromethyl)pyridin-2-yl]formamido}acetyl)-octahydropyrrolo[3,2-b]pyrrole-1-carboxylate (1.8 g, 4.07 mmol, 1 eq) in dichloromethane (20 mL) at 0 °C was added 4 N HCl in 1,4-dioxane (15 mL) drop wise and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was evaporated under reduced pressure to afford the mixture of isomers of *N*-(2-{octahydropyrrolo[3,2-*b*]pyrrol-1-yl}-2-oxoethyl)-6-(trifluoromethyl)pyridine-2-carboxamide hydrochloride (1.9 g, crude) which was purified using chiral prep. HPLC. Isomer 1 (500 mg) and Isomer 2 (650 mg). (Overall 1.15 g, 70.8% Yield). LC-MS (ES) m/z : 343.2 $[M+H]^+$.

[0617] Chiral Prep. HPLC Conditions: Column: CHIRALPAK IC (250 mm X 30 mm X 5 µm); Mobile phase: n-hexane: IPA with 0.1% DEA (50:50); Flow rate: 40 mL/min.

Procedure 79: Compounds synthesized using Scheme 76 to Scheme 78 were converted into corresponding final compound using below general scheme.

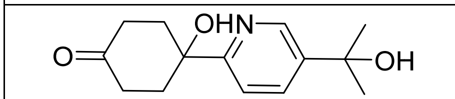
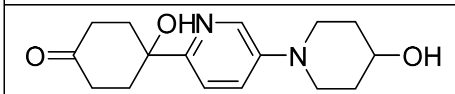


Step-1: General procedure for de-protection of 1,3-dioxalane group

[0618] To a stirred solution of Intermediate **1** (3 mmol) in THF (10 mL), 4N HCl in water (10 mL) was added drop wise under cooling condition (0 ºC), then the reaction mixture was stirred at room temperature for 2 h, reaction progress was monitored by TLC (50% E.A in heptane). Upon completion reaction mixture was concentrated under reduced pressure at rotavapor to get the aqueous residue, which was basified with saturated Na_2CO_3 to pH 8~9 (pH paper), then the aqueous layer was extracted with ethyl acetate (2 x 40 mL).

The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the Intermediate **2**.

[0619] The following compounds were synthesized using step-1.

Structure	LCMS (ESI) m/z
	250.1 $[M+H]^+$
	291.2 $[M+H]^+$

Step-2: General procedure for reductive amination

[0620] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-3-(trifluoromethyl)benzamide (**3**) (20 mmol) in THF (10 mL) at 0 °C were added corresponding keto compound (Intermediate **2**) and triethylamine (100 mmol). The reaction mixture was stirred at room temperature for 0.5 h, then sodium triacetoxy borohydride (20 mmol) was added and stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with aq sodium bicarbonate solution at rt and diluted with water (10 mL). The aqueous layer was extracted using ethyl acetate (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure to get the crude product. Crude compound was further purified using preparative TLC using (1 to 10% methanolic ammonia in DCM or in ethylacetate) to afford non polar and polar isomer.

[0621] (Or)

[0622] To a stirred solution of N-(2-{octahydropyrrolo[3,2-b]pyrrol-1-yl}-2-oxoethyl)-6-(trifluoromethyl)pyridine-2-carboxamide (0.2 g, 0.548 mmol, 1 eq) in DMA (6 mL) was added keto compound (Intermediate-**2**) (146 mg, 0.584 mmol, 1 eq) and stirred for 10 min at rt. Sodium triacetoxy borohydride (307 mg, 1.46 mmol, 2.5 eq) was added to the reaction mixture and stirred at rt for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated. The residue was quenched with sat. solution of NaOH and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (90% THF in heptane) isolated both the isomers (135 mg, impure). This impure compound once again purified by prep. TLC (90% THF in heptane) to afford non polar and polar isomer.

[0623] The compounds below were synthesized using experimental protocol of Procedure 79.

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
224	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (Diastereoisomer_Non Polar (Cis))	1H NMR (400 MHz, DMSO-d6): δ ppm 8.77 – 8.70 (m, 1H), 8.33 – 8.29 (m,2 H), 8.20 – 8.19 (m, 1 H), 8.17 – 8.12 (m, 1 H), 7.41 – 7.39 (m, 1 H), 7.33 – 7.30 (m, 1 H), 4.76 (s, 1 H), 4.68 (d, *J* = 3.6 Hz, 1 H), 4.43 – 4.08 (m, 1 H), 4.06 – 4.02 (m, 2 H), 3.65 – 3.61 (m, 1 H), 3.60 – 3.52 (m, 4 H), 3.42 – 3.34 (m, 1 H), 2.89 – 2.66 (m, 3 H), 2.45 – 2.41 (m, 1 H), 2.33 – 2.26 (m, 3 H), 2.12 – 2.10 (m, 1 H), 1.92 – 1.64 (m, 7 H), 1.63 – 1.48 (m, 4 H) , 1.47 – 1.43 (m, 2 H).	617
225	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(4-hydroxypiperidin-1-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (Diastereoisomer_Polar (Trans))	1H NMR (400 MHz, DMSO-d6): δ ppm 8.77 – 8.71 (m, 1H), 8.34 – 8.32 (m,2 H), 8.17 – 8.13 (m, 2 H), 7.45 – 7.43 (m, 1 H), 7.32 – 7.29 (m, 1 H), 4.83 – 4.82 (m, 1 H), 4.68 (d, *J* = 4 Hz, 1 H), 4.30 – 4.16 (m, 1 H), 4.12 – 4.00 (m, 1 H), 3.69 – 3.34 (m, 6 H), 3.28 – 3.15 (m, 1 H), 2.98 – 2.82 (m, 3 H), 2.49 – 2.35 (m, 3 H), 2.30 – 2.12 (m, 1 H), 1.97 – 1.86 (m, 6 H), 1.83 – 1.80 (m, 2 H), 1.75 – 1.71 (m, 2 H), 1.70 – 1.62 (m, 2 H), 1.50 – 1.40 (m, 2 H)	617
252	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (Single isomer (Peak 2)_Non Polar (Cis))	1H NMR (400 MHz, DMSO-d6): δ 8.78 - 8.71 (m, 1H), 8.6 (d, *J* = 2 Hz, 1 H), 8.33 - 8.3 (m, 2 H), 8.17 - 8.13 (m, 1 H), 7.81 (dd, *J* = 10.4 Hz, 1H), 7.4 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 4.92 (s, 1H). 4.43 - 4.02 (m, 3 H), 3.56 - 3.34 (m, 3 H), 2.85 - 2.78 (m, 1 H), 2.43 - 2.07 (m, 3 H), 1.96 - 1.64 (m, 5 H), 1.58 - 1.5 (m, 3 H), 1.45 (s, 6 H), 1.41 - 1.23 (m, 3 H).	576.5

Ex.	IUPAC name	1H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (m/z) $[M+H]^+$
253	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (single isomer (peak 2)_Polar (Trans))	1H NMR (400 MHz, DMSO-d6): δ 8.78 - 8.71 (m, 1H), 8.58 (d, *J* = 2 Hz, 1 H), 8.34 - 8.3 (m, 2 H), 8.17 - 8.14 (m, 1 H), 7.82 (dd, *J* = 10.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 5.12 (s, 1H), 4.96 (s, 1H). 4.31 - 4.01 (m, 3 H), 3.72 - 3.42 (m, 3 H), 3.001 - 2.9 (m, 1 H), 2.33 - 2.15 (m, 2 H), 2.07 - 1.88 (m, 3 H), 1.87 - 1.68 (m, 6 H), 1.65 - 1.5 (m, 3 H), 1.44 (s, 6 H).	576.5
258	N-(2-(4-((1r,4r)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (Single isomer (Peak 1)_Non Polar (Cis))	1H NMR (400 MHz, DMSO-d6): δ 8.78-8.71 (m, 1H), 8.60 (d, 1H), 8.33 (d, *J* = 4.8 Hz, 2H), 8.17-8.13 (m, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 4.92 (s, 1H), 4.47-4.02 (m, 4H). 3.54 (m, 2H), 3.43-3.36 (m, 1H), 2.90-2.70 (m, 1H), 2.43-2.25 (m, 4H), 2.19-2.10 (m, 1H), 1.96-1.70 (m, 4H), 1.69-1.57 (m, 3H), 1.45-1.30 (m, 8H).	576.5
259	N-(2-(4-((1s,4s)-4-hydroxy-4-(5-(2-hydroxypropan-2-yl)pyridin-2-yl)cyclohexyl)hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl)-2-oxoethyl)-6-(trifluoromethyl)picolinamide (single isomer (peak 1)_Polar (Trans))	1H NMR (400 MHz, DMSO-d6): δ 8.78-8.71 (m, 1H), 8.60 (d, 1H), 8.33 (d, *J* = 4.8 Hz, 2H), 8.17-8.13 (m, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 4.92 (s, 1H), 4.47-4.02 (m, 4H). 3.54 (m, 2H), 3.43-3.36 (m, 1H), 2.90-2.70 (m, 1H), 2.43-2.25 (m, 4H), 2.19-2.10 (m, 1H), 1.96-1.70 (m, 4H), 1.69-1.57 (m, 3H), 1.45-1.30 (m, 8H).	576.5

[0624] Data for select compounds is provided in the Table below:

