

NOVEL COMPOUNDS AS GLUCOCORTICOID RECEPTOR MODULATORS AND USES THEREOF

FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to novel compounds or pharmaceutically acceptable salts thereof, which are useful as glucocorticoid receptor (GR) modulators. The present disclosure further relates to pharmaceutical compositions comprising one or more of such compounds or pharmaceutically acceptable salts thereof as an active ingredient, and use of such compounds or pharmaceutically acceptable salts thereof in the treatment of diseases or disorders.

BACKGROUND

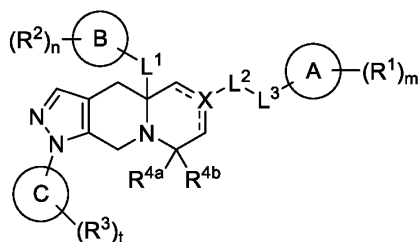
[0002] Glucocorticoid receptor (GR) is a member of the nuclear receptor superfamily. GR, mineralocorticoid receptor (MR), progesterone receptor (PR), androgen receptor (AR) and estrogen receptor (ER) are steroid hormone receptors, a subclass of the nuclear receptor superfamily. By activating GR, glucocorticoids regulate gene expression, including a variety of cellular functions, such as metabolism, inflammation, cell growth and differentiation.

[0003] Recent study shows, at least in animals, that deactivation of the GR and/or recovery of the MR:GR balance may be a neuropharmaceutical treatment strategy for attenuating the damaging impact of hypercortisolemia in neurodegenerative diseases.

[0004] Therefore, there are still unsatisfied needs for novel compounds as GR modulators.

SUMMARY

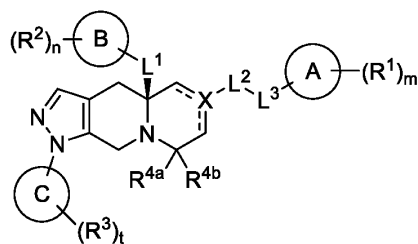
[0005] In one aspect, the present disclosure provides a compound of Formula (I):



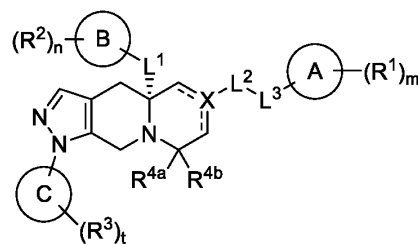
Formula (I),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

[0006] In one aspect, the present disclosure provides a compound of Formula (Ia) or Formula (Ib):



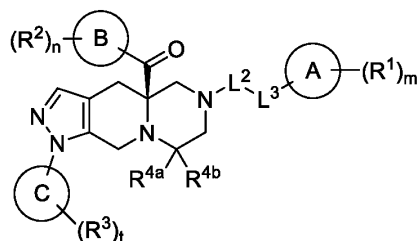
Formula (Ia),



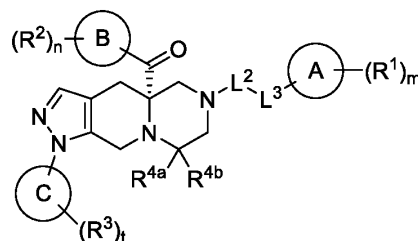
Formula (Ib),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

[0007] In one aspect, the present disclosure provides a compound of Formula (Ia-1) or Formula (Ib-1):



Formula (Ia-1),



Formula (Ib-1),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

[0008] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ia-1), Formula (Ib-1), or a compound set forth in Table 1, Table 2 or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0009] Also disclosed herein is a method of modulating (e.g., inhibiting) GR in a subject, the method comprising administering to the subject the compound disclosed herein (e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ia-1), Formula (Ib-1), or a compound set forth in Table 1, Table 2 or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[0010] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ia-1), Formula (Ib-1), or a compound set forth in Table 1, Table 2 or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for modulating (e.g., inhibiting) GR in a subject.

