COMPOUNDS, COMPOSITIONS, AND METHODS

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.

[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] In another embodiment, provided is a method for treating a disease or condition, at least in part, by inhibiting 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.

[0013] 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

[0014] 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

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] "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., $-CH(CH_3)_2$).

[0020] 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.

[0021] "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).

[0022] "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.

[0023] "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.

[0024] "Alkoxyalkyl" refers to the group "alkyl-O-alkyl".

[0025] "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.

[0026] "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.

[0027] "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.

[0028] "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.

[0029] "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.

[0030] "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.

[0031] "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., $C_{6\text{-}20}$ aryl), 6 to 12 carbon ring atoms (i.e., $C_{6\text{-}12}$ aryl), or 6 to 10 carbon ring atoms (i.e., $C_{6\text{-}10}$ 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.

[0032] "Arylalkyl" or "Aralkyl" refers to the group "aryl-alkyl-".

[0033] "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.

[0034] "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.

[0035] "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.

[0036] "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.

[0037] "Cycloalkoxy" refers to "-O-cycloalkyl."

[0038] "Cycloalkylalkyl" refers to the group "cycloalkyl-alkyl-".

[0039] "Cycloalkylalkoxy" refers to "-O-alkyl-cycloalkyl."

[0040] "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.

[0041] "Hydrazino" refers to $-NHNH_2$.

[0042] "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.

[0043] "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.

[0044] "Halogen" or "halo" refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0045] "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.

[0046] "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.

[0047] "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.

[0048] "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.

[0049] "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.

[0050] "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, 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.

[0051] "Heteroarylalkyl" refers to the group "heteroaryl-alkyl-".

[0052] "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 containing at least one heteroatom 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 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, thiophenyl (i.e., thienyl), 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.

[0053] "Heterocyclylalkyl" refers to the group "heterocyclyl-alkyl-".

[0054] "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.

[0055] "Sulfonyl" refers to the group $-S(O)_2R^y$, 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.

[0056] "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.

[0057] "Sulfonamido" refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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 $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^gR^h$, $-CH_2SO_2R^g$, or $-CH_2SO_2NR^gR^h$. 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] The term “hydrate” refers to the complex formed by the combining of a compound described herein and water.

[0072] 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.

[0073] 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.

[0074] The compounds of the invention, 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 invention 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.

[0075] 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 invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

[0076] "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

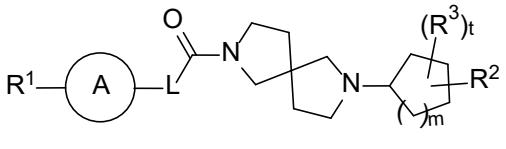
[0077] Relative centers of the compounds as depicted herein are indicated graphically using the "thick bond" style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[0078] "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

[0079] Provided herein are compounds that are modulators of chemotactic cytokines (chemokine) receptor CCR2 (e.g., CCR2 antagonists).

[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:

L is [a]-NR^4CH_2-, -NR^4-, -4 to 10-membered cycloalkyl-, [a]-NR^4-4 to 10-membered cycloalkyl-, -4 to 10-membered heterocyclyl-, or [a]-4 to 10 membered heterocyclyl-NR^4-, [a]-C(O)-4 to 10 membered heteroaryl-, -5 to 10-membered heteroaryl-; wherein bond [a]- is attached to ring A; and further wherein the cycloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to five R^5;

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}, -$N(R^{13})_2$, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{13})_2$, -$NR^{13}C(O)R^{13}$, -$OC(O)N(R^{13})_2$, -$NR^{13}C(O)OR^{13}$, -$S(O)_{0-2}R^{13}$, -$NR^{13}S(O)_{1-2}R^{13}$, -$NR^{13}C(O)N(R^{13})_2$, 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;

each R^5 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^{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}$$R^{15}$, -N$R^{15}$S(O)$_{1-2}$$R^{15}$, -N$R^{15}$C(O)N($R^{15}$)$_2$, or -N$R^{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}$$R^{10}$, -N$R^{10}$S(O)$_{1-2}$$R^{10}$, -N$R^{10}$C(O)N($R^{10}$)$_2$, or -N$R^{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 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}$$R^{10a}$, -N$R^{10a}$S(O)$_{1-2}$$R^{10a}$, -N$R^{10a}$C(O)N($R^{10a}$)$_2$, or -N$R^{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 $-NHS(O)_2NH-$;

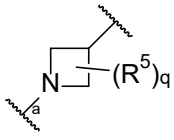
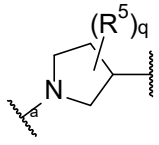
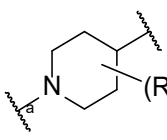
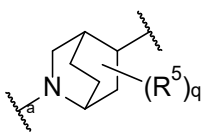
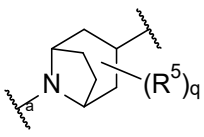
wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, 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^4 is hydrogen.

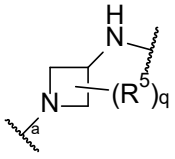
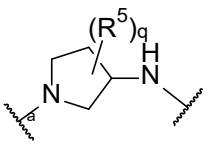
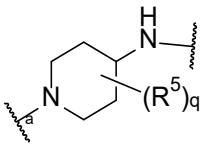
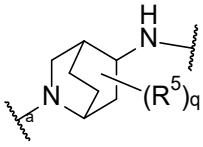
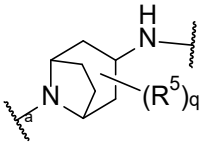
[0082] In certain embodiments, L is ^{a}-$NHCH_2$-.

[0083] In certain embodiments, L is ^{a}-NH-.

[0084] In certain embodiments, L is a 4 to 10-membered monocyclic or bridged heterocyclyl optionally substituted with one to five R^5.

[0085] In certain embodiments, L is  ,  ,  ,  , or  , wherein q is 0, 1, 2, 3, 4, or 5.

[0086] In certain embodiments, L is ^{a}-4 to 10 membered monocyclic or bridged heterocyclyl-NR^4- optionally substituted with one to five R^5.

[0087] In certain embodiments, L is  ,  ,  ,  , or  , wherein q is 0, 1, 2, 3, 4, or 5.

[0088] In certain embodiments, L is a 5 to 6-membered heteroaryl optionally substituted with one to five R^5.

[0089] In certain embodiments, L is ^{a}-C(O)-4 to 10 membered heteroaryl- optionally substituted with one to five R^5.

[0090] In certain embodiments, L is imidazolyl or oxazolyl.

[0091] In certain embodiments, L is a 4 to 10-membered cycloalkyl optionally substituted with one to five R^5.

[0092] In certain embodiments, L is ^{a}-NR^4-4 to 10-membered cycloalkyl- optionally substituted with one to five R^5.

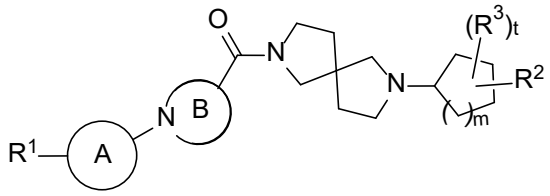
[0093] In certain embodiments, the cyclobutyl or bicyclo[1.1.1]pentyl.

[0094] In certain embodiments, each R^5 is independently halo or C_{1-6} alkyl.

[0095] In certain embodiments, each R^5 is independently fluoro or methyl.

[0096] In certain embodiments, q is 0, 1 or 2.

[0097] In certain embodiments, provided is a compound of Formula IA:



IA

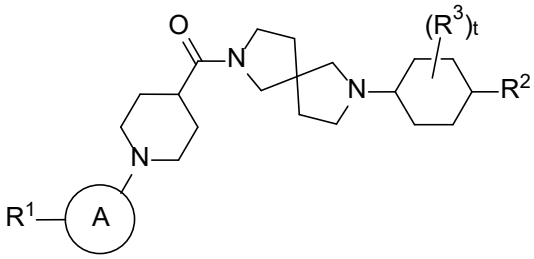
wherein R^1, R^2, R^3, t, m, and ring A are each independently as defined herein, and ring B is a 4 to 10-membered monocyclic or bridged heterocyclyl optionally substituted with one to five R^5.

[0098] In certain embodiments, m is 0.