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z [M+H]$^+$
1	8.96-8.87 (m,1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.92 (t, *J* = 7.6 Hz, 1 H), 7.74 (t, *J*= 7.6 Hz, 1 H), 7.31-7.23 (m, 4 H), 7.19-7.14 (m, 1 H), 4.23-4.17(m, 1 H), 4.08-4.03 (m, 1 H), 4.00-3.91 (m, 1 H), 3.69-3.58 (m, 1 H), 3.53-3.49 (m, 1 H), 3.18-2.95 (m, 1 H), 2.80 (t, *J* = 11.6, 2 H), 2.18-1.99 (m, 6 H), 1.86-1.77 (m, 3 H), 1.67 (d, *J* = 12 Hz, 1 H), 1.52 (s, 4 H), 1.40-1.30 (m, 1 H), 1.24-1.13 (m, 1 H).	514.2
2	8.96-8.87 (m, 1 H), 8.22 (s, 1 H), 8.18 (*d, J* = 7.6 Hz, 1 H), 7.92 (*t*, *J* = 7.6 Hz, 1 H), 7.74 (*t*, *J* = 7.6 Hz, 1 H), 7.31-7.23 (m, 4 H), 7.19-7.14 (m, 1 H), 4.23-4.17 (m, 1 H), 4.08-4.03 (m, 1 H), 4.00-3.91 (m, 1 H), 3.69-3.58 (m, 1 H), 3.53-3.49 (m, 1 H), 3.18-2.95 (m, 1 H), 2.80 (t, *J* =1 1.6 Hz, 2 H), 2.18-1.99 (m, 6 H), 1.86-1.77 (m, 3 H), 1.67 (*d*, *J* = 12 Hz, 1 H), 1.52 (s, 4 H), 1.40-1.30 (m, 1 H), 1.24-1.13 (m, 1 H).	514.2
3	8.96(*d*, *J* =4.8 Hz, 2 H), 8.71 (d, *J* = 6.8 Hz, 2 H), 8.17 (t, *J* = 10.8 Hz, 2 H), 7.91 (s, 1 H), 7.73 (s, 1 H), 7.4(d, *J* = 4.8 Hz, 1 H), 3.48 (s, 3 H), 2.3 (s, 3 H), 2.15-2.11 (m, 3 H), 1.21(s, 2 H).	609.2
4	9.41 (s, 1H), 8.92 (d, *J*= 4.8 Hz, 2 H), 8.17 (t, J=10.8 Hz, 2 H), 7.91 (s, 1 H), 7.73 (s, 1H), 7.4 (d, *J*= 4.8 Hz, 1 H), 3.48 (s, 3 H), 2.3 (s, 3 H), 2.15-2.11 (m, 3 H), 1.21 (s, 2 H)	609.2
5	1.569 - 1.675 (m, 6 H), 1.831 - 1.934 (m, 6 H), 2.050 - 2.196 (m, 2 H), 2.529 - 2.587 (m, 2 H), 2.963 - 3.610 (m, 3 H), 4.086 - 4.475 (m, 3 H), 7.148 - 7.313 (m, 5 H), 7.731 (t, *J* = 15.6 Hz, 1H), 7.886 (d, *J* = 8 Hz, 1 H), 8.173 (d, *J* = 7.6 Hz, 1 H), 8.202 (s, 1 H), 8.602 (s, 1 H).	500.3
6	1.278 - 1.417 (m, 4 H), 1.461 - 1.599 (m, 4 H), 1.890 - 1.99 (m, 4 H), 2.034 - 2.175 (m, 4 H), 3.145 - 3.658 (m, 3 H), 4.058 - 4.44 (m, 3 H), 7.152 - 7.304 (m, 5 H), 7.732 (t, *J* = 15.6 Hz, 1H), 7.886 (d, *J* = 7.6 Hz, 1 H), 8.173 (d, *J* = 8 Hz, 1 H), 8.202 (s, 1 H), 8.599 (s, 1 H).	500.3
7	1.18 - 1.24 (m, 2 H), 1.32 - 1.36 (m 1 H), 1.45 - 1.51 (m, 2 H), 1.51 - 1.64 (m, 4 H), 1.82 - 1.85 (m, 2 H), 1.96 - 1.95 (m, 2 H), 2.05 - 2.20 (m, 4 H), 3.37 - 3.39 (m, 1 H), 3.47 - 3.51 (m, 1 H), 3.57 - 3.60 (m, 1 H), 3.83 - 3.84 (m, 3 H), 3.87 - 3.95 (m, 1 H), 3.98 - 4.07 (m, 2 H), 4.84 (s, 1 H), 6.76 - 6.78 (m, 1 H), 7.72 - 7.76 (m, 2 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.24 (m, 3 H), 8.88 - 8.95 (m, 1 H).	561.3