[0011] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I), Formula (Ia), Formula (Ib), Formula (Ia-1), Formula (Ib-1), or a compound set forth in Table 1, Table 2 or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof. In some embodiments, the disease or disorder is a GR associated disease or disorder.

INCORPORATION BY REFERENCE

[0012] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

Definitions

[0013] In the following description, certain specific details are set forth to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0014] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0015] The terms below, as used herein, have the following meanings, unless indicated otherwise.

[0016] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Organic Chemistry, Thomas Sorrell, 2nd Edition, University Science Books, Sausalito, 2006; Smith and March March’s Advanced Organic Chemistry, 6th Edition, John Wiley & Sons, Inc., New York, 2007; Larock, Comprehensive Organic Transformations, 3rd Edition, VCH Publishers, Inc., New York, 2018; Carruthers, Some Modern Methods of Organic Synthesis, 4th Edition, Cambridge University Press, Cambridge, 2004; the entire contents of each of which are incorporated herein by reference.

[0017] At various places in the present disclosure, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl”, then it is understood that the “alkyl” represents a linking alkylene group.

[0018] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0019] When any variable (e.g., R^i) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^i moieties, then the group may optionally be substituted with up to two R^i moieties and R^i at each occurrence is selected independently from the definition of R^i . Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0020] As used herein, the term “ C_i-C_j ” indicates a range of the carbon atoms numbers, wherein i and j are integers and the range of the carbon atoms numbers includes the endpoints (i.e. i and j) and each integer point in between, and wherein j is greater than i . For examples, C_1-C_6 indicates a range of one to six carbon atoms, including one carbon atom, two carbon atoms, three carbon atoms, four carbon atoms, five carbon atoms and six carbon atoms. In some embodiments, the term “ C_{1-12} ” indicates 1 to 12, particularly 1 to 10, particularly 1 to 8, particularly 1 to 6, particularly 1 to 5, particularly 1 to 4, particularly 1 to 3 or particularly 1 to 2 carbon atoms.

[0021] “Oxo” refers to =O.

[0022] “Cyano” refers to -CN.

[0023] “Amino”, whether as part of another term or used independently, refers to the group - NR^aR^b , wherein R^a and R^b are independently selected from groups consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or other suitable organic groups and each of which may be optionally substituted.

[0024] “Hydroxy” or “hydroxyl”, whether as part of another term or used independently, refers to -OH.

[0025] “Alkyl”, whether as part of another term or used independently, refers to a straight-chain, or branched-chain saturated hydrocarbon radical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-

pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁₋₆alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0026] “Alkenyl”, whether as part of another term or used independently, refers to a straight-chain, or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation, or alternatively, *E* or *Z* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or “C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkenyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0027] “Alkynyl”, whether as part of another term or used independently, refers to a straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butyne, 1,3-butadiynyl and the like. Whenever

it appears herein, a numerical range such as “C₂-C₆alkynyl” or “C₂₋₆alkynyl”, means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkynyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0028] “Alkoxy”, whether as part of another term or used independently, refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined herein. Whenever it appears herein, a numerical range such as “C₁-C₆ alkoxy” or “C₁₋₆alkoxy”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkoxy” where no numerical range is designated. In some embodiments, the alkoxy is a C₁₋₁₀alkoxy. In some embodiments, the alkoxy is a C₁₋₆alkoxy. In some embodiments, the alkoxy is a C₁₋₅alkoxy. In some embodiments, the alkoxy is a C₁₋₄alkoxy. In some embodiments, the alkyl is a C₁₋₃alkoxy. In some embodiments, the alkyl is a C₁₋₂alkoxy. In some embodiments, the alkyl is methoxy. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0029] “Aryl”, whether as part of another term or used independently, refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system. The polycyclic ring system may include fused (for example, an aromatic ring fused with a cycloalkyl ring) or bridged (for example, an aromatic ring fused with a bridged cycloalkyl ring) ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with

one or more substituents, such as halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the aryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0030] “Cycloalkyl”, whether as part of another term or used independently, refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (for example, fused with another cycloalkyl ring), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. In some embodiments, the cycloalkyl is partially saturated.

Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C₃-C₁₅ fully saturated cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (C₃-C₁₀ fully saturated cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms (C₃-C₈ fully saturated cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (C₃-C₆ fully saturated cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (C₃-C₅ fully saturated cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (C₃-C₄ fully saturated cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl.

Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0031] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0032] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0033] “Hydroxylalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyl radicals, as defined above, *e.g.*, hydroxymethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 1,2-dihydroxypropyl, and the like.

[0034] “Heteroalkyl”, whether as part of another term or used independently, refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.*, -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In some embodiments, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, *e.g.*, oxygen, nitrogen (*e.g.*, -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂NHCH₃, or -CH₂CH₂N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0035] “Heteroalkenyl”, whether as part of another term or used independently, refers to an alkenyl group in which one or more skeletal atoms of the alkenyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, or combinations thereof. A heteroalkenyl is attached to the rest of the molecule at a carbon atom of the heteroalkenyl. In some embodiments, a heteroalkenyl is a C₂-C₆ heteroalkenyl wherein the heteroalkenyl is comprised of 2 to 6 carbon atoms and one or more atoms other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, or combinations thereof wherein the heteroalkenyl is attached to the rest of the molecule at a carbon atom of the heteroalkenyl. Examples of such heteroalkenyl are, for example, -CH=CHOCH₃, -CH=CHOCH₂CH₂OCH₃, -CH₂CH₂OCH=CHOCH₃, -C(=CH₂)OCH₃, -CH=NCH₃, -CH₂N=CH₂, -CH=CHNHCH₃, or -CH=CHN(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkenyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkenyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkenyl is optionally substituted with oxo,

halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkenyl is optionally substituted with halogen.

[0036] “Heteroalkynyl”, whether as part of another term or used independently, refers to an alkynyl group in which one or more skeletal atoms of the alkynyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof. A heteroalkynyl is attached to the rest of the molecule at a carbon atom of the heteroalkynyl. In some embodiments, a heteroalkynyl is a C₂-C₆ heteroalkynyl wherein the heteroalkynyl is comprised of 2 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus, or combinations thereof wherein the heteroalkynyl is attached to the rest of the molecule at a carbon atom of the heteroalkynyl. Examples of such heteroalkynyl are, for example, -C≡COCH₃, -C≡COCH₂CH₂OCH₃, -CH₂CH₂OC≡COCH₃, -C≡C-NHCH₃, or -C≡C-N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkynyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkynyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkynyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkynyl is optionally substituted with halogen.

[0037] “Heterocyclyl”, whether as part of another term or used independently, refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from 1 to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocyclyl is fully saturated. In some embodiments, the heterocyclyl is partially unsaturated. In some embodiments, the heterocyclyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocyclyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocyclyl comprises one to three nitrogens. In some embodiments, the heterocyclyl comprises one or two nitrogens. In some embodiments, the heterocyclyl comprises one nitrogen. In some embodiments, the heterocyclyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system. The polycyclic ring system may include fused (for example, a heterocyclyl ring fused with a cycloalkyl or another heterocyclyl ring), spiro, or bridged ring systems. The nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocyclyls include, but are not limited to, heterocyclyls having from two to fifteen carbon atoms (C₂-C₁₅ heterocyclyl), from two to ten carbon atoms (C₂-C₁₀ heterocyclyl), from two to eight carbon atoms (C₂-C₈ heterocyclyl), from two to seven carbon atoms (C₂-C₇ heterocyclyl), from two to six carbon atoms (C₂-C₆ heterocyclyl), from two to five carbon atoms (C₂-C₅ heterocyclyl), or two to four carbon atoms (C₂-C₄ heterocyclyl). Examples of such

heterocyclyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, dihydrofuryl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocyclyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocyclyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocyclyl, the number of carbon atoms in the heterocyclyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocyclyl (i.e. skeletal atoms of the heterocyclyl ring). In some embodiments, the heterocyclyl is a 3- to 8-membered fully saturated heterocyclyl. In some embodiments, the heterocyclyl is a 3- to 7-membered fully saturated heterocyclyl. In some embodiments, the heterocyclyl is a 3- to 6-membered fully saturated heterocyclyl. In some embodiments, the heterocyclyl is a 4- to 6-membered fully saturated heterocyclyl. In some embodiments, the heterocyclyl is a 5- to 6-membered fully saturated heterocyclyl. Unless stated otherwise specifically in the specification, a heterocyclyl may be optionally substituted as described below, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the heterocyclyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heterocyclyl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocyclyl is optionally substituted with halogen.

[0038] “Heteroaryl”, whether as part of another term or used independently, refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic or polycyclic (such as, bicyclic, tricyclic, or tetracyclic) ring system. The polycyclic ring system may include fused (for example, a heteroaryl ring fused with a cycloalkyl, heterocyclyl or aryl ring), bridged (for example, an aryl or heteroaryl ring fused with a

bridged cycloalkyl or heterocyclyl ring) or spiro (for example, an aryl ring fused with a spiro heterocyclyl ring, or an heteroaryl ring fused with a spiro cycloalkyl or spiro heterocyclyl ring) ring systems. The nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyridyl, pyridyl 1-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with one or more substituents, such as halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heteroaryl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0039] The term “partially saturated” or “partially unsaturated” refers to a radical that includes at least one double or triple bond and is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (i.e., fully unsaturated) moieties.

[0040] The term “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. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined above. Further, an optionally substituted group may be un-substituted (e.g., -CH₂CH₃), fully substituted (e.g., -CF₂CF₃), mono-substituted (e.g., -CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH₂CHF₂, -CH₂CF₃, -CF₂CH₃, -CFHCHF₂, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to

introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0041] The term “one or more” when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, four substituents, or more substituents. In some embodiments, the subject group is optionally substituted with one, two, three, or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

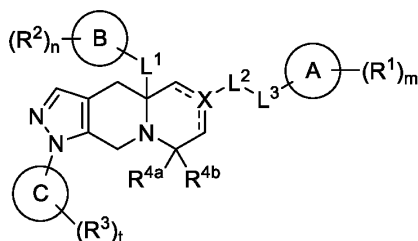
[0042] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0043] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

Compounds

[0044] Described herein are compounds, or pharmaceutically acceptable salts thereof useful as GR antagonists and in the treatment of diseases or disorders.

[0045] In one aspect, provided herein is a compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof,

wherein:

each $\equiv$ is independently a single bond or double bond;

X is N, C or CH;

L^1 is $-C(=O)-$, $-C(=O)O-$, $-C(=O)N(R^a)-$, $-C(R^a)_2-$, $-N(R^a)-$, $-O-$, $-S-$, $S(=O)$ or $-S(=O)_2-$;

each of L^2 and L^3 is independently a bond, $-N(R^a)-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)N(R^a)-$, $-O-$, $-S-$, $S(=O)-$, $-S(=O)_2-$, $-S(=O)(=NR^a)-$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, or oxo;

each of Ring A, Ring B and Ring C is independently cycloalkyl, aryl, heterocyclyl or heteroaryl;

each of R^1 , R^2 and R^3 is independently halogen, hydroxy, cyano, $-OR^b$, $-N(R^b)_2$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)N(R^b)_2$, $-S(=O)R^b$, $-S(=O)_2R^b$, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, alkoxy, cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the alkyl, haloalkyl, hydroxyalkyl, alkoxy, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, oxo, alkyl, alkenyl, alkynyl, haloalkyl, or hydroxyalkyl;

each of R^{4a} and R^{4b} is independently hydrogen, halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxyalkyl or alkoxy;

or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a cycloalkyl or heterocyclyl, each optionally substituted with one or more groups independently selected from halogen, hydroxyl, amino or alkyl;

each of R^a and R^b is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

or two R^b together with the nitrogen atom to which they are attached form a heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxyl, amino or alkyl;

n is any integer of 0-5;

m is any integer of 0-5; and

t is any integer of 0-5.