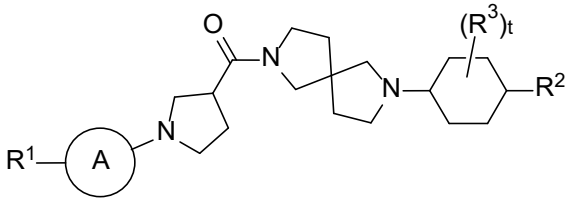
[0099] In certain embodiments, m is 1.

[0100] In certain embodiments, m is 2.

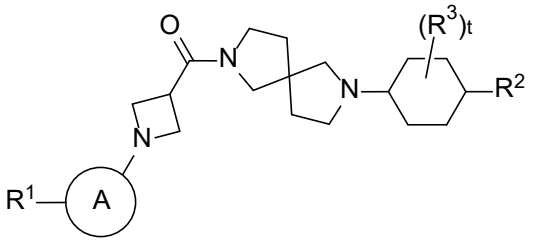
[0101] In certain embodiments, provided is a compound of Formula IIA, IIB, IIC, or IID:



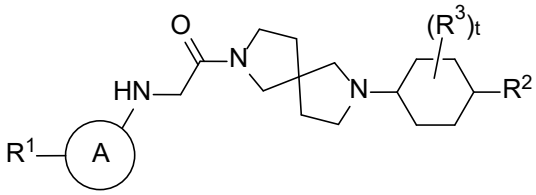
IIA



IIB



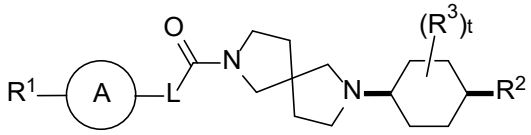
IIC



IID

wherein R^1, R^2, R^3, L, t, and ring A are each independently as defined herein.

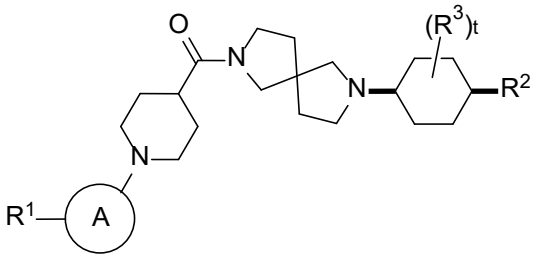
[0102] In certain embodiments, provided is a compound of Formula III:



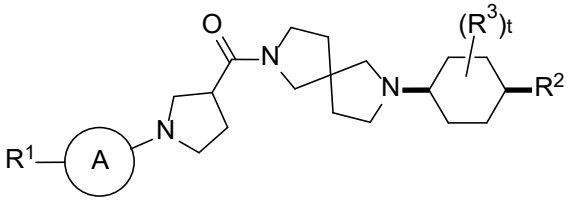
III

wherein R^1, R^2, R^3, L, t, and ring A are each independently as defined herein.

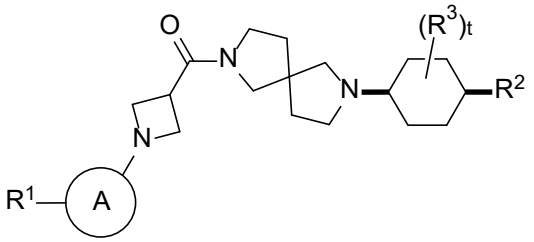
[0103] In certain embodiments, provided is a compound of Formula IIIA, IIIB, IIIC, or IIID:



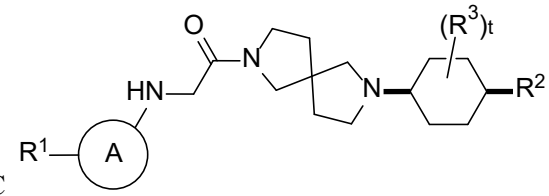
IIIA



IIIB



IIIC



IIID

wherein R^1, R^2, R^3, t, and ring A are each independently as defined herein.

[0104] In certain embodiments, ring A is aryl.

[0105] In certain embodiments, ring A is phenyl.

[0106] In certain embodiments, ring A is heteroaryl.

[0107] In certain embodiments, ring A is benzo[d]isoxazole.

[0108] In certain embodiments, R^1 is C_{1-6} haloalkyl.

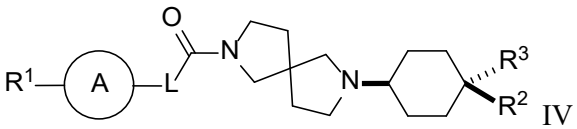
[0109] In certain embodiments, R^1 is trifluoromethyl.

[0110] In certain embodiments, each R^3 is independently halo or hydroxy.

[0111] In certain embodiments, t is 0 or 1.

[0112] In certain embodiments, t is 1; and R^3 is hydroxy.

[0113] In certain embodiments, provided is a compound of Formula IV:

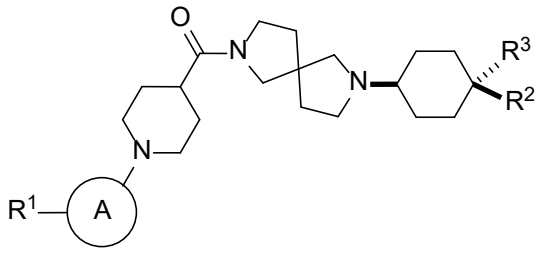


IV

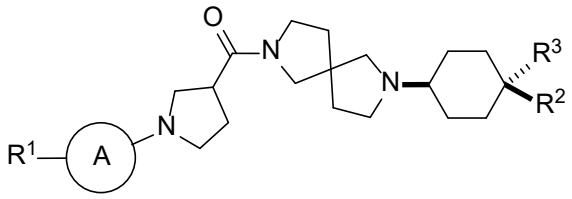
wherein R^1, R^2, R^3, L, and ring A are each independently as defined herein.

[0114] In certain embodiments, R^3 is hydroxy.

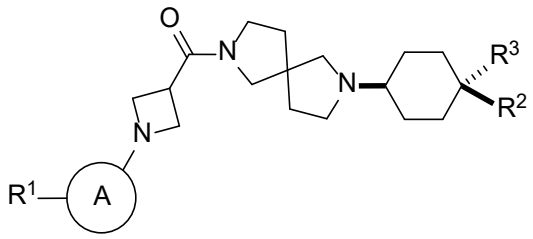
[0115] In certain embodiments, provided is a compound of Formula IVA, IVB, IVC, or IVD:



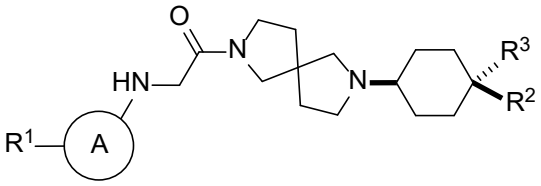
IVA



IVB



IVC



IVD

wherein R^1, R^2, R^3, and ring A are each independently as defined herein.

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

[0117] In certain embodiments, R^2 is aryl optionally substituted with one to five Z^1.

[0118] In certain embodiments, R^2 is phenyl optionally substituted with one to five Z^1.

[0119] In certain embodiments, R^2 is heteroaryl optionally substituted with one to five Z^1.

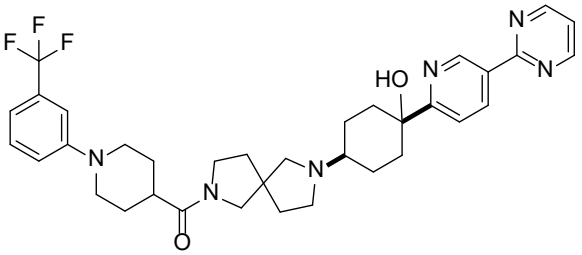
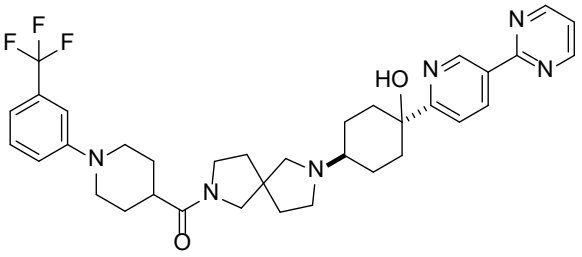
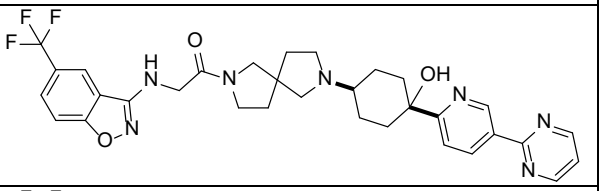
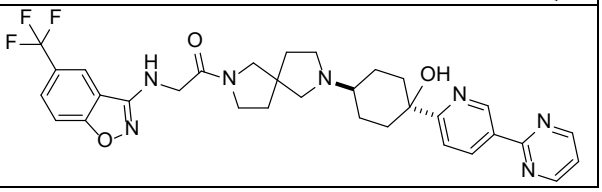
[0120] In certain embodiments, R^2 is pyridyl optionally substituted with one to five Z^1.