Ex. No.	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm**	**LC-MS (ES) m/z [M+H]$^+$**
8	1.17 - 1.44 (m, 3 H), 1.54 - 1.80 (m, 10 H), 1.98 - 2.06 (m, 2 H), 2.06 - 2.22 (m, 2 H), 3.38 - 3.41 (m, 1 H), 3.43 - 3.51 (m, 1 H), 3.60 - 3.66 (m, 1 H), 3.89 - 3.95 (m, 4 H), 3.95 - 4.19 (m, 2 H), 4.83 (s, 1 H), 6.73 - 6.75 (m, 1 H), 7.73 - 7.79 (m, 2 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.24 (m, 3 H), 8.89 - 8.97 (m, 1 H).	561.3
9	1.563 - 1.636 (m, 5 H), 1.785 - 1.99 (m, 8 H), 2.553 - 2.562 (m, 2 H), 2.607 - 2.681 (m, 1 H), 3.37 - 3.63 (m, 3 H), 4.013 - 4.091 (m, 2 H), 4.106 - 4.331 (m, 1 H), 7.152 - 7.311 (m, 5H), 7.753 (t, *J* = 15.6 Hz, 1 H), 7.947 - 7.928 (d, *J* = 7.6 Hz, 1 H), 8.189 (d, *J* = 7.6 Hz, 1 H), 8.23 (s, 1 H), 8.928 - 9.00 (m, 1 H).	500.3
10	1.536 - 1.627 (m, 5 H), 1.697 - 2.133 (m, 8 H), 2.541 - 2.554 (m, 2 H), 2.673 - 2.2.863 (m, 1 H), 3.408 - 3.658 (m, 2 H), 3.989 - 4.184 (m, 1 H), 4.309 - 4.323 (m, 1 H), 7.144 - 7.303 (m, 5 H), 7.745 (t, *J* = 17.6 Hz,1 H), 7.921 (d, *J* = 8 Hz, 1 H), 8.171 - 8.221 (m, 2 H), 8.904 - 9.004 (m, 1 H).	500.3
13	1.24 (m, 1 H), 1.45 - 1.65 (m, 5 H), 1.69 - 2.09 (m, 5 H), 2.09 - 2.29 (m, 3 H), 2.77 - 2.86 (m, 1 H), 3.39 - 3.49 (m, 1 H), 3.51 - 3.61 (m, 2 H), 3.98 - 4.30 (m, 2 H), 4.30 - 4.72 (m, 1 H), 4.72 (s, 1 H), 7.18 - 7.22 (m, 1 H), 7.30 - 7.34 (m, 2 H), 7.46 - 7.48 (m, 2 H), 7.73 - 7.76 (m, 1 H), 7.92 - 7.94 (m, 1 H), 8.17 - 8.19 (m, 1 H), 8.22 (s, 1 H), 8.88 - 8.98 (m, 1 H).	516.3
14	1.47 - 1.77 (m, 8 H), 1.79 - 1.85 (m, 2 H), 1.88 - 2.10 (m, 1 H), 2.07 - 2.16 (m, 1 H), 2.34 - 2.48 (m, 1 H), 2.88 - 2.99 (m, 1 H), 3.17 - 3.30 (m, 1 H), 3.39 - 3.45 (m, 1 H), 3.60 - 3.65 (m, 2 H), 3.93 - 3.99 (m, 1 H), 4.11 - 4.17 (m, 1 H), 4.24 - 4.52 (m, 1 H), 4.70 (m, 1 H), 7.14 - 7.29 (m, 3 H), 7.46 - 7.48 (m, 2 H), 7.71 - 7.74 (m, 1 H), 7.90 - 7.923 (m, 1 H), 8.15 - 8.17 (m, 1 H), 8.20 (s, 1 H), 8.89 - 8.98 (m, 1 H).	516.3
15	8.99 - 8.89 (m, 1H), 8.45 (s, 1H), 8.38 (d, *J = 4.0 Hz*, 1H), 8.20 (s, 1H), 8.16 (d, *J = 7.6 Hz*, 1H), 7.91 (d, *J = 8.0 Hz*, 1H), 7.73 (t, *J = 7.6 Hz*, 1H), 7.62 (d, *J = 8.0 Hz*, 1H), 7.30 (t, *J = 6.0 Hz*, 1H), 4.50 - 4.44 (m, 1H), 4.32 - 4.27 (m, 1H), 4.15 - 3.98 (m, 2H), 3.65 - 3.30 (m, 4H), 2.83 - 2.80 (m, 1H), 2.77 - 2.60 (m, 1H), 2.58 - 2.48 (m, 1H), 2.13 -2.11 (m, 1H), 1.98 - 1.69 (m, 6H), 1.62 - 1.57 (m, 4H)	501.3
16	8.98 - 8.89 (m, 1H), 8.45 (s, 1H), 8.38 (d, *J = 4.0 Hz*, 1H), 8.20 (s, 1H), 8.16 (d, *J = 7.6 Hz*, 1H), 7.91 (d, *J = 8.0 Hz*, 1H), 7.73 (t, *J = 8.0 Hz*, 1H), 7.63 (d, *J = 8.0 Hz*, 1H), 7.29 (t, *J = 6.0 Hz*, 1H), 4.46 - 4.41 (m, 1H), 4.29 - 4.10 (m, 1 H), 3.99 - 3.93 (m, 1H), 3.67 - 3.40 (m, 3H), 3.30 - 3.17 (m, 1H), 2.98 - 2.87 (m, 2H), 2.31 - 2.01 (m, 1H), 1.90 - 1.72 (m, 7H), 1.59 - 1.32 (m, 5H)	501.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
17	8.99 - 8.91 (m, 1 H), 8.29 (s, 1 H), 8.22 - 8.14 (m, 3 H), 7.93 (d, J = 8 Hz, 1 H), 7.76 (t, J = 8 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.33 - 7.29 (m, 1 H), 4.62 (s, 1 H), 4.46 (d, J = 6.8 Hz, 1 H), 4.29 - 3.96 (m, 2 H), 3.64 - 3.59 (m, 3 H), 2.93 - 2.85 (m, 1 H), 2.13 (d, J = 6.8 Hz, 1 H), 1.93 - 1.74 (m, 4 H), 1.67 - 1.64 (m, 8 H).	517.3
18	8.99 - 8.27 (m, 1 H), 8.26 (d, J = 2.4 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, J = 8 Hz, 1 H), 8.13 (d, J = 4.4 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.32 - 7.29 (m, 1 H), 4.62 (s, 1 H), 4.46 - 4.42 (m, 1 H), 4.38 - 4.25 (m, 1 H), 4.19 - 4.10 (m, 4 H), 4.03 - 3.95 (m, 1 H), 3.65 - 3.42 (m, 2 H), 2.94 - 2.86 (m, 1H), 2.09 (d, J = 7.6 Hz, 3H), 1.94 - 1.86 (m, 5H), 1.80 - 1.64 (m, 2H), 1.53 - 1.24 (m, 4H)	517.3
19	8.91 - 9.0 (m, 1 H), 8.48 (s, 1 H), 8.22 (s, 1 H), 8.17 - 8.19 (m, 1 H), 7.92 - 9.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.33 - 7.37 (m, 1 H), 4.27 - 4.49 (m, 1 H), 3.98 - 4.18 (m, 2 H), 3.40 - 3.52 (m, 3 H), 2.67 - 2.83 (m, 2 H), 1.71 - 2.16 (m, 8 H), 1.14 - 1.68 (m, 6 H).	519.3
20	8.91 - 9.0 (m, 1 H), 8.46 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.33 - 7.36 (m, 1 H), 4.20 - 4.46 (m, 1 H), 3.95 - 4.18 (m, 2 H), 3.40 - 3.53 (m, 3 H), 3.22 - 3.32 (m, 1 H), 2.87 - 3.0 (m, 2 H), 1.73 - 2.14 (m, 7 H), 1.39 - 1.74 (m, 6 H).	519.3
21	1.221 (s, 1 H), 1.630 (m, 6 H), 1.871 - 1.919 (m, 5 H), 2.122 (m, 1 H), 2.836 (m, 1 H), 3.400 (m, 1 H), 3.517 - 3.598 (m, 2 H), 3.959 - 4.00 (m, 1 H), 4.015 - 4.095 (m, 2 H), 4.121 - 4.132 (m, 1 H), 4.261 - 4.276 (m, 1 H), 5.134 (s, 1 H), 6.761 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 12 Hz, 1 H), 7.642 - 7.749 (m, 3 H), 7.915 (d, J = 8 Hz, 2 H), 8.115 - 8.204 (m, 3 H), 8.904 - 8.965 (m, 1 H).	517.3
22	1.316 - 1.627 (m, 6 H), 1.734 - 1.842 (m, 2 H), 1.864 - 1.954 (m, 3 H), 2.119 (m, 3 H), 2.854 - 2.973 (m, 1 H), 3.464 - 3.685 (m, 3 H), 3.951 - 4.163 (m, 2 H), 4.182 - 4.462 (m, 1 H), 4.916 - 4.925 (m, 1 H), 6.742 (d, J = 8.4 Hz, 1 H), 6.933 (t, J = 12 Hz, 1 H), 7.652 - 7.695 (m, 1 H), 7.750 (t, J = 15.6 Hz, 1 H), 7.935 (d, J = 7.6 Hz, 1 H), 8.14 - 8.226 (m, 3 H), 8.914 - 9.002 (m, 1 H)	517.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
23	8.97 - 8.89 (m, 1 H), 8.21 (t, *J* = 11.6 Hz, 2 H), 8.02 (d, *J* = 2 Hz, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.76 (t, *J* = 8 Hz, 1 H), 7.58 - 7.56 (m, 1 H), 6.76 - 6.74 (m, 1 H), 4.49 (d, *J* = 6.4 Hz, 1 H), 4.14 - 4.01 (m, 2 H), 3.87 - 3.77 (m, 3 H), 3.64 - 3.48 (m, 4 H), 2.87 - 2.79 (m, 1 H), 2.68 - 2.67 (m, 1 H), 2.16 - 1.59 (m, 8 H), 1.56 - 1.52 (m, 4 H), 1.07 - 1.04 (m, 1H)	531.3
24	8.97 - 8.89 (m, 1 H), 8.21 (t, *J* = 12 Hz, 2 H), 8.02 (s, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.76 (t, *J* = 8 Hz, 1 H), 7.60 - 7.57 (m, 1 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 4.46 - 4.45 (m, 1 H), 4.31 - 4.26 (m, 2 H), 4.03 - 3.69 (m, 3 H), 3.68 - 3.49 (m, 3 H), 2.99 - 2.87 (m, 1 H), 2.68 - 2.67 (m, 1 H), 2.17 - 1.75 (m, 9 H), 1.74 - 1.24 (m, 5 H)	531.3
25	8.88 - 8.98 (m, 1 H), 8.26 - 8.28 (m, 1 H), 8.22 (s, 1 H), 8.17 - 8.19 (m, 1 H), 7.91 - 7.96 (m, 3 H), 7.70 - 7.76 (m , 2 H), 7.52 - 7.56 (m, 1 H), 7.47 - 7.49 (m, 1 H), 4.29 - 4.50 (m, 1 H), 3.99 - 4.19 (m, 2 H), 3.45 - 352 (m, .3 H), 3.0 - 3.05 (m, 1 H), 2.68 - 2.88 (m, 1 H), 2.55 - 2.56 (m, 1 H), 2.33 - 2.34 (m, 1 H), 2.08 - 2.18 (m, 3 H), 1.81 - 2.08 (m, 4 H), 1.55 - 1.80 (m, 5 H).	551.3
26	8.90 - 8.99 (m, 1 H), 8.24 - 8.26 (m, 1 H), 8.21 (s, 1 H), 8.16 - 8.18 (m, 1 H), 7.89 - 7.92 (m, 3 H), 7.67 - 7.73 (m , 2 H), 7.50 - 7.54 (m, 1 H), 7.45 - 7.47 (m, 1 H), 4.28 - 4.48 (m, 1 H), 3.96 - 4.25 (m, 2 H), 3.42 - 3.68 (m, 3 H), 3.24 - 3.31 (m, 1 H), 2.80 - 3.0 (m, 2 H), 2.31 - 2.48 (m, 1 H), 1.81 - 2.16 (m, 6 H), 1.63 - 1.1.77 (m, 3 H), 1.40 - 1.52 (m, 3 H).	551.3
27	8.99-8.89 (m, 1 H), 8.47 (*d*, *J* = 4.4 Hz, 1 H), 8.17 (*t, J* = 12.4 Hz, 2 H), 7.91 (*d*, *J* = 8 Hz, 1 H) , 7.74-7.66 (m, 2 H), 7.25 (*d*, J = 7.6 Hz, 1 H), 7.17-7.14 (m, 1 H), 4.48-4.25 (m, 1 H), 4.12-3.91 (m, 2 H), 3.60-3.38 (m, 3 H), 2.80-2.73 (m, 3 H), 2.65-2.54 (m, 1 H), 2.31-2.11 (m, 2 H), 2.05-1.92 (m, 3 H), 1.88-1.56 (m, 3 H), 1.52-1.32 (m, 4 H)	501.1
28	8.97-8.91(m,1 H), 8.45(d, J= 4.4 Hz, 1 H), 8.17(t, *J* =12 Hz, 2 H), 7.91(*d*, *J* =7.6 Hz, 1 H) , 7.75-7.65(m, 2 H), 7.23(*d*, *J* = 7.6 Hz, 1 H), 7.18-7.15(m, 1 H), 4.48-4.25(s, 1 H), 4.12-3.91(m, 2 H), 3.60 -3.38(m, 3 H), 2.80-2.73(m, 3 H), 2.65-2.54(m, 1 H),2.31-2.11(m, 2 H), 2.05-1.92(m, 3 H), 1.88-1.56(m, 3 H),1.52-1.32(m, 4 H)	501.1
29	8.97-8.90 (m, 1 H), 8.49 (d, *J* = 4.4 Hz, 1 H), 8.22 (s, 2 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 7.30 (m, 2 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.17-7.14 (m, 1 H), 4.48-4.25 (s, 1 H), 4.12-3.91(m, 2 H), 3.60-3.38 (m, 3 H), 2.80-2.73 (m, 3 H), 2.65-2.54 (m, 1 H), 2.31-2.11 (m, 2 H),2.05-1.92 (m, 3 H), 1.88-1.56 (m, 3 H), 1.52-1.32 (m, 4 H)	501.1