[0046] In some embodiments, L^1 is $-C(=O)-$.

[0047] In some embodiments, L^2 is a bond, $-N(R^a)-$ or alkyl (such as C_{1-6} (*e.g.*, C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl), and L^3 is $-S(=O)_2-$ or $-S(=O)(=NR^a)-$; or L^2 is $-S(=O)_2-$ or $-S(=O)(=NR^a)-$ and L^3 is a bond, $-N(R^a)-$ or alkyl (such as C_{1-6} (*e.g.*, C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl).

[0048] In some embodiments, L^2 is a bond, $-N(R^a)-$ or alkyl (such as C_{1-6} (*e.g.*, C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl) and L^3 is $-S(=O)_2-$ or $-S(=O)(=NR^a)-$.

[0049] In some embodiments, L^2 is $-S(=O)_2-$ or $-S(=O)(=NR^a)-$ and L^3 is a bond, $-N(R^a)-$ or alkyl (such as C_{1-6} (*e.g.*, C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl).

[0050] In some embodiments, $-L^2-L^3-$ is $-S(=O)_2-$, $-N(R^a)-S(=O)_2-$ or $-S(=O)(=NR^a)-$.

[0051] In some embodiments, R^a is hydrogen or alkyl (such as C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl).

[0052] In some embodiments, -L²-L³- is -S(=O)₂- or -S(=O)(=NH)-.

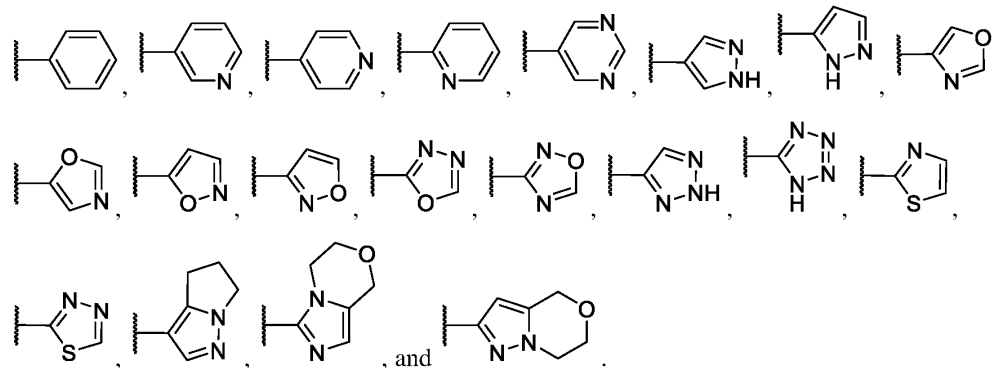
[0053] In some embodiments, Ring A is aryl or heteroaryl.

[0054] In some embodiments, Ring A is a C₆₋₁₂ aryl, C₆₋₁₁ aryl, C₆₋₁₀ aryl, C₆₋₉ aryl, C₆₋₈ aryl or C₆₋₇ aryl. In some embodiments, Ring A is a C₁₂ aryl, C₁₁ aryl, C₁₀ aryl, C₉ aryl, C₈ aryl, C₇ aryl or C₆ aryl. In some embodiments, Ring A is a monocyclic or bicyclic aryl. In some embodiments, Ring A is a monocyclic aryl. In some embodiments, Ring A is a bicyclic aryl.