[0121] In certain embodiments, R^2 is optionally substituted with one to five heteroaryl or $-OR^{10}$.

[0122] In certain embodiments, R^2 is optionally substituted with pyrimidyl or methoxy.

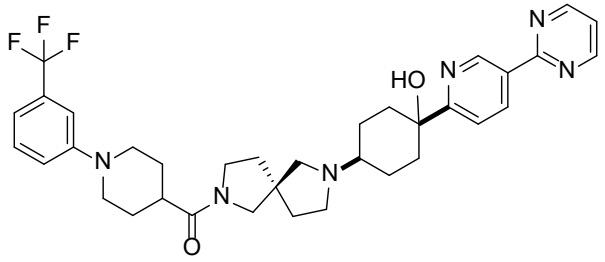
[0123] In certain embodiments, provided is a compound selected from Table 1, or a pharmaceutically acceptable salt, isotopically enriched analog, stereoisomer, mixture of stereoisomers, or prodrug thereof.

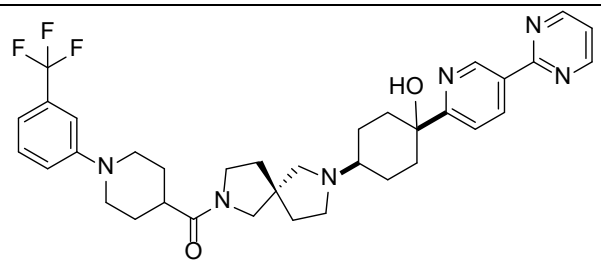
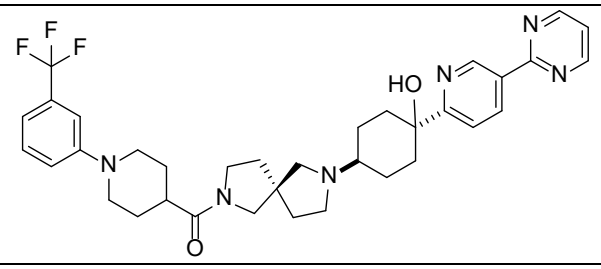
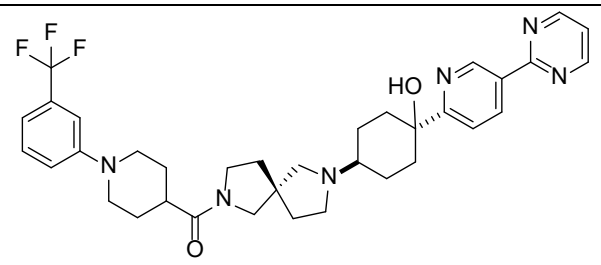
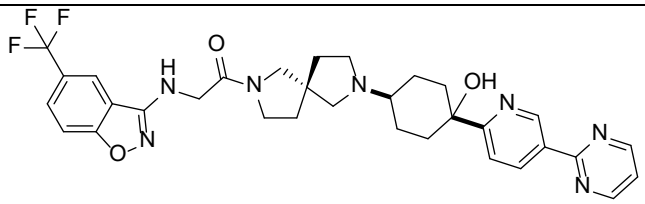
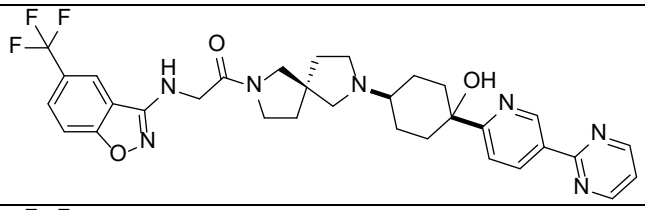
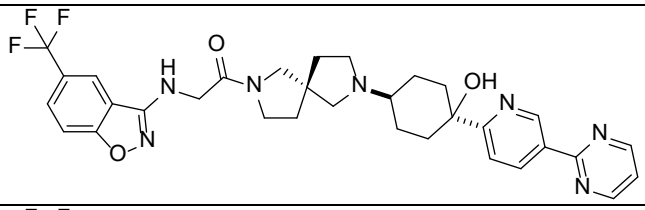
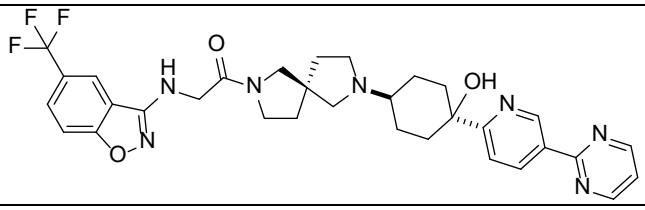
Table 1

Ex. No.	Structure
1	
2	
3	
4	

[0124] 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








3. Methods

[0125] "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.

[0126] "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.

[0127] "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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] In certain embodiments, the compounds disclosed herein can be used to treat an allergy.

[0134] 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.

[0135] In certain embodiments, the compounds disclosed herein can be used to treat inflammatory disorders.

[0136] 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.

[0137] 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.

[0138] 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 Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, insulin resistance or Tabes dorsalis.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] In embodiments, provided herein are compounds or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.

[0144] 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

[0145] 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.

[0146] 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

[0147] 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.).

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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

[0156] 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

[0157] 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.

[0158] 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.

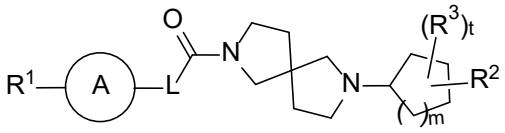
[0159] Additionally, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well 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.

[0160] 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.

[0161] 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).

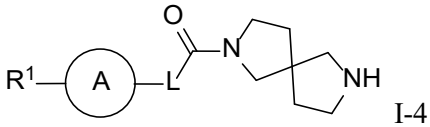
General Synthesis Method I

[0162] In certain embodiments, provided is a method of preparing a compound of Formula I:



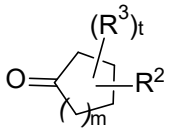
I

comprising coupling a compound of Formula I-4:



I-4

with a compound of Formula I-5:

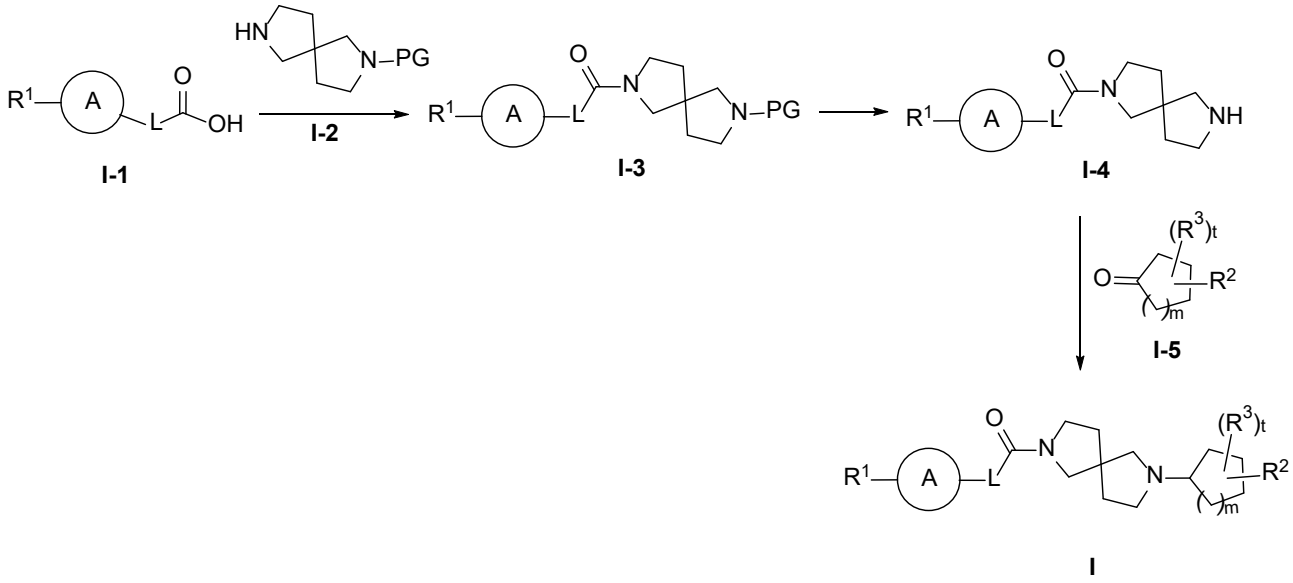


I-5

under conditions suitable to provide a compound of Formula I, wherein L, ring A, R^1, R^2, R^3, m, and t are as defined herein.