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
30	8.96-8.89(m ,1 H), 8.47 (d, *J* = 4.4 Hz, 1 H), 8.17 (t, *J* = 11.6 Hz, 2 H), 7.91 (d, *J* = 8 Hz, 1 H) , 7.74-7.66 (m, 2 H), 7.25 (d, *J*= 7.6 Hz, 1 H), 7.16 (*t*, *J* = 5.2 Hz, 1 H), 4.45 (s, 1 H), 4.29 (s, 1 H), 4.12-3.97 (m, 2 H), 3.56-3.43 (m, 4 H), 2.77-2.48 (m, 3 H), 2.31-1.96 (m, 6 H),1.58-1.22 (m, 5 H).	501.1
31	8.96 - 8.90 (m, 1 H), 8.27 - 8.12 (m, 2 H), 7.99 - 7.92 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 6.95 - 6.89 (m, 3 H), 4.75 - 4.40 (m, 2 H), 4.30 - 3.9 (m, 3 H), 3.75 - 3.40 (m, 4 H), 3.05 - 2.75 (m, 1 H), 2.35 - 2.1 (m, 1 H), 1.80 - 1.40 (m, 8 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 2 H).	516.2
32	8.96 - 8.90 (m, 1 H), 8.28 - 8.13 (m, 2 H), 7.99 - 7.92 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 6.96 - 6.88 (m, 3 H), 4.75 - 4.40 (m, 2 H), 4.30 - 3.9 (m, 3 H), 3.75 - 3.40 (m, 4 H), 3.05 - 2.75 (m, 1 H), 2.35 - 2.1 (m, 1 H), 1.80 - 1.40 (m, 8 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 2 H).	516.2
33	9.45 - 9.44 (m, 1H), 8.96 - 8.94 (m, 2 H), 8.90 - 8.83 (m, 1 H), 8.67 - 8.65 (m, 1 H), 8.22 (s, 1 H), 8.19 - 8.17 (m, 1 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.76 - 7.74 (m, 1 H), 7.50 (t, *J* = 4.8 Hz, 1 H), 5.11 (s, 1 H), 4.40 - 4.45 (m, 1 H), 4.30 - 4.00 (m, 2 H), 3.75 - 3.75 (m, 3 H), 2.45 - 2.35 (m, 3 H), 2.30 - 2.1 (m ,1 H), 2.00 - 1.75 (m, 5 H), 1.25 - 1.1 (m, 4 H), 1.50 - 1.40 (m, 2 H).	595.3
34	9.42 - 9.43 (m, 1 H), 8.89 - 8.99 (m, 3 H), 8.65 - 8.67 (m, 1 H), 8.18 - 8.23 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.84 - 7.86 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.50 (t, *J* = 5.4 Hz, 1 H), 5.12 (s, 1 H), 4.21 - 4.32 (m, 1 H), 3.98 - 4.19 (m, 2 H), 3.44 - 3.68 (m, 3 H), 2.91 - 3.03 (m , 1 H), 1.97 - 2.25 (m, 4 H), 1.49 - 1.91 (m, 10 H).	595.3
35	8.96-8.90 (m, 1H), 8.73 (d, *J*=4.8 Hz, 2H), 8.19 (s, 1H), 8.16 (d, *J*=4 Hz, 1H), 7.91 (d, *J*=8 Hz, 1H), 7.73 (t, *J*=7.6 Hz, 1H), 7.31-7.29 (m, 1H), 4.45-4.43 (m, 2H), 4.15-3.97 (m, 3H), 3.55-3.49 (m, 3H), 2.95-2.74 (m, 3H). 2.31-2.06 (m, 2H), 1.89 (s, 1H), 1.73-1.49 (m, 6H), 1.28-1.22 (m, 2H)	502.3
36	8.97-8.91 (m, 1H), 8.75 (d, *J*=4.8 Hz, 2H), 8.22 (s, 1H), 8.18 (d, *J*=4 Hz, 1H), 7.93 (d, *J*=8 Hz, 1H), 7.75 (t, *J*=7.6 Hz, 1H), 7.33-7.31 (m, 1H), 4.48-4.28 (m, 1H), 4.18-3.99 (m, 2H), 3.57-3.41 (m, 3H), 2.98 (m, 1H), 2.84-2.72 (m, 1H) 2.33-2.17 (m, 3H), 1.91 (s, 2H), 1.88-1.40 (m, 9H), 1.34-1.27 (m, 3H).	502.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
37	9.00 - 8.90 (m, 1 H), 8.59 - 8.52 (m, 1 H), 8.22 - 8.17 (m, 2 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.88 - 7.83 (m, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.36 - 7.33 (m, 1 H), 4.51 - 4.47 (m, 0.5 H), 4.35 - 4.29 (m, 0.5 H), 4.19 - 3.99 (m, 2 H), 3.68 - 3.52 (m, 3 H), 2.89 - 2.75 (m, 1 H), 2.65 - 2.55 (m, 2 H), 2.42 - 2.32 (m, 1 H), 2.05 - 1.55 (m, 11 H).	519.5
38	8.98 - 8.89 (m, 1 H), 8.53 - 8.52 (m, 1 H), 8.20 - 8.15 (m, 2 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.83 (t, *J* = 7.8 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.54 - 7.52 (m, 1 H), 7.33 - 7.30 (m, 1 H), 4.50 - 4.10 (m, 2 H), 4.09 - 3.90 (m, 2 H), 3.65 - 240 (m, 3 H), 3.15 - 3.3 (m, 1 H), 2.65 - 2.5 (m, 2 H), 2.30 - 1.4 (m, 11 H).	519.5
39	8.97 - 8.90 (m, 1 H), 8.51 (d, *J* = 4.4 Hz, 1 H), 8.20 (t, *J* = 12 Hz, 2 H), 7.93 (d, *J* = 8 Hz, 1 H), 7.79 - 7.73 (m, 2 H), 7.63 (d, *J* = 8 Hz, 1 H), 7.23 (t, *J* = 5.2 Hz, 1 H), 4.97 (s, 1 H), 4.48 - 4.44 (m, 1 H), 4.30 - 3.94 (m, 2 H), 3.59 - 3.41 (m, 3 H), 2.98 - 2.78 (m, 1 H), 2.20 - 2.07 (m, 2 H), 1.91 - 1.70 (m, 5 H), 1.60 - 1.51 (m, 4 H), 1.37 - 1.24 (m, 3 H).	517.3
40	8.96 - 8.89 (m, 1 H), 8.47 (d, *J* = 4.4 Hz, 1 H), 8.19 (t, *J* = 12 Hz, 2 H), 7.91 (d, *J* = 8 Hz, 1 H), 7.77 - 7.64 (m, 3 H), 7.20 (t, *J* = 6 Hz, 1 H), 7.23 (t, *J* = 5.2 Hz, 1 H), 4.99 (s, 1 H), 4.27 - 4.26 (m, 1 H), 4.15 - 3.95 (m, 3 H), 3.62 - 3.40 (m, 3 H), 3.30 - 3.23 (m, 1 H), 2.89 (m, 1 H), 2.13 - 1.92 (m, 4 H), 1.82 - 1.56 (m, 7 H).	517.3
41	8.94 - 8.89 (m, 1 H), 8.22 - 8.17 (m,, 2 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.30 - 7.15 (m, 5 H), 4.28 - 4.06 (m, 1 H), 4.05 - 3.96 (m, 2 H), 3.69- 3.42 (m, 3 H), 3.35 - 3.25 (m, 1 H), 2.98- 2.89 (m, 1 H), 2.33 - 2.16 (m, 8 H), 1.60 - 1.26 (m, 5 H), 1.40-1.30 (m, 1 H)	500
42	8.98 - 8.90 (m, 1 H), 8.20 (s, 1 H), 8.17 - 8.15 (m, 1 H), 7.91 (d, *J* = 7.2 Hz, 1 H), 7.73 (t, *J* = 8 Hz, 1 H), 7.28 - 7.13 (m, 5 H), 4.55 - 4.25 (m, 1 H), 4.22 - 3.85 (m, 2 H), 3.75 - 3.9 (m, 3 H), 3.35 - 3.15 (m, 2 H), 3.05 - 2.85 (m, 1 H), 2.3 - 2.4 (m, 1 H), 2.25 - 1.7 (m, 7 H), 1.65 - 1.25 (m, 5 H)	500
43	8.974 - 8.918 (m, 1 H), 8.215 - 8.168 (m, 2 H), 7.932 (d, *J* = 7.6 Hz, 1 H), 7.767 - 7.728 (m, 2 H), 7.605 (s, 1 H), 4.31 (m, 1 H), 4.179 - 3.973 (m, 2 H), 3.585 (m, 3 H), 2.9 (m, 3 H), 2.076 (m, 4 H), 1.915 - 1.716 (m, 9 H).	507.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
44	8.963 - 8.906 (m, 1 H), 8.224 - 8.176 (m, 2 H), 7.936 (d, *J* = 7.6 Hz, 1 H), 7.772 - 7.707 (m, 2 H), 7.575 (s, 1 H), 4.465 - 4.282 (m, 1 H), 4.2 - 4.109 (m, 3 H), 3.642 - 3.407 (m, 2 H), 2.968 - 2.889 (m, 3 H), 2.339 - 2.33 (m, 4 H), 2.289 - 1.735 (m, 4 H), 1.591 - 1.184 (m, 5 H).	507.3
45	8.89 - 8.97 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.76 (m, 1 H), 7.16 - 7.32 (m, 5 H), 4.27 - 4.51 (m, 1 H), 3.93 - 4.17 (m, 2 H), 3.48 - 3.85 (m, 3 H), 3.06 - 3.22 (m, 3 H), 2.87 - 3.06 (m, 1 H), 2.33 - 2.45 (m, 1 H), 2.07 - 2.30 (m, 2 H), 1.95 - 2.04 (m, 2 H), 1.63 - 1.97 (m, 1 H), 1.45 - 1.63 (m, 2 H).	472.3
46	8.91 - 8.95 (m, 1 H), 8.17 - 8.22 (m, 2 H), 7.92 - 7.94 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.16 - 7.33 (m, 5 H), 4.27 - 4.51 (m, 1 H), 3.97 - 4.17 (m, 2 H), 3.48 - 3.75 (m, 4 H), 2.87 - 3.22 (m, 4 H), 2.38 - 2.46 (m, 2 H), 2.08 - 2.33 (m, 2 H), 1.66 - 2.06 (m, 3 H)	472.3
47	8.97- 8.91 (m, 1 H), 8.19 (t, *J* = 11.2 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 6.8 Hz, 1 H), 7.04 (d, *J* = 6.8 Hz, 2 H), 4.30- 3.98 (m, 3 H), 3.59 - 3.54 (m, 3 H), 2.77 – 2.73 (m, 2 H), 2.46 (s, 3 H), 2.18 – 2.16 (m, 1 H), 2.08 - 2.06 (m, 2 H), 1.97 (s, 3 H), 1.60 - 1.58 (m, 4 H), 1.37 - 1.33 (m, 1 H), 1.30- 1.19 (m, 3 H)	515.3
48	8.97 (s, 1 H), 8.19 (t, *J* = 11.2 Hz, 2 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.59 (s, 1 H), 7.05 (d, *J* = 6.8 Hz, 2 H), 4.65- 4.03 (m, 4 H), 3.64 - 3.61 (m, 3 H), 3.00 - 2.97 (m, 2 H), 2.45 (s, 3 H), 2.20 - 2.15 (m, 2 H), 1.91-1.87 (m, 4 H), 1.73 - 1.67 (m, 4 H), 1.34 (s, 1 H), 1.30- 1.19 (m, 2 H).	515.3
49	8.96-8.90 (m, 1 H), 8.50 (m, 1 H), 8.22 (s, 1 H), 8.19-8.17 (d, *J* =8 Hz, 1H), 7.94 (m, 1 H) 7.74 (m, 1 H), 7.68 (m, 1 H), 7.28 (m, 1 H), 7.18 (m, 1 H), 4.48 (m, 1 H), 4.01 (m, 2 H), 3.65 (m, 2 H), 3.17 (m, 2 H), 2.97 (m, 2 H), 2.40 (m, 1 H), 2.18 (m, 1 H), 1.99 (m, 5 H), 1.76 (m, 2 H), 1.64 (m, 1 H), 1.51 (m, 1 H).	487.2
50	8.97-8.88 (m, 1 H), 8.50 (m, 1 H), 8.22 (s, 1 H), 8.19-8.17 (d, *J* =8Hz, 1 H), 7.94 (m, 1 H) 7.74 (m, 1 H), 7.68 (m, 1 H), 7.29 (m, 1 H), 7.18 (m, 1 H), 4.48 (m, 1 H), 4.01 (m, 2 H), 3.96 (m, 2 H), 3.22 (m, 2 H), 3.01 (m, 1 H), 2.33 (m, 2 H), 1.96 (m, 6 H), 1.76 (m, 1 H), 1.54 (m, 3 H)	487.2
51	8.88 (m, 1H), 8.49-8.48 (m, 1H), 8.22 (s, 1H), 8.19-8.17 (m, 1H), 7.94-7.92 (m, 1H), 7.77-7.73 (m, 2H), 7.68-7.66 (m, 1H), 7.23-7.21 (m, 1H), 4.97 (s, 1H), 4.34-4.05 (m, 3H), 3.70 (m, 1H), 3.35-2.68 (m, 6H), 2.18-1.91(m, 3H), 1.80-1.59 (m, 7H), 1.41-1.24 (m, 7H)	531.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
52	8.93 (d, **J** = 26.4, 1H), 8.19 (s, 1H), 8.15 (d, **J** = 7.6 Hz, 1 H), 7.91 (t, **J** = 7.6 Hz, 1 H), 7.84 (s, 1 H), 7.70 (t, **J** = 7.6 Hz, 1 H), 7.35 (d, *J = 8.4 Hz*, 1H), 6.89(d, **J**=14.4, 1H), 4.69 (s, 1 H), 4.43-4.15 (m, 2 H), 4.14-3.94 (m, 3 H), 3.52 (m, 4 H), 3.30-3.20 (m, 4 H), 2.82-2.74 (m, 2 H), 2.08-2.05 (m, 3 H), 1.95-1.61 (m, 7 H), 1.48-1.21 (m, 4 H)	586.2
53	8.94 (d, *J* =23.2, 1H), 8.20 (s, 1H), 8.16 (d, *J* = 8 Hz, 1 H), 7.91 (t, *J* = 7.6 Hz, 1 H), 7.81(s, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* =8.4, 1H), 6.90- 6.87 (m, 1H), 4.78 (s, 1 H), 4.43-4.27 (m, 2 H), 4.18-3.80 (m, 3 H), 3.62-3.38 (m, 4 H), 3.30-3.19 (m, 4 H), 2.97-2.65 (m, 2 H), 2.12-2.05 (m, 1 H), 1.94-1.91 (m, 4 H), 1.87-1.56 (m, 9 H)	586.2
54	8.96-8.95 (m,1 H), 8.64 (7.79 (d, *J* = 8 Hz, 1 H), 8.15 (m, 2 H), 7.91 (m, 3 H), 7.72 (t, *J* = 8 Hz,1 H), 7.63 (d, *J* = 8 Hz, 1 H), 7.36 (m, 1 H), 4.41 (m, 1 H), 4.08 (m, 2 H), 3.52 (m, 3 H), 3.20 (m, 1 H), 2.80 (m, 1 H), 2.35 (m, 1 H), 2.05 (m, 1 H), 1.80 (m, 4 H), 1.66 (m, 4 H), 1.41 (m, 4 H).	553.04
55	8.96-8.89 (m, 1 H), 8.64 (d, *J* = 8 Hz, 1 H), 8.15 (m, 2 H), 7.89 (m, 2 H), 7.74 (t, *J* = 8 Hz,1 H), 7.63 (d, *J* = 8 Hz, 1 H), 7.36 (m, 1 H), 4.49 (m, 1 H), 4.10 (m, 2 H), 3.67-3.40 (m, 2 H), 3.52 (m, 2 H), 3.20 (m, 1 H), 2.70 (m, 2 H), 2.65 (m, 1 H), 2.34 (m, 1 H), 2.12-1.82 (m, 3 H), 1.57 (m, 6 H), 1.31 (m, 1 H).	553.04
56	8.89 (d, *J* = 4.4 Hz, 3 H), 8.36 (d, *J* = 7.6 Hz, 2 H), 8.22 (s,1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 4.8 Hz, 1 H), 4.88 (s, 1 H), 4.49 (s, 1 H), 4.00- 4.18 (m, 3 H), 3.44- 3.59 (m, 3 H), 2.88- 2.98 (m, 2 H), 2.19 (d, *J* = 10.4 Hz, 3 H), 2.08 (d, *J* = 6.0 Hz, 3 H), 1.61-1.79 (m, 5 H).	592.4
57	8.89 (d, *J* = 4.4 Hz, 3 H), 8.34 (d, *J* = 7.6 Hz, 2 H), 8.23 (s,1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 4.8 Hz, 1 H), 4.86 (s, 1 H), 4.30- 4.46 (m, 1 H), 4.00- 4.19 (m, 3 H), 3.43- 3.66 (m, 3 H), 2.92- 3.00 (m, 2 H), 2.15- 2.33 (m, 2 H), 1.74- 1.98 (m, 8 H), 1.53 (s,1 H).	592.3
58	8.98 - 8.95 (m, 2 H), 8.91 - 8.80 (m, 2 H), 8.14 (d, *J* = 2.8 Hz, 1 H), 8.18 (t, *J* = 12.0 Hz, 2 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 4.8 Hz, 1 H), 5.98 (s, 1 H), 4.28 (d, *J* = 6.0 Hz, 1 H), 4.12 - 3.97 (m, 4 H), 3.60 - 3.54 (m, 4 H), 2.78 – 2.75 (m, 2 H), 2.39 - 2.22 (m, 4 H), 1.89 - 1.57 (m, 5 H).	601.3