[0055] In some embodiments, Ring A is a 5- to 12- membered heteroaryl, 5- to 11- membered heteroaryl, 5- to 10- membered heteroaryl, 5- to 9- membered heteroaryl, 5- to 8- membered heteroaryl, 5- to 7- membered heteroaryl or 5- to 6- membered heteroaryl. In some embodiments, Ring A is a 12-membered heteroaryl, 11-membered heteroaryl, 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl. In some embodiments, Ring A is a monocyclic or bicyclic heteroaryl. In some embodiments, Ring A is a monocyclic heteroaryl. In some embodiments, Ring A is a bicyclic heteroaryl.

[0056] In some embodiments, Ring A is selected from phenyl, pyridyl, pyrazolyl, pyrimidinyl, triazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, tetrazolyl, dihydropyrrolopyrazolyl, dihydroimidazooxazinyll, or dihydropyrazoloxazinyll.

[0057] In some embodiments, Ring A is selected from the group consisting of:



[0058] In some embodiments, each R¹ is independently halogen, cyano, -OR^b, alkyl, haloalkyl, cycloalkyl or heterocyclyl. In some embodiments, each R¹ is independently halogen, cyano, -OR^b, C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl, C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) haloalkyl, C₃₋₆ (*e.g.*, C₃₋₅ or C₃₋₄) cycloalkyl or 3- to 6-membered (*e.g.*, 3- to 5-membered or 3- to 4-membered) heterocyclyl. In some embodiments, the alkyl, haloalkyl, cycloalkyl and heterocyclyl are deuterated.

[0059] In some embodiments, one or more R¹ is alkyl. In some embodiments, one or more R¹ is C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl. In some embodiments, the alkyl is deuterated alkyl. In some embodiments, the C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl is deuterated C₁₋₆ (*e.g.*, C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl. In some embodiments, one or more R¹ is -CH₃. In some embodiments, one or more R¹ is -CD₃.

[0060] In some embodiments, each R^1 is independently -F, -Cl, cyano, -OCH₃, -CH₃, -CH₂CH₃, -

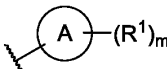
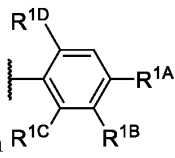
CH₂F, -CHF₂, -CF₃, cyclopropyl or . In some embodiments, -OCH₃, -CH₃, -CH₂CH₃, -CH₂F,

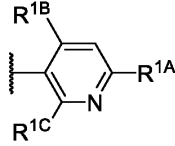
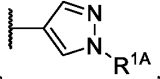
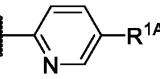
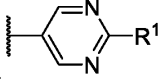
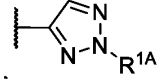
-CHF₂, cyclopropyl and  are deuterated. In some embodiments, -CH₃ is -CD₃. In some embodiments, -OCH₃ is -OCD₃.

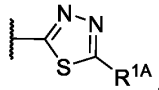
[0061] In some embodiments, m is 1.

[0062] In some embodiments, m is 2.

[0063] In some embodiments, m is 3.

[0064] In some embodiments, the moiety  is selected from ,

, , , , , and

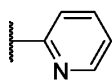
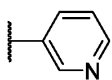
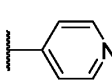
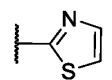
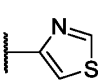
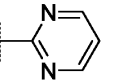
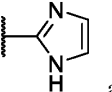
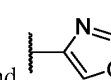
, wherein each of R^{1A} , R^{1B} , R^{1C} and R^{1D} is independently hydrogen or R^1 . In some embodiments, each of R^{1A} , R^{1B} , R^{1C} and R^{1D} is independently hydrogen, alkyl (such as C₁₋₆ (e.g., C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl), haloalkyl (such as C₁₋₆ (e.g., C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) haloalkyl), cycloalkyl (such as C₃₋₆ (e.g., C₃₋₅ or C₃₋₄) cycloalkyl) or heterocyclyl (such as 3- to 6-membered (e.g., 3- to 5-membered or 3- to 4-membered) heterocyclyl). In some embodiments, each of R^{1A} , R^{1B} , R^{1C} and R^{1D}

is independently hydrogen, -CH₃, -CH₂CH₃, -CH₂F, -CHF₂, -CF₃, cyclopropyl or .