[0163] 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, L, ring A, R^1, R^2, R^3, m, and t are as defined herein, and PG is a suitable amine protecting group (e.g., BOC).

Scheme I



[0164] Referring to Scheme I, compound I-3 can be provided by contacting I-1 with compound I-2 under amide coupling conditions. Deprotection of compound I-3 provides compound I-4, or a salt thereof. Coupling of compound I-4 with compound I-5 under reductive amination conditions provides Formula I.

[0165] Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art. For any compound shown in Scheme I, it should be understood that various derivatives can be provided by functional group interconversion at any step. In some embodiments, the various substituents of Formula I-1, I-2, I-3, I-4, or I-5 are as defined herein. However, derivatization of compounds I-1, I-2, I-3, I-4, or I-5 prior to reacting in any step, and/or further derivatization of the resulting reaction product, provides various compounds of Formula I. Appropriate starting materials and reagents can be purchased or prepared by methods known to one of skill in the art. Upon each reaction completion, each of the intermediate or final compounds can be recovered, and optionally purified, by conventional techniques such as neutralization, extraction, precipitation, chromatography, filtration, and the like. Other modifications to arrive at compounds of this disclosure are within the skill of the art.

[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. It should be appreciated that various isomers of Formula I can be separated as well.

EXAMPLES

[0167] 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

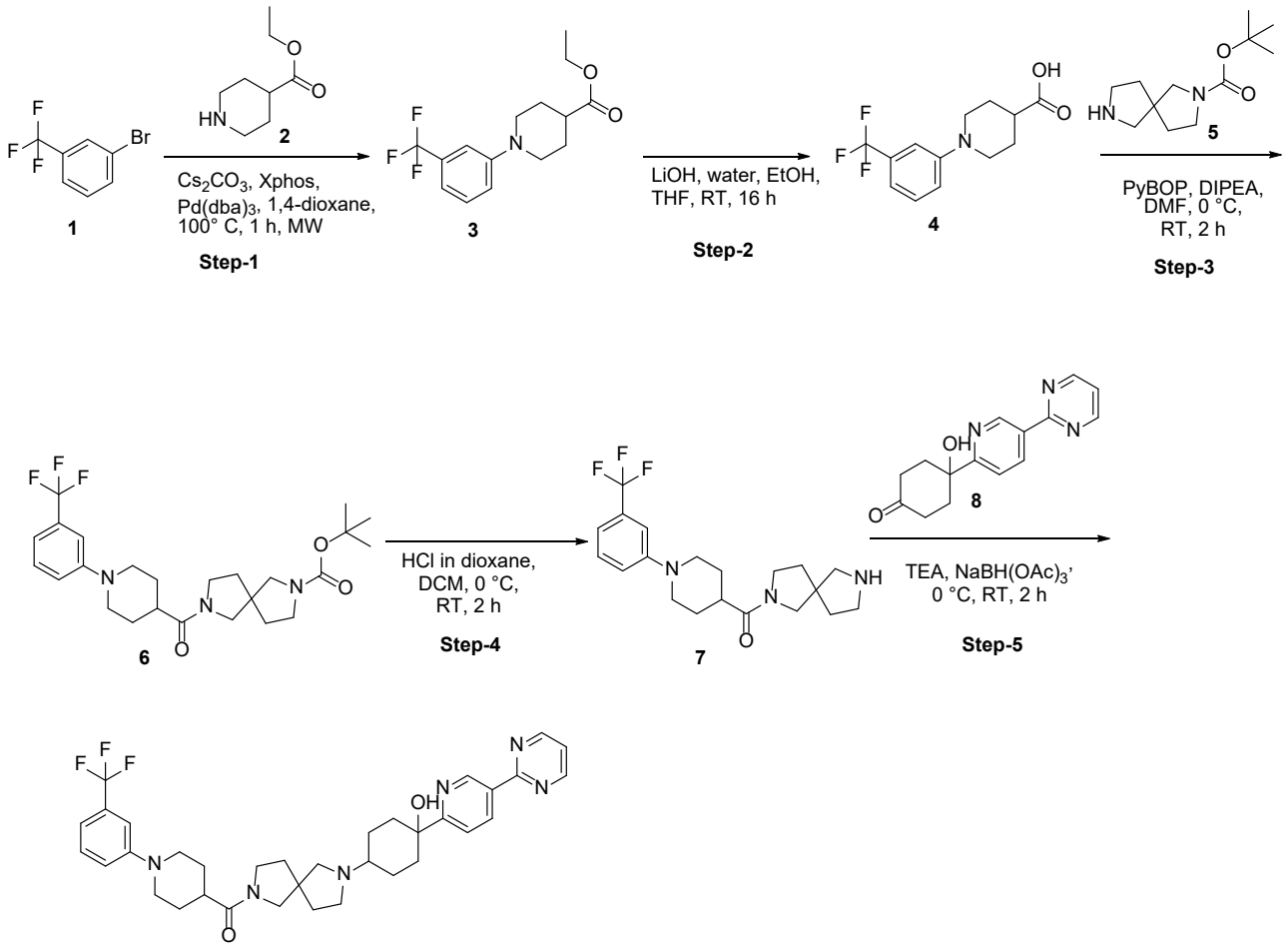
[0168] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[0169] **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.

[0170] **Thin Layer Chromatography:** Analytical TLC plates from Merck were used for reaction monitoring using solvent system as mentioned in the procedures described below. For preparative TLC for compound purification, silica loaded preparative thin layer chromatography plates were used and solvent systems used are mentioned in the procedures described below.

[0171] **Liquid Chromatography-Mass Spectrometry and High-Performance Liquid Chromatography Analysis:** LCMS and HPLC data were generated using instruments from Water both for LCMS and HPLC (preparative and analytical).

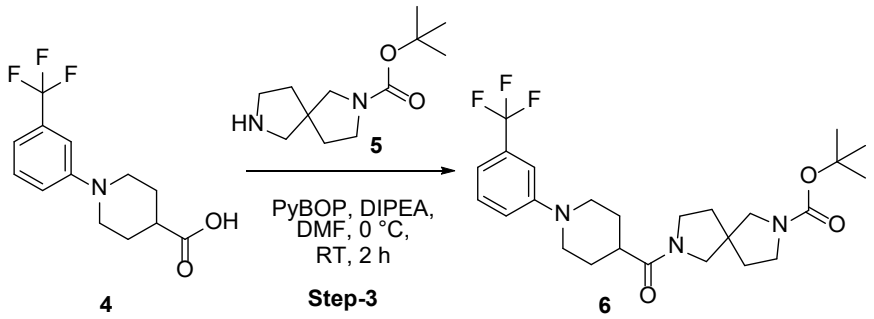
Procedure 1: Synthesis of Example 1 & Example 2



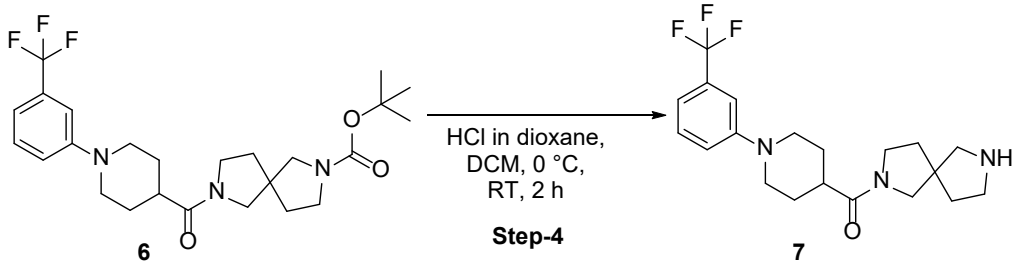
[0172] Preparation of ethyl 1-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylate: To a stirred solution of 1-bromo-3-(trifluoromethyl)benzene (1 g, 4.44 mmol,) in 1,4-dioxane (12 mL) was added ethyl piperidine-4-carboxylate (908 mg, 5.78 mmol) and caesium carbonate (2.90 g, 8.89 mmol). Reaction mixture was purged with N_2 for 10 minutes, after that dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (212 mg, 0.444 mmol) and tris(1,5-diphenylpenta-1,4-dien-3-one) dipalladium (203 mg, 0.222mmol) were added, and the reaction mixture was stirred at 100 °C for 1 h in microwave. The reaction 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 provided crude product, which was purified by flash column to afford ethyl 1-[3-(trifluoromethyl)phenyl]piperidine-4-carboxylate. LC-MS (ESI) m/z: 301.0 $[M+H]^+$.