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
59	8.96 - 8.90 (m, 1 H), 8.81 (d, *J* = 4.8 Hz, 2 H), 8.40 (s, 1 H), 8.19 (t, *J* = 11.6 Hz, 2 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 2 H), 6.00 (s, 1 H), 4.10 (m, 6 H), 3.62 (m, 4H), 1.96 - 1.71 (m, 9 H), 1.24 - 1.21 (m, 2 H)	601.4
60	8.95 - 8.90 (m, 2 H), 8.26 - 8.15 (m, 3 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 5.23 (d, *J* = 9.2 Hz, 1 H), 4.52 - 4.51 (m, 2 H), 4.27 - 4.25 (m, 1 H), 4.11 - 3.97 (m, 2 H), 3.56 - 3.53 (m, 4 H), 2.65 - 2.64 (m, 2 H), 2.33 - 2.28 (m, 2 H), 1.89 - 1.76 (m, 4 H), 1.62 - 1.35 (m, 6 H)	542.2
61	8.98 - 8.89 (m, 2 H), 8.28 - 8.11 (m, 3 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 4.45 (s, 1 H), 4.26 - 3.93 (m, 2 H), 3.62 - 3.49 (m, 3 H), 3.24 - 2.89 (m, 2 H), 3.56 - 3.53 (m, 4 H), 2.13 - 1.48 (m, 10 H)	542.2
62	8.97 (brs, 1H), 8.91-8.88 (m, 1H), 8.20 (s, 1H), 8.16 (d, *J*=8Hz, 1H), 7.91 (d, *J* =8Hz, 1H), 7.75-7.71 (m, 2H), 5.44 (s, 1H), 4.44-4.43 (m, 1H), 4.27-4.25 (m, 1H), 4.17-4.13(m, 1H), 4.10-3.99 (m, 1H), 3.65-3.49 (m, 3H), 3.47 - 3.43 (m, 1H), 3.23-3.22 (m, 1H), 2.95-2.87 (m, 2H), 2.12 - 2.09 (m, 1H), 1.93-1.70 (m, 8H), 1.64-1.49 (m, 1H)	523.3
63	9.08 (s, 1H), 8.88 - 8.98 (m, 1H), 8.28 - 8.31 (d, 1H), 8.22 (s, 1H), 8.18 (d, *J*= 8 Hz, 1H), 7.99 (d, *J* = 3.2 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.73 - 7.79 (m, 2H), 5.11 (s, 1H), 4.14 - 4.49 (m, 1H), 3.98 - 4.28 (m, 2H), 3.35 - 3.62 (m, 3H), 2.81 - 2.86 (m ,1H), 2.33 - 2.41 (m, 2H), 2.07 - 2.14 (m, 1H), 1.75 - 1.93 (m, 5H), 1.44 - 1.69 (m, 4H), 1.44 - 1.51 (m, 2H)	600.3
64	9.06 (m, 1H), 8.89 - 8.98 (m, 1H), 8.28 - 8.31 (d, 1H), 8.23 (s, 1H), 8.19 (d, *J*= 7.6 Hz, 1H), 7.99 (d, *J* = 3.2 Hz, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.82 (m, 1H), 7.73 - 7.77 (m, 1H) 5.11 (s, 1H), 4.19 - 4.48 (m, 1H), 4.12 - 4.17 (m, 1H), 3.97 - 4.04 (m, 1H), 3.35 - 3.70 (m, 3H), 3.18 - 3.24 (m, 1H), 2.92 - 3.01 (m ,1H), 2.15 - 2.265 (m, 1H), 1.86 - 2.09 (m, 3H), 1.67 - 1.91 (m, 5H), 1.51 - 1.53 (m, 3H), 1.24 (m, 1H)	600.3
65	9.30 (s,1H), 9.00 (s, 1H), 8.90 (s, 1H), 8.28 (s, 1H), 8.19 (s, 2H), 8.15 (d, *J* = 8Hz, 1H), 7.92 (d, *J* = 8Hz,1H), 7.80 (d, *J* = 8Hz,1H), 7.70 (t, *J* = 8Hz,1H), 5.12 (s, 1H), 4.47 – 4.45 (m, 1H), 4.28 – 4.25 (m, 1H), 4.07 – 4.03 (m, 3H), 3.55 – 3.53 (m, 2H), 3.41 – 3.37 (m, 1H), 2.79 -2.76 (m, 2H), 2.33 – 2.30 (m, 1H), 2.09 – 2.07 (m, 1H), 1.89 – 1.85 (m, 4H), 1.60 – 1.55 (m, 3H), 1.44- 1.38 (m, 2H)	584.4