[0065] In some embodiments, Ring B is heteroaryl. In some embodiments, Ring B is a 5- to 12-membered heteroaryl, 5- to 11-membered heteroaryl, 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl or 5- to 6-membered heteroaryl. In some embodiments, Ring B is a 12-membered heteroaryl, 11-membered heteroaryl, 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl. In some embodiments, Ring B is a monocyclic or bicyclic heteroaryl. In some embodiments, Ring B is a monocyclic heteroaryl. In some embodiments, Ring B is a bicyclic heteroaryl.

[0066] In some embodiments, Ring B is pyridyl, thiazolyl, pyrimidinyl, imidazolyl or oxazolyl.

[0067] In some embodiments, Ring B is selected from the group consisting of:

, , , , , , , and .

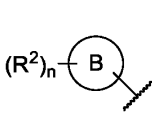
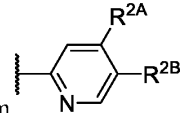
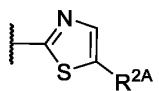
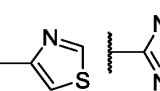
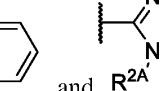
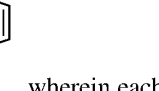
[0068] In some embodiments, each R^2 is independently halogen, alkyl, haloalkyl or cycloalkyl. In some embodiments, each R^2 is independently halogen, C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl, C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) haloalkyl, or C_{3-6} (e.g., C_{3-5} or C_{3-4}) cycloalkyl. In some embodiments, the alkyl, haloalkyl, or cycloalkyl are deuterated.

[0069] In some embodiments, one or more R^2 is alkyl. In some embodiments, one or more R^2 is C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, the alkyl is deuterated alkyl. In some embodiments, the C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl is deuterated C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, one or more R^2 is $-CH_3$. In some embodiments, one or more R^2 is $-CD_3$.

[0070] In some embodiments, each R^2 is independently $-CH_3$, $-F$, $-Cl$, $-CH_2F$, $-CHF_2$, $-CF_3$ or cyclopropyl. In some embodiments, the $-CH_3$, $-CH_2F$, $-CHF_2$, or cyclopropyl are deuterated. In some embodiments, $-CH_3$ is $-CD_3$.

[0071] In some embodiments, n is 0.

[0072] In some embodiments, n is 1.

[0073] In some embodiments, the moiety  is selected from , , , , and , wherein each of R^{2A} and R^{2B} is independently hydrogen or R^2 .

[0074] In some embodiments, Ring C is aryl. In some embodiments, Ring C is a C_{6-12} aryl, C_{6-11} aryl, C_{6-10} aryl, C_{6-9} aryl, C_{6-8} aryl or C_{6-7} aryl. In some embodiments, Ring C is a C_{12} aryl, C_{11} aryl, C_{10} aryl, C_9 aryl, C_8 aryl, C_7 aryl or C_6 aryl. In some embodiments, Ring A is a monocyclic or bicyclic aryl. In some embodiments, Ring A is a monocyclic aryl. In some embodiments, Ring A is a bicyclic aryl.

[0075] In some embodiments, Ring C is phenyl.

[0076] In some embodiments, each R^3 is independently halogen, alkyl, or haloalkyl. In some embodiments, each R^3 is independently halogen, C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl, or C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) haloalkyl. In some embodiments, the alkyl or haloalkyl are deuterated.

[0077] In some embodiments, one or more R^3 is alkyl. In some embodiments, one or more R^3 is C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, the alkyl is deuterated alkyl. In some embodiments, the C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl is deuterated C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, one or more R^3 is $-CH_3$. In some embodiments, one or more R^3 is $-CD_3$.