[0173] Preparation of 1-(3-(trifluoromethyl)phenyl)piperidine-4-carboxylic acid: To a stirred solution of ethyl 1-[3-(trifluoromethyl)phenyl]piperidine-4-carboxylate (1.2 g, 4.65 mmol) in THF (10 mL) and ethanol (2 mL) was added lithium hydroxide (585 mg, 13.9 mmol) in water (4 mL), and the reaction mixture was stirred at RT for 16h. The reaction mixture was concentrated and the residue was extracted with EtOAc

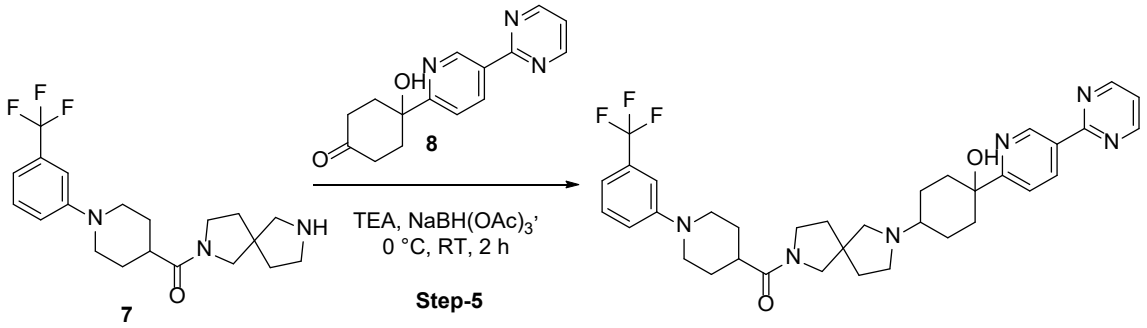
to remove organic impurities. The aqueous layer was neutralised with 1N HCl and then extracted with EtOAc and the organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford 1-[3-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid. LC-MS (ESI) m/z: 273.3 $[M+H]^+$.



[0174] Preparation of tert-butyl 7-(1-(3-(trifluoromethyl)phenyl)piperidine-4-carbonyl)-2,7-diazaspiro[4.4]nonane-2-carboxylate: To a stirred solution of 1-[3-(trifluoromethyl)phenyl]piperidine-4-carboxylic acid (0.25 g, 0.91 mmol, 1 eq) in N,N-dimethylformamide (3 mL) was added tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (0.24 g, 1.1 mmol, 1.2 eq) and DIPEA (1.0 mL, 5.74 mmol, 3 eq), and at 0 °C was added (1H-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)phosphanium; hexafluoro-λ^5-phosphanuide (0.6 g, 1.83 mmol, 2 eq). The reaction mixture was stirred at rt for 2 hours. 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), extracted with ethyl acetate (2x100 mL), and concentrated in vacuo to give the crude product. The crude was purified by flash column chromatography, eluted on 40% EtOAc - Heptane as eluent, to afford tert-butyl 7-{1-[3-(trifluoromethyl)phenyl]piperidine-4-carbonyl}-2,7-diazaspiro[4.4]nonane-2-carboxylate. LC-MS (ESI) m/z: 482.3 $[M+H]^+$.



[0175] Preparation of (2,7-diazaspiro[4.4]nonan-2-yl)(1-(3-(trifluoromethyl)phenyl)piperidin-4-yl)methanone: To a stirred solution of tert-butyl 7-{1-[3-(trifluoromethyl)phenyl]piperidine-4-carbonyl}-2,7-diazaspiro[4.4]nonane-2-carboxylate (0.35 g, 0.72 mmol, 1 eq) in dichloromethane (5 mL) at 0 °C was added 1,4-dioxane hydrochloride (3 mL) drop wise, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure, and then the reaction mixture was triturated with Diethyl ether (20 mL) and pentane (20 mL) to afford 2-{1-[3-(trifluoromethyl)phenyl]piperidine-4-carbonyl}-2,7-diazaspiro[4.4]nonane. LC-MS (ESI) m/z: 382.1 $[M+H]^+$.

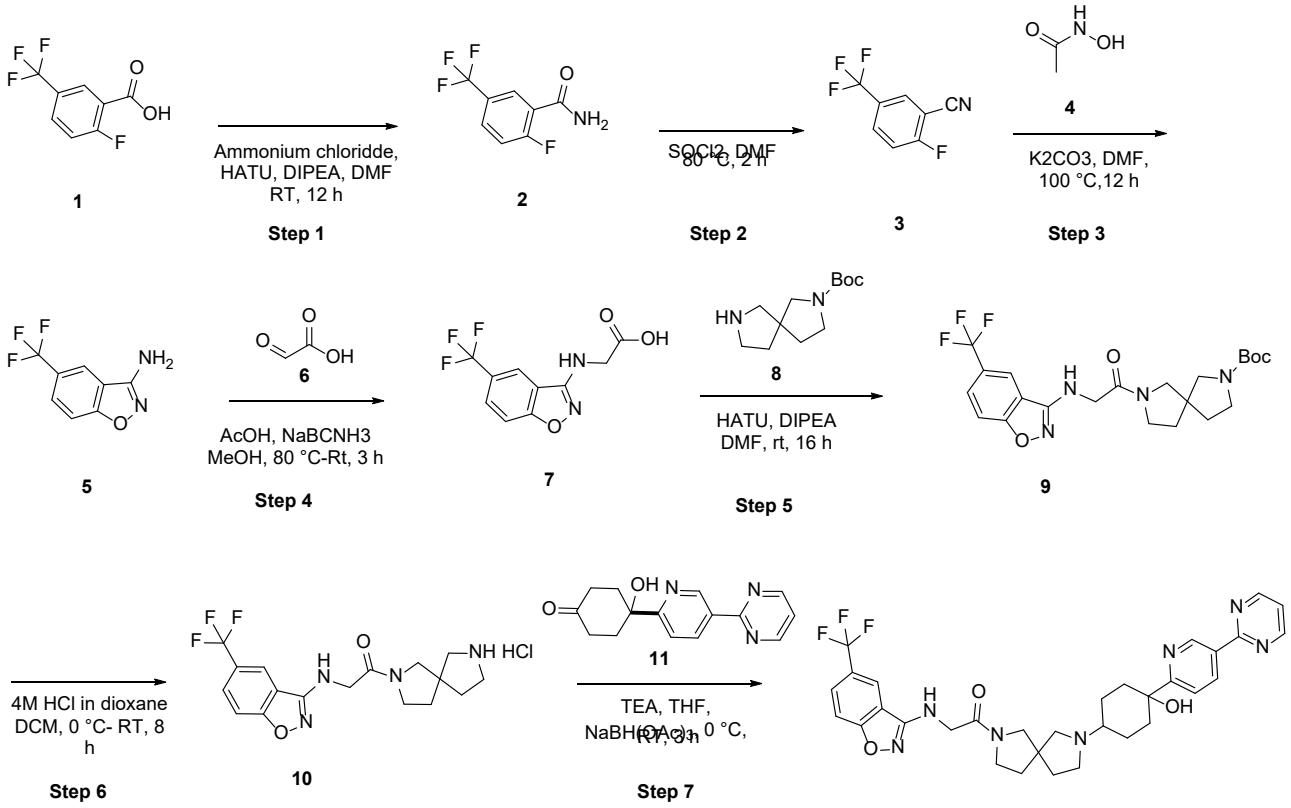


[0176] Preparation of (7-(4-hydroxy-4-(5-(pyrimidin-2-yl)pyridin-2-yl)cyclohexyl)-2,7-diazaspiro[4.4]nonan-2-yl)(1-(3-(trifluoromethyl)phenyl)piperidin-4-yl)methanone: To a stirred solution of 2-{1-[3-(trifluoromethyl)phenyl]piperidine-4-carbonyl}-2,7-diazaspiro[4.4]nonane (0.02 g, 0.52 mmol, 1 eq) in THF (5 mL) was added 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (0.14 g, 0.52 mmol, 1 eq) and at 0 °C, triethylamine (0.04 mL, 3.15 mmol, 6 eq). The reaction mixture was stirred at rt for 0.5 h and then cooled to 0 °C, and sodium bis(acetyloxy)boranuidyl acetate (0.2 g, 1.05 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 give the crude product, which was loaded on a preparative TLC plate. The preparative TLC plate was developed with 4% MeOH.NH_3 in DCM. Non-polar and polar bands of compound were separated and isolated to afford non-polar isomer (**Example 1**) and polar isomer (**Example 2**).