Ex. No.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm	LC-MS (ES) m/z $[M+H]^+$
66	9.30 (s,1H), 8.97 (s, 1H), 8.91 (s, 1H), 8.27 (s, 1H), 8.20 (s, 2H), 8.15 (d, *J* = 4Hz, 1H), 7.92 (d, *J* = 8Hz,1H), 7.85 (d, *J* = 8Hz,1H), 7.75 (t, *J* = 8Hz,1H), 5.14 (s, 1H), 4.45 – 4.41 (m, 1H), 4.27 – 4.25 (m, 1H), 4.16 – 4.10 (m, 2H), 3.99 – 3.95 (m, 2H), 3.62 – 3.57 (m, 1H), 3.48 – 3.45 (m, 2H), 2.98 – 2.93 (m, 2H), 2.13 – 2.11 (m, 1H), 2.02 – 1.99 (m, 3H), 1.77 – 1.65 (m, 6H)	584.4
67	8.96 - 8.89 (m, 2 H), 8.18 (t, *J* = 12.4 Hz, 2 H), 8.05 (s, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.74 - 7.68 (m, 2 H), 7.49 (s, 1 H), 5.07 (s, 1 H), 4.44 – 4.41 (m, 1 H), 4.28 – 4.25 (m, 1 H), 4.15 - 3.96 (m, 2 H), 3.95 - 3.48 (m, 4 H), 2.82 - 2.76 (m, 1 H), 2.33 - 2.30 (m, 2 H), 2.09 - 2.05 (m, 2 H), 1.88 - 1.86 (m, 3 H), 1.58 (s, 3 H), 1.39 - 1.21 (m, 3 H)	560.3
68	8.97 - 8.91 (m, 2 H), 8.21 (t, *J* = 11.2 Hz, 3 H), 8.07 (s, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.77 - 7.74 (m, 2 H), 7.49 (s, 1 H), 5.10 (s, 1 H), 4.46 (s, 1 H), 4.29 - 3.96 (m, 2 H), 3.65 - 3.40 (m, 3 H), 3.01 - 2.92 (m, 1 H), 2.18 - 1.96 (m, 5 H), 1.82 - 1.52 (m, 8 H), 1.34 - 1.24 (m, 1 H)	560.3
70	9.08 (s, 1H), 8.88 - 8.98 (m, 1H), 8.15 - 8.21 (d, 1H), 8.22 (s, 1H), 8.18 (d, *J*= 8 Hz, 1H), 7.99 (d, *J* = 3.2 Hz, 1H), 7.93 (d, J = 8 Hz, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.73 - 7.79 (m, 2H), 5.11 (s, 1H), 4.14 - 4.49 (m, 1H), 3.98 - 4.28 (m, 2H), 3.35 - 3.62 (m, 3H), 2.81 - 2.86 (m ,1H), 2.33 - 2.41 (m, 2H), 2.07 - 2.14 (m, 1H), 1.75 - 1.93 (m, 5H), 1.44 - 1.69 (m, 4H), 1.44 - 1.51 (m, 2H)	583.6
80	8.97- 8.91 (m, 1 H), 8.19 (t, *J* = 11.2 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 6.8 Hz, 1 H), 7.04 (d, *J* = 6.8 Hz, 2 H), 4.30- 3.98 (m, 3 H), 3.59 - 3.55 (m, 3 H), 2.75 – 2.70 (m, 2 H), 2.46 – 2.43 (m, 3 H), 2.18 – 2.14 (s, 1 H), 2.08 – 2.03 (m, 2 H), 1.97 – 1.95 (m, 3 H), 1.60 – 1.55 (m, 4 H), 1.34 – 1.30 (m, 1 H), 1.30- 1.19 (m, 3 H)	600.3
81	8.97- 8.91 (m, 1 H), 8.19 (t, *J* = 11.2 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 6.8 Hz, 1 H), 7.04 (d, *J* = 6.8 Hz, 2 H), 4.30- 3.98 (m, 3 H), 3.58 – 3.55 (m, 3 H), 2.75 – 2.72 (m, 2 H), 2.46 - 2.42 (m, 3 H), 2.18 – 2.15 (m, 1 H), 2.08 – 2.03 (m, 2 H), 1.97 – 1.94 (m, 3 H), 1.60 – 1.56 (s, 4 H), 1.34 - 1.31 (m, 1 H), 1.30- 1.19 (m, 3 H)	600.3

BIOLOGICAL EXAMPLE 1

Chemiluminescence assay of the Compounds

[0625] The ability of compounds to inhibit the activation of CCR2 receptor was measured using PathHunter β-Arrestin engineered cell lines (DiscoverX; 93-0192C1) and Chemiluminescence method, by detecting β-Arrestin recruitment. The assay procedure is as follows: 5000 cells in 20 µL of plating medium (DiscoverX; 93-0563R7A) were seeded into a white Opaque 384-well microplate (Perkin Elmer Cat# 6007680) and incubated overnight at 37 °C and 5% CO_2. Next, 5 µL of diluted compounds (6X) in assay buffer (HBSS; 20mM HEPES) was added to the 384 well plate and incubated at 37 °C and 5% CO_2 for 30min. Following this 5 µL of 6X agonist/ligand MCP-1 (PeproTech; 300-04-250) to final 10 nM concentration was added and incubated at 37 °C and 5% CO_2 for 90 min. Finally, the reaction was terminated by addition of 15 µL of detection reagent (DiscoverX; 93-0001) which, was incubated at room temperature for 1 h in dark. Plates were then read on a Perkin Elmer Envision for Luminescence signal (using luminescence 700 filter). Each assay plate included wells with no ligand added (unstimulated cell control), wells with ligand alone (MAX stimulated cell control), wells with ligand and reference compound (100% inhibition-MIN control). Percent inhibition was calculated after normalizing to MIN & MAX controls. The IC_{50} of compounds was calculated by GraphPad Prism software (5) using non-linear regression, by plotting percent inhibition versus compound concentration.

[0626] Activity of the tested compounds is provided in Table 3 as follows: ++++ = $IC_{50} \leq 0.5$ µM; +++ = $IC_{50} > 0.5$ µM to < 1 µM; ++ = IC_{50} 1 to < 3 µM; + = $IC_{50} \geq 3$ µM.