[0177] Non-Polar Isomer (Example 1): LC-MS (ESI) m/z: 635.49 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.44 (s, 1 H), 8.95 (d, *J* = 5.2 Hz, 1 H), 8.80 (s, 1 H), 8.64 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8 Hz, 1 H), 7.51 - 7.29 (m, 2 H), 7.22 - 6.96 (m, 3 H), 5.05 (s, 1 H), 3.82 (d, *J* = 11.2 Hz, 2 H), 3.67 - 3.60 (m, 3 H), 3.40 - 3.33 (m, 2 H), 2.82 (t, *J* = 12.4 Hz, 1 H), 2.67 - 2.60 (m, 2 H), 2.37 - 2.24 (m, 3 H), 2.24 - 1.64 (m, 15 H), 1.39 (s, 2H).

[0178] Polar Iosmer (Example 2): LC-MS (ESI) m/z: 635.49 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.39 (d, *J* = 2 Hz, 1 H), 8.92 (d, *J* = 4.8 Hz, 2 H), 8.63 (d, *J* = 7.2 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 4.8 Hz, 1 H), 7.39 (t, *J* = 8.4 Hz, 1 H), 7.13 (s, 1 H), 7.01 (d, *J* = 7.6 Hz, 1 H), 5.10 (s, 1 H), 3.82 (d, *J* = 12.4 Hz, 2 H), 3.57 - 3.39 (m, 3 H), 3.15 (m, 2 H), 2.80 (t, *J* = 9.6 Hz, 4 H), 2.65 - 2.58 (m, 2 H), 2.10 - 1.97 (m, 5 H), 1.69 - 1.60 (m, 13 H).

Procedure 2: Synthesis of Example 3 & Example 4



[0179] Preparation of 2-fluoro-5-(trifluoromethyl)benzamide: To a stirred solution of 2-fluoro-5-(trifluoromethyl)benzoic acid (10 g, 48.1 mmol) in N,N-dimethylformamide (80 mL) was added HATU (27.4 g, 72.1 mmol) and ammonium chloride (5.14 g, 96.1 mmol). The reaction mixture was stirred at RT for 5 minutes and then ethylbis(propan-2-yl)amine (33.5 mL, 192 mmol) was added, and resultant mixture was stirred at room temperature for 12 h. Progress of the reaction was monitored by TLC (30% EtOAc in hexane). Once the reaction was completed, the reaction mixture was quenched with water and extracted with EtOAc (2 * 100 mL). The combined organic layers were washed with water, brine, and evaporated under reduced pressure to give the crude. The crude compound was purified by silica gel column chromatography, using EtOAc in n-hexane as an eluent, to afford 2-fluoro-5-(trifluoromethyl)benzamide. LC-MS (ESI) m/z: 208.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.83- 7.95(m, 4 H), 7.52 (t, J = 9.6 Hz, 1 H).

[0180] Preparation of 2-fluoro-5-(trifluoromethyl)benzonitrile: To a solution of 2-fluoro-5-(trifluoromethyl)benzamide (8 g, 38.6 mmol) in N,N-dimethylformamide (80 mL) was added sulfurooyl dichloride (8.46 mL, 116 mmol) at 0 °C, and the reaction was stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC (30% EtOAc in n-hexane). Once the reaction was completed, the reaction mixture was diluted with 40.0 mL of pentane and neutralized by dropwise addition of a saturated potassium carbonate solution and filtered. The pentane solution was dried and distilled under vacuum to

yield crude 2-fluoro-5-(trifluoromethyl)benzonitrile. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.85- 7.94 (m, 2 H), 7.38 (t, *J* = 8.4 Hz, 1 H).

[0181] Preparation of 5-(trifluoromethyl)-1,2-benzoxazol-3-amine: A stirred solution of 2-fluoro-5-(trifluoromethyl)benzonitrile (5 g, 26.4 mmol), N-hydroxyacetamide (2.98 g, 39.7 mmol), and dipotassium carbonate (5.48 g, 39.7 mmol) in N,N-dimethylformamide (50 mL) were heated at 80 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. Once the reaction was completed, the reaction mixture was diluted with ice cold water and extracted with Ethyl acetate. Combined organic extracts were washed with water, brine, and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude was purified by silica gel column chromatography, using EtOAc in n-heptane as an eluent, to afford 5-(trifluoromethyl)-1,2-benzoxazol-3-amine. LC-MS (ESI) m/z: 203.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.34 (s, 1 H), 7.85 (d, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 6.65 (s, 2 H).

[0182] Preparation of 2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}acetic acid: A solution of 5-(trifluoromethyl)-1,2-benzoxazol-3-amine (1 g, 4.95 mmol) and 2-oxoacetic acid (366 mg, 4.95 mmol) in MeOH (15.0 mL) was treated with a few drop of AcOH and heated at 80 °C for 30 min. The reaction was then cooled to room temperature and then was added boron(3+) sodium iminomethanide trihydride (466 mg, 1.5 eq., 7.42 mmol) in one portion, and the resulting solution was stirred at room temperature for another 2 hours. The solvent was removed and the residue was partitioned between ether and 1 N NaOH. The aqueous layer was then acidified with 1 N HCl to pH=3, and then extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give crude 2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}acetic acid. LC-MS (ESI) m/z: 261.1 $[M+H]^+$.

[0183] Preparation of tert-butyl 7-(2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}acetyl)-2,7-diazaspiro[4.4]nonane-2-carboxylate: To a stirred solution of 2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}acetic acid (190 mg, 0.73 mmol) in DMF (3.0 mL) was added tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (150 mg, 0.66 mmol), [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-λ^5-phosphanuide (504 mg, 2 eq., 1.33 mmol) portion wise, and finally ethylbis(propan-2-yl)amine (0.47 mL, 2.65 mmol) was added drop wise at room temperature. The reaction mixture was stirred at room temperature for 16 h. Progress of the reaction was monitored by TLC and LCMS. 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 washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was purified using flash chromatography, using ethylacetate in n- Heptane as an eluent, to afford the title compound. LC-MS (ESI) m/z: 469.2 $[M+H]^+$.

[0184] Preparation of 1-{2,7-diazaspiro[4.4]nonan-2-yl}-2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}ethan-1-one hydrochloride: To a solution of tert-butyl 7-(2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}acetyl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (150 mg, 0.32 mmol) in DCM (2.0 mL) was added 4 N HCl in 1,4 dioxane (1.5 mL) at 0 °C, and the reaction mixture was stirred at RT for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated under reduced pressure to give crude 1-{2,7-diazaspiro[4.4]nonan-2-yl}-2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}ethan-1-one hydrochloride. LC-MS (ESI) m/z: 369.1 $[M+H]^+$.

[0185] Preparation of 1-{7-[(4r)-4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl]-2,7-diazaspiro[4.4]nonan-2-yl}-2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}ethan-1-one and 1-{7-[(4s)-4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexyl]-2,7-diazaspiro[4.4]nonan-2-yl}-2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}ethan-1-one: To a stirred solution of 1-{2,7-diazaspiro[4.4]nonan-2-yl}-2-{[5-(trifluoromethyl)-1,2-benzoxazol-3-yl]amino}ethan-1-one (120 mg, 0.32 mmol) in THF (3 mL) was added 4-hydroxy-4-[5-(pyrimidin-2-yl)pyridin-2-yl]cyclohexan-1-one (87.7 mg, 0.32 mmol) and triethylamine (0.27 mL, 1.95 mmol). The reaction mixture was stirred at rt for 0.5 h and then cooled to 0 °C. Sodium bis(acetyloxy)boranuidyl acetate (137 mg, 0.65 mmol) 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 25 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was purified by prep TLC, using 1% Methanolic ammonia in 5% MeOH in DCM as an eluent, to afford non-polar isomer (**Example 3**) and polar isomer (**Example 4**).

[0186] Non-Polar Isomer (Example 3): LC-MS (ESI) m/z: 622.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.42 (d, *J* =3.6 Hz, 1 H), 8.94 (d, *J* =4.8 Hz, 1 H), 8.85 (d, *J* = 4.8 Hz, 1 H), 8.54- 8.68 (m, 2 H), 7.86 (t, *J* = 6.8 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.65- 7.75 (m, 1 H), 7.43- 7.52 (m, 2 H), 5.05 (s, 1 H), 4.07 (d, *J* = 5.2 Hz, 2 H), 3.55- 3.60 (m, 1 H), 3.41 (d, *J* = 10.8 Hz, 2 H), 3.30 (s, 2 H), 2.75 (d, *J* = 6.4 Hz, 1 H), 2.67 (s, 1 H), 2.39 (d, *J* = 9.6 Hz, 3 H), 2.34 (d, *J* = 4.8 Hz, 1 H), 1.77-1.90 (m, 6 H), 1.64 (s, 2 H), 1.39 (d, *J* = 12.0 Hz, 2 H).

[0187] Polar Isomer (Example 4): LC-MS (ESI) m/z: 622.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.42 (s,1 H), 8.94 (d, *J* =4.8 Hz, 2 H), 8.65 (d, *J* = 8.4 Hz, 1 H), 8.60 (s, 1 H), 7.83-7.90 (m, 2 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.47- 7.51 (m, 2 H), 5.10 (s, 1 H), 4.09 (d, *J* = 6.0 Hz, 2 H), 3.57 (d, *J* = 6.4 Hz, 1 H), 3.38-3.46 (m, 3 H), 2.67 (t, *J* = 1.6 Hz, 1 H), 2.45 (s, 1 H), 1.85- 2.07 (m, 5 H), 1.63- 1.79 (m,10 H).

[0188] Data for select compounds is provided in the Table below:

Ex. No.	LC-MS (ES) m/z $[M+H]^+$	Ex. No.	LC-MS (ES) m/z $[M+H]^+$	Ex. No.	LC-MS (ES) m/z $[M+H]^+$	Ex. No.	LC-MS (ES) m/z $[M+H]^+$
1	635.5	2	635.5	3	622.3	4	622.3

BIOCHEMICAL EXAMPLE 1

Chemiluminescence assay of the Compounds

[0189] 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 20µL 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, 5µL 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 5µL 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 90min. Finally, the reaction was terminated by addition of 15µL 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.

[0190] 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
1	+++

Ex.	Activity
3	++++

Ex.	Activity
4	++++

BIOLOGICAL EXAMPLE 2

Calcium mobilization assay

[0191] 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; 20mM HEPES) was added to the 384 well plate and incubated at room temperature for 30 min. Following this 10µL 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.

[0192] In the table below, activity of the tested compounds is provided in Table 4 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 4

Ex.	Activity
1	+++

Ex.	Activity
3	++++

Ex.	Activity
4	++++

[0193] 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 invention belongs.

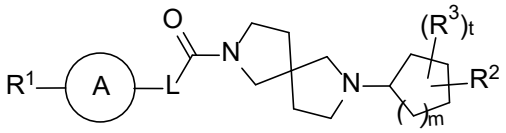
[0194] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," "containing", etc. shall be read expansively and without limitation. 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 invention claimed.

[0195] 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.

[0196] 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:

L is ^{a}-NR^4CH_2-, -NR^4-, -4 to 10-membered cycloalkyl-, ^{a}-NR^4-4 to 10-membered cycloalkyl-, -4 to 10-membered heterocyclyl-, or ^{a}-4 to 10 membered heterocyclyl-NR^4-, ^{a}-C(O)-4 to 10 membered heteroaryl-, -5 to 10-membered heteroaryl-; wherein bond ^{a}- is attached to ring A; and further wherein the cycloalkyl, heterocyclyl, or heteroaryl is independently optionally substituted with one to five R^5;

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}, -$N(R^{13})_2$, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$C(O)N(R^{13})_2$, -$NR^{13}C(O)R^{13}$, -$OC(O)N(R^{13})_2$, -$NR^{13}C(O)OR^{13}$, -$S(O)_{0-2}R^{13}$, -$NR^{13}S(O)_{1-2}R^{13}$, -$NR^{13}C(O)N(R^{13})_2$, 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;

each R^5 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, $-NO_2$, $-SF_5$, $-OR^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{15})_2$, $-NR^{15}C(O)R^{15}$, $-OC(O)N(R^{15})_2$, $-NR^{15}C(O)OR^{15}$, $-S(O)_{0-2}R^{15}$, $-NR^{15}S(O)_{1-2}R^{15}$, $-NR^{15}C(O)N(R^{15})_2$, 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 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 $-NHS(O)_2NH-$;

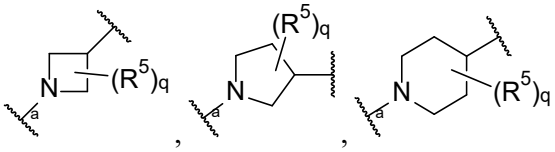
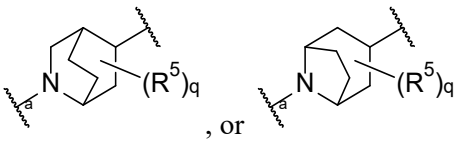
wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl, or heteroaryl of Z^{1b} and L is further independently optionally substituted with one to five halo, cyano, hydroxy, -SH, $-NH_2$, $-NO_2$, $-SF_5$, C_{1-6} alkyl, C_{2-6} alkenyl, 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^4 is hydrogen.

3. The compound of claim 1, wherein L is ^{a}-$NHCH_2$-.

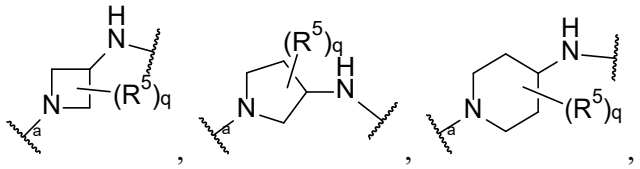
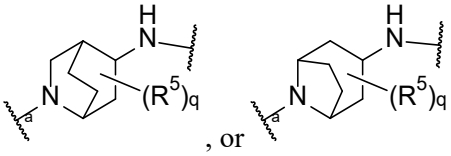
4. The compound of claim 1, wherein L is ^{a}-NH-.

5. The compound of claim 1, wherein L is a 4 to 10-membered monocyclic or bridged heterocyclyl optionally substituted with one to five R^5.

6. The compound of claim 5, wherein L is  ,  , or .

wherein q is 0, 1, 2, 3, 4, or 5.

7. The compound of claim 1, wherein L is [a]-4 to 10 membered monocyclic or bridged heterocyclyl-NR^4- optionally substituted with one to five R^5.

8. The compound of claim 7, wherein L is  ,  , or

wherein q is 0, 1, 2, 3, 4, or 5.

9. The compound of claim 1, wherein L is a 5 to 6-membered heteroaryl optionally substituted with one to five R^5.

10. The compound of claim 9, wherein L is imidazolyl or oxazolyl.

11. The compound of claim 1, wherein L is a 4 to 10-membered cycloalkyl optionally substituted with one to five R^5.

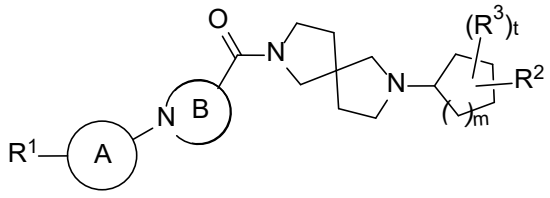
12. The compound of claim 11, wherein L is cyclobutyl or bicyclo[1.1.1]pentyl.

13. The compound of any one of claims 1-12, wherein each R^5 is independently halo or C_{1-6} alkyl.

14. The compound of any one of claims 1-13, wherein each R^5 is independently fluoro or methyl.

15. The compound of any one of claims 6-14, wherein q is 0, 1 or 2.

16. The compound of claim 1, wherein the compound is represented by Formula IA:



IA

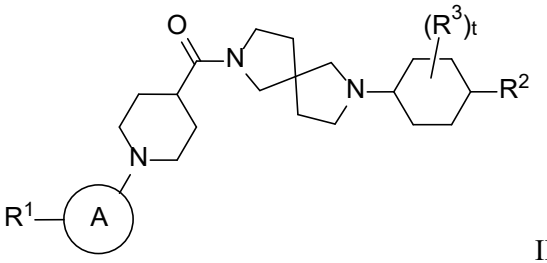
wherein ring B is a 4 to 10-membered monocyclic or bridged heterocyclyl optionally substituted with one to five R^5.