Table 3

Ex.	Activity	Ex.	Activity	Ex.	Activity	Ex.	Activity
1	++++	16	++	31	+++	45	+
2	++	17	+++	32	+	46	+
3	++	18	+	33	++++	47	++++
4	++	19	++++	34	++++	48	+
5	++++	20	+	35	++++	49	+
6	++	21	++	36	+	50	+
7	+	22	+	37	++++	51	+
9	+++	23	++++	38	+	52	++++
10	++++	24	+	39	++++	53	++++
11	+	25	++++	40	+	54	+
12	+	27	++++	41	+	55	+
13	+++	28	++	42	+	56	++++
14	+	29	++++	43	++++	57	++
15	++++	30	+++	44	+	58	+++

Ex.	Activity
59	+
60	++++
61	+
62	+
63	++++
64	++
65	++++
66	++
67	++++
68	+
70	++++
80	++++
81	++++
82	+
83	++
84	++++
85	++++
86	++
87	++++
88	++
89	+
90	++++
91	++
92	++++
93	++
94	++++
95	++++
96	++
97	++
98	+
99	++
100	+++
101	Not soluble

Ex.	Activity
102	++++
103	+
104	++++
105	++++
106	++++
107	++
108	++++
109	++
110	++++
111	++++
112	+
113	++
114	+
115	++++
116	++++
117	++++
118	+
119	+
120	++++
121	+
122	++++
123	++++
124	++++
125	++
126	+
127	+
128	+
129	+
130	++++
131	++++
132	++
133	+
134	++++

Ex.	Activity
135	++++
136	++++
137	++
138	++++
139	++++
140	++
141	++++
142	+
143	+
144	++++
145	++++
146	+
147	++++
148	+
149	++++
150	++
151	++++
152	++++
153	++++
154	+
155	++++
156	+
157	++++
158	++
159	++++
160	++
161	++++
162	++
163	++++
164	+
165	+
166	+
167	++++

Ex.	Activity
168	++++
169	++++
170	++++
171	++++
172	+
173	++++
174	++
175	++++
176	++
177	++++
178	+++
179	+
180	+
181	+++
182	+
183	++++
184	+
185	++++
186	+++
187	++++
188	++++
189	++++
190	++++
191	++++
192	++++
193	++++
194	++++
195	++++
196	++++
197	+
198	++++
199	++++
200	++++

Ex.	Activity
201	+
202	++++
203	++++
204	++++
205	++
206	++++
207	++++
208	++++
209	++++
210	++++
211	++
212	+++
213	+
214	++++
215	++
216	++++

Ex.	Activity
217	++++
218	++++
219	+++
220	++++
221	++
222	++
223	+
224	++++
225	++
226	++++
227	+
228	+
229	+
230	+
231	+
232	+

Ex.	Activity
233	+
234	++++
235	++++
236	++++
237	++++
238	++++
239	++++
240	++++
241	++++
242	++++
243	++++
244	++++
245	++
246	++++
247	++++
248	++++

Ex.	Activity
249	++++
250	++++
251	+++
252	++++
253	++++
254	++++
255	++++
256	++++
257	+
258	++
259	+
260	++++
261	++
262	++++
263	+++

BIOLOGICAL EXAMPLE 2

Calcium mobilization assay

[0627] The ability of compounds to inhibit the activation of CCR2 receptor was measured in THP-1 cells (ATCC; TIB-202) using a fluorescence method by detecting intracellular calcium flux. The assay procedure is as follows: 20000 cells in 20 µL of assay buffer (HBSS; 20 mM HEPES) were seeded into an optically clear bottom 384-well microplate (Perkin Elmer Cat# 6007550) and incubated for 1 h at 37 °C and 5% CO_2. Then cells were loaded with calcium 6 dye (Molecular devices; R8191) following 1 h incubation at 37 °C and 5% CO_2. Next 10 µL of diluted compounds (5X) in assay buffer (HBSS; 20 mM HEPES) was added to the 384 well plate and incubated at room temperature for 30min. Following this 10 µL of 6X agonist/ligand MCP-1 (PeproTech; 300-04-250) to final 100 nM conc. was dispensed to the cell plate by FLIPR Penta instrument (Molecular devices) and scanned fluorescent signal at every second over 1 minute to measure changes in intracellular calcium levels. Each assay plate included wells with no ligand added (unstimulated cell control), wells with ligand alone (MAX stimulated cell control), wells with ligand and reference compound (100% inhibition-MIN control). Percent inhibition was calculated after normalizing to MIN & MAX controls. The IC_{50} of compounds was calculated by GraphPad Prism software (5) using non-linear regression, by plotting percent inhibition versus compound concentration.

[0628] In the table below, activity of the tested compounds is provided in Table 4 as follows: ++++ = $IC_{50} \leq 0.5\ \mu M$; +++ = $IC_{50} > 0.5\ \mu M$ to $< 1\ \mu M$; ++ = IC_{50} 1 to 3 μM; + = $IC_{50} > 3\ \mu M$.

Table 4

Ex.	Activity	Ex.	Activity	Ex.	Activity	Ex.	Activity
1	++++	60	++++	131	++++	185	++++
2	++++	63	++++	134	++++	186	++++
3	++	65	++++	135	++++	187	++++
4	+	70	++++	136	++++	189	++++
5	++++	80	++++	138	++++	190	++++
6	+	83	++	139	++++	191	++++
7	+	84	++++	141	++++	192	++
9	++	85	++++	144	++++	193	++++
10	++++	87	++++	145	++++	194	++++
13	+	90	++++	147	++++	195	++++
15	+++	92	++++	149	++++	196	++++
16	+	94	++++	151	++++	197	+
17	+	95	++++	152	+++	198	++++
19	++++	100	++++	153	++++	199	++++
21	+	102	++++	155	++++	200	++++
23	+++	104	++++	157	++++	202	++++
25	++++	105	++++	159	++++	206	++++
27	++++	106	++++	161	++++	207	++++
28	+	108	++++	163	++++	208	++++
29	++++	110	++++	167	++++	210	++++
30	++	111	+++	168	++++	214	++++
31	++	115	++++	169	++++	216	++++
33	++++	116	++++	170	++++	218	++++
35	++++	117	++++	171	++++	220	++++
37	++++	118	+	173	++++	224	++++
39	++++	119	+	175	++++	234	++++
43	++++	120	++++	177	++++	235	+++
47	++++	122	++++	178	++++	236	++++
52	++++	123	++++	181	++++	238	++++
53	++++	124	++++	183	++++	239	++++
58	++++	130	++++	184	+	240	++++

Ex.	Activity
242	++++
244	++++

Ex.	Activity
246	++++
247	++++

Ex.	Activity
248	++++
249	++++

[0629] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

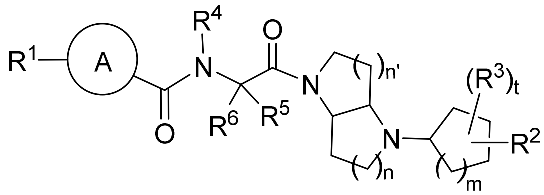
[0630] The disclosure illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including,” “containing”, etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure.

[0631] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

[0632] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 1 or 2;

n′ is 1 or 2;

m is 0, 1, or 2;

t is 0, 1, 2, 3, 4, 5, or 6;

ring A is aryl or heteroaryl; wherein the aryl or heteroaryl is independently optionally substituted with one to five Z^1;

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-OC(O)R^{11}$, $-C(O)N(R^{11})_2$, $-NR^{11}C(O)R^{11}$, $-OC(O)N(R^{11})_2$, $-NR^{11}C(O)OR^{11}$, $-S(O)_{0-2}R^{11}$, $-NR^{11}S(O)_{1-2}R^{11}$, $-NR^{11}C(O)N(R^{11})_2$, or $-NR^{11}S(O)_{1-2}N(R^{11})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to six Z^1;

R^2 is C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, $-L^1-C_{3-10}$ cycloalkyl, $-L^1$-heterocyclyl, $-L^1$-aryl, or $-L^1$-heteroaryl; wherein each C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to five Z^1; or

R^2 and R^3 together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1;

L^1 is -O-, $-NR^7C(O)-$, $-C(O)NR^7-$, $-C(O)NR^7-C_{1-3}$ alkylene-, or $-NR^7(O)-C_{1-3}$ alkylene-;

each R^3 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{13}$, $-N(R^{13})_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{13})_2$, $-NR^{14}C(O)R^{13}$, $-OC(O)N(R^{13})_2$, $-NR^{13}C(O)OR^{13}$, $-S(O)_{0-2}R^{13}$, $-NR^{13}S(O)_{1-2}R^{13}$, $-NR^{13}C(O)N(R^{13})_2$, or $-NR^{13}S(O)_{1-2}N(R^{13})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to six Z^1; or two R^3 together with the atoms to which they are attached form a cycloalkyl, heterocyclyl, aryl, or heteroaryl ring; wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to eight Z^1;

R^4 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one to eight Z^1;

R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{15})_2$, $-NR^{15}C(O)R^{15}$, $-OC(O)N(R^{15})_2$, $-NR^{15}C(O)OR^{15}$, $-S(O)_{0-2}R^{15}$, $-NR^{15}S(O)_{1-2}R^{15}$, $-NR^{15}C(O)N(R^{15})_2$, or $-NR^{15}S(O)_{1-2}N(R^{15})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