17. The compound of any one of claims 1-16, wherein m is 0.

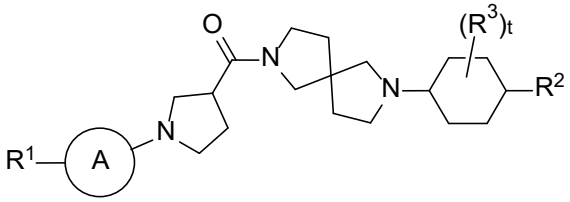
18. The compound of any one of claims 1-16, wherein m is 1.

19. The compound of any one of claims 1-16, wherein m is 2.

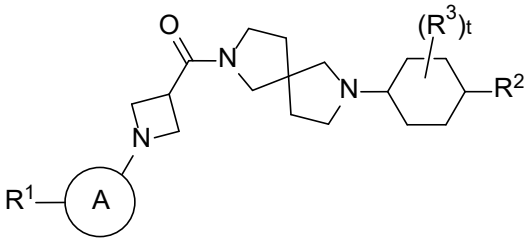
20. The compound of claim 1, wherein the compound is represented by Formula IIA, IIB, IIC, or IID:



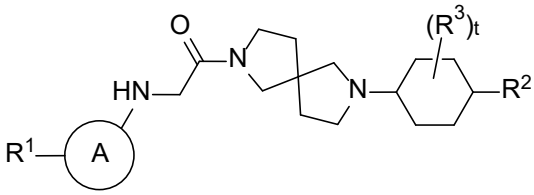
IIA



IIB

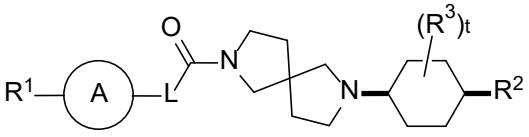


IIC



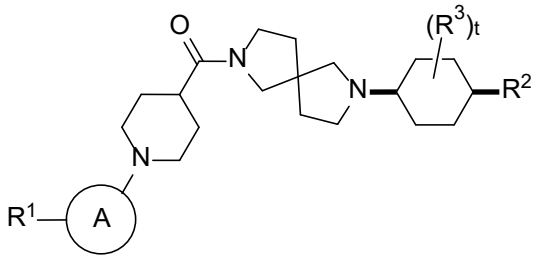
IID.

21. The compound of claim 1, wherein the compound is represented by Formula III:

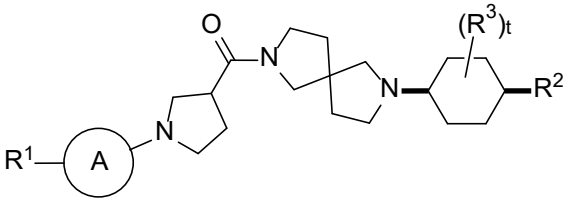


III.

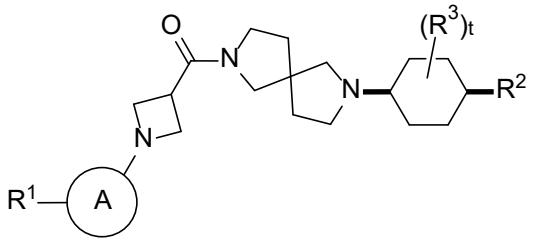
22. The compound of claim 1, wherein the compound is represented by Formula IIIA, IIIB, IIIC, or IIID:



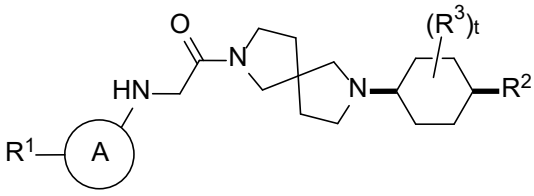
IIIA



IIIB



IIIC



IIID.

23. The compound of any one of claims 1-22, wherein ring A is aryl.

24. The compound of claim 23, wherein ring A is phenyl.

25. The compound of any one of claims 1-22, wherein ring A is heteroaryl.

26. The compound of claim 18, wherein ring A is benzo[d]isoxazole.

27. The compound of any one of claims 1-19, wherein R^1 is C_{1-6} haloalkyl.

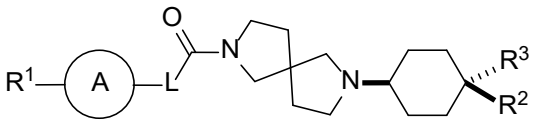
28. The compound of claim 20, wherein R^1 is trifluoromethyl.

29. The compound of any one of claims 1-21, wherein each R^3 is independently halo or hydroxy.

30. The compound of any one of claims 1-22, wherein t is 0 or 1.

31. The compound of any one of claims 1-21, wherein t is 1; and R^3 is hydroxy.

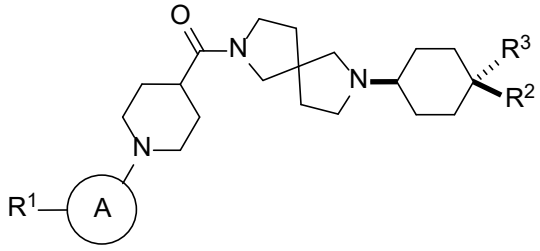
32. The compound of claim 1, wherein the compound is represented by Formula IV:



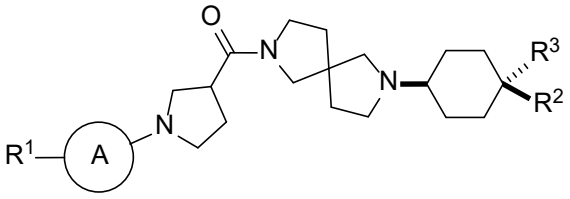
IV.

33. The compound of claim 25, wherein R^3 is hydroxy.

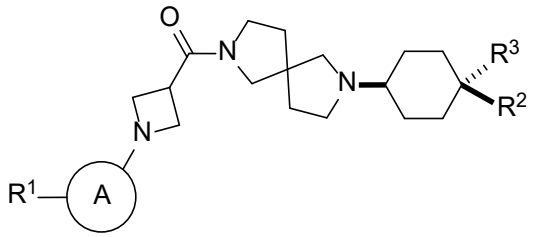
34. The compound of claim 1, wherein the compound is represented by Formula IVA, IVB, IVC, or IVD:



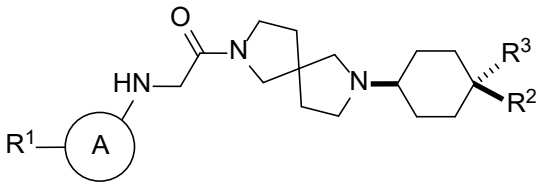
IVA



IVB



IVC



IVD

35. The compound of any one of claims 1-34, wherein R^2 is aryl or heteroaryl; wherein each aryl or heteroaryl is optionally substituted with one to five Z^1.

36. The compound of claim 35, wherein R^2 is aryl optionally substituted with one to five Z^1.

37. The compound of claim 36, wherein R^2 is phenyl optionally substituted with one to five Z^1.

38. The compound of any one of claims 1-34, wherein R^2 is heteroaryl optionally substituted with one to five Z^1.

39. The compound of claim 38, wherein R^2 is pyridyl optionally substituted with one to five Z^1.

40. The compound of any one of claims 1-39, wherein R^2 is optionally substituted with one to five heteroaryl or $-OR^{10}$.

41. The compound of any one of claims 1-40, wherein R^2 is optionally substituted with pyrimidyl or methoxy.

42. A compound selected from Table 1 or Table 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof.

43. 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.

44. 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 43 to a subject in need thereof.

45. A method for treating 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 43 to a subject in need thereof.

46. The method of claim 45, wherein the disease is systemic lupus erythematosus or lupus nephritis.

47. Use of a compound of any one of claims 1-42, 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.

48. The use of claim 47, 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.

49. A compound of any one of claims 1-42, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or prodrug thereof, for use in therapy.

50. A compound of any one of claims 1-42, 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.