R^7 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl;

each Z^1 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10}$, $-N(R^{10})_2$, $-C(O)R^{10}$, $-C(O)OR^{10}$, $-OC(O)R^{10}$, $-C(O)N(R^{10})_2$, $-NR^{10}C(O)R^{10}$, $-OC(O)N(R^{10})_2$, $-NR^{10}C(O)OR^{10}$, $-S(O)_{0-2}R^{10}$, $-NR^{10}S(O)_{1-2}R^{10}$, $-NR^{10}C(O)N(R^{10})_2$, or $-NR^{10}S(O)_{1-2}N(R^{10})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{10} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{11} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{13} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each R^{15} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1a};

each Z^{1a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, $-NO_2$, $-SF_5$, $-OR^{10a}$, $-N(R^{10a})_2$, $-C(O)R^{10a}$, $-C(O)OR^{10a}$, $-OC(O)R^{10a}$, $-C(O)N(R^{10a})_2$, $-NR^{10}C(O)R^{10a}$, $-OC(O)N(R^{10a})_2$, $-NR^{10a}C(O)OR^{10a}$, $-S(O)_{0-2}R^{10a}$, $-NR^{10a}S(O)_{1-2}R^{10a}$, $-NR^{10a}C(O)N(R^{10a})_2$, or $-NR^{10a}S(O)_{1-2}N(R^{10a})_2$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each R^{10a} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl is independently optionally substituted with one to five Z^{1b};

each Z^{1b} is independently halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, heteroaryl, -L-C_{1-6} alkyl, -L-C_{2-6} alkenyl, -L-C_{2-6} alkynyl, -L-C_{1-6} haloalkyl, -L-C_{3-10} cycloalkyl, -L-heterocyclyl, -L-aryl, or -L-heteroaryl; and

each L is independently -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, -N(C_{1-6} alkyl)-, -N(C_{2-6} alkenyl)-, -N(C_{2-6} alkynyl)-, -N(C_{1-6} haloalkyl)-, -N(C_{3-10} cycloalkyl)-, -N(heterocyclyl)-, -N(aryl)-, -N(heteroaryl)-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N(C_{1-6} alkyl)-, -C(O)N(C_{2-6} alkenyl)-, -C(O)N(C_{2-6} alkynyl)-, -C(O)N(C_{1-6} haloalkyl)-, -C(O)N(C_{3-10} cycloalkyl)-, -C(O)N(heterocyclyl)-, -C(O)N(aryl)-, -C(O)N(heteroaryl)-, -OC(O)NH-, -OC(O)N(C_{1-6} alkyl)-, -OC(O)N(C_{2-6} alkenyl)-, -OC(O)N(C_{2-6} alkynyl)-, -OC(O)N(C_{1-6} haloalkyl)-, -OC(O)N(C_{3-10} cycloalkyl)-, -OC(O)N(heterocyclyl)-, -OC(O)N(aryl)-, -OC(O)N(heteroaryl)-, -NHC(O)-, -N(C_{1-6} alkyl)C(O)-, -N(C_{2-6} alkenyl)C(O)-, -N(C_{2-6} alkynyl)C(O)-, -N(C_{1-6} haloalkyl)C(O)-, -N(C_{3-10} cycloalkyl)C(O)-, -N(heterocyclyl)C(O)-, -N(aryl)C(O)-, -N(heteroaryl)C(O)-, -NHC(O)O-, -N(C_{1-6} alkyl)C(O)O-, -N(C_{2-6} alkenyl)C(O)O-, -N(C_{2-6} alkynyl)C(O)O-, -N(C_{1-6} haloalkyl)C(O)O-, -N(C_{3-10} cycloalkyl)C(O)O-, -N(heterocyclyl)C(O)O-, -N(aryl)C(O)O-, -N(heteroaryl)C(O)O-, -NHC(O)NH-, -NHS(O)-, $-NHS(O)_2NH$, -S(O)NH-, $-S(O)_2NH$, -NHS(O)NH-, or $-NHS(O)_2NH-$;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, -OH, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl.

2. The compound of claim 1, wherein R^5 and R^6 are both hydrogen or are both C_{1-3} alkyl.

3. The compound of claim 1 or 2, wherein R^4 is hydrogen.

4. The compound of any one of claims 1-3, wherein n′ is 1.

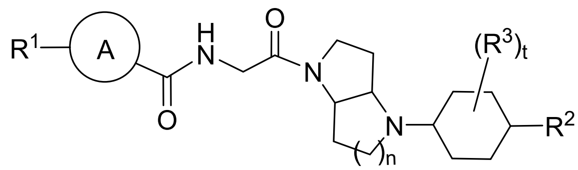
5. The compound of any one of claims 1-3, wherein n′ is 2.

6. The compound of any one of claims 1-5, wherein m is 0.

7. The compound of any one of claims 1-5, wherein m is 1.

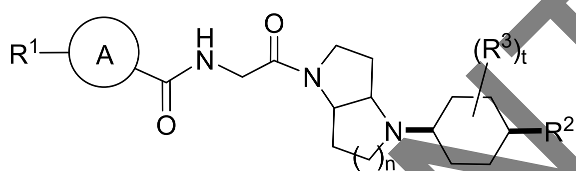
8. The compound of any one of claims 1-5, wherein m is 2.

9. The compound of claim 1, wherein the compound is represented by Formula IA:



IA.

10. The compound of claim 1, wherein the compound is represented by Formula IIA:



IIA.

11. The compound of any preceding claim, wherein t is 0 or 1.

12. The compound of any preceding claim, wherein t is 0, 1, or 2; and each R^3 is independently fluoro, $-NH_2$, -OH, $-C(O)NH_2$, -C(O)OH, or R^2 and R^3 together with the atom(s) to which they are attached form a heterocyclyl or heteroaryl ring.

13. The compound of any of claims 1-10, wherein t is 2.

14. The compound of claim 13, wherein one R^3 is methyl or fluoro, and a second R^3 is hydroxy.

15. The compound of any preceding claim, wherein ring A is aryl.

16. The compound of claim 15, wherein ring A is phenyl.

17. The compound of any preceding claim, wherein ring A is heteroaryl.

18. The compound of claim 17, wherein ring A is pyridyl.

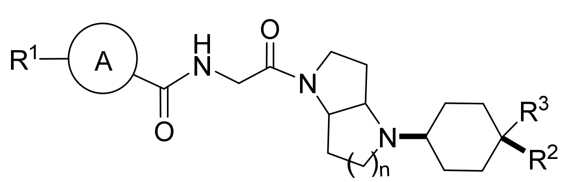
19. The compound of claim 17, wherein ring A is benzo[d]isoxazole.

20. The compound of any preceding claim, wherein R^1 is halo, $-C(O)OR^{11}$, or C_{1-6} haloalkyl.

21. The compound of claim 20, wherein R^1 is fluoro, -C(O)OH, $-C(O)OCH_3$, or trifluoromethyl.

22. The compound of any preceding claim, wherein each R^3 is independently halo, $-NH_2$, or -OH.

23. The compound of claim 1, wherein the compound is represented by Formula IIIA:



IIIA.

24. The compound of any one of claims 1-23, wherein n is 1.

25. The compound of any one of claims 1-23, wherein n is 2.

26. The compound of any one of claims 1-25, wherein R^2 is C_6 aryl, 5 or 6-membered heteroaryl, -O-aryl, or -O-heteroaryl; wherein each aryl or heteroaryl is optionally substituted with one to five Z^1.

27. The compound of any one of claims 1-25, wherein R^2 is aryl or heteroaryl; wherein the aryl or heteroaryl is optionally substituted with one to five Z^1.

28. The compound of claim 27, wherein R^2 is phenyl optionally substituted with one to five Z^1.

29. The compound of claim 27, wherein R^2 is phenyl, pyridyl, -O-pyridyl, -NHC(O)-pyridyl, -C(O)NHCH$_2$-pyridyl, -O-phenyl, quinolinyl, pyrimidinyl, thiazolyl, oxazolyl, imizadolyl, imidazo[1,2-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, or imidazo[1,5-a]pyridinyl; wherein each is optionally substituted with one to five Z^1.

30. The compound of claim 27, wherein R^2 is [1,2,4]triazolo[1,5-a]pyridinyl or oxazolyl; wherein each is optionally substituted with one to five Z^1.

31. The compound of any one of claims 1-26, wherein R^2 is O-aryl or -O-heteroaryl; wherein each aryl or heteroaryl is optionally substituted with one to five Z^1.

32. The compound of claim 31, wherein R^2 is O-phenyl or -O-pyridyl; wherein each is optionally substituted with one to five Z^1.

33. The compound of any preceding claims, wherein each Z^1 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, -OR^{10}, -N(R^{10})$_2$, -C(O)OR^{10}, -C(O)N(R^{10})$_2$, -NR^{10}C(O)R^{10}, pyrimidinyl, pyridazinyl, oxazolyl, imidazolyl, pyrrolidinyl, triazolyl, thiazolyl, tetrazolyl, pyridinyl, piperazinyl, pyrazinyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, oxadiazolyl, 1,1-dioxothiomorpholinyl, 3-oxopiperazinyl, 2-oxo-1,2-dihydropyridinyl, 2-oxopyrrolidinyl, piperidin-2-onyl, imidazolidin-2-onyl, 1,3,4-oxadiazol-2(3H)-onyl, 6-azaspiro[2.5]octanyl, 1,2,3,6-tetrahydropyridinyl, azetidinyl, 8-azabicyclo[3.2.1]octanyl, or morpholino, wherein each is independently substituted with one to five Z^{1a}.

34. A compound selected from Table 1 or Table 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof.

35. A pharmaceutical composition comprising a compound of any preceding claim, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, and a pharmaceutically acceptable carrier.

36. A method for treating a disease or condition mediated, at least in part, by CCR2, the method comprising administering an effective amount of the pharmaceutical composition of claim 35 to a subject in need thereof.

37. A method for treating inflammation, inflammation, rheumatoid arthritis, atherosclerosis, neuropathic pain, lupus, systemic lupus erythematosus, fibrosis, immune disorders, transplant rejection,

neuroinflammation, acute brain injury, solid tumors, metabolic disease, or cancer, comprising administering an effective amount of the pharmaceutical composition of claim 35 to a subject in need thereof.

38. The method of claim 37, wherein the disease is systemic lupus erythematosus or lupus nephritis.

39. Use of a compound of any one of claims 1-34, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for treating a disease or condition mediated, at least in part, by CCR2.

40. The use of claim 39, wherein the disease or condition is inflammation, rheumatoid arthritis, atherosclerosis, neuropathic pain, lupus, systemic lupus erythematosus, fibrosis, immune disorders, transplant rejection, neuroinflammation, acute brain injury, solid tumors, metabolic disease, or cancer.

41. A compound of any one of claims 1-34, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.

42. A compound of any one of claims 1-34, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in treating systemic lupus erythematosus or lupus nephritis.

ABSTRACT

The present disclosure relates generally to small molecule modulators of chemotactic cytokines (chemokine) receptors CCR2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, and methods of making and using thereof.