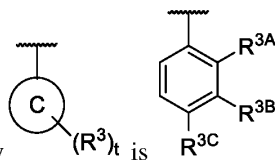
[0078] In some embodiments, each R^3 is $-F$, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, $-CH_3$, $-CH_2F$, and $-CHF_2$ are deuterated. In some embodiments, $-CH_3$ is $-CD_3$.

[0079]

[0080] In some embodiments, t is 0.

[0081] In some embodiments, t is 1.

[0082] In some embodiments, t is 2.



[0083] In some embodiments, the moiety $(R^3)_t$ is $(R^3)_t$, wherein each of R^{3A} , R^{3B} and R^{3C} is independently hydrogen or R^3 .

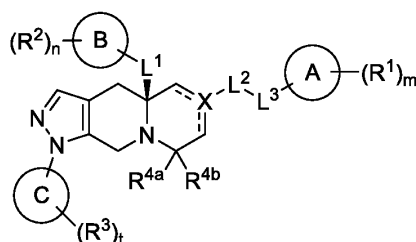
[0084] In some embodiments, R^{4a} is hydrogen or alkyl. In some embodiments, R^{4a} is hydrogen or C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, R^{4a} is hydrogen.

[0085] In some embodiments, R^{4b} is hydrogen or alkyl. In some embodiments, R^{4b} is hydrogen or C_{1-6} (e.g., C_{1-5} , C_{1-4} , C_{1-3} or C_{1-2}) alkyl. In some embodiments, R^{4b} is hydrogen.

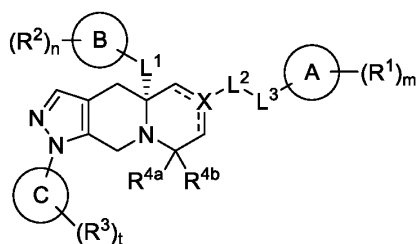
[0086] In some embodiments, both R^{4a} and R^{4b} are hydrogen.

[0087] In some embodiments, R^{4a} and R^{4b} together with the carbon atom to which they are attached form a C_{3-6} (e.g., C_{3-5} or C_{3-4}) cycloalkyl. In some embodiments, R^{4a} and R^{4b} together with the carbon atom to which they are attached form a cycloalkyl (such as C_{3-6} cycloalkyl, C_{3-5} cycloalkyl, or C_{3-4} cycloalkyl). In some embodiments, R^{4a} and R^{4b} together with the carbon atom to which they are attached form cyclopropyl.

[0088] In some embodiments, the compound disclosed herein is of Formula (Ia) or Formula (Ib):

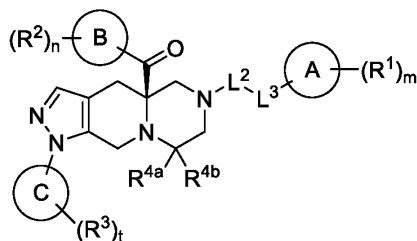


Formula (Ia),

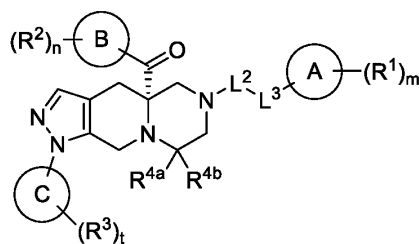


Formula (Ib).

[0089] In some embodiments, the compound disclosed herein is of formula selected from:



Formula (Ia-1)



Formula (Ib-1).

[0090] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring A is aryl or heteroaryl. In some embodiments, Ring A is a C₆₋₁₂ aryl, C₆₋₁₁ aryl, C₆₋₁₀ aryl, C₆₋₉ aryl, C₆₋₈ aryl or C₆₋₇ aryl. In some embodiments, Ring A is a C₁₂ aryl, C₁₁ aryl, C₁₀ aryl, C₉ aryl, C₈ aryl, C₇ aryl or C₆ aryl. In some embodiments, Ring A is a 5- to 12- membered heteroaryl, 5- to 11- membered heteroaryl, 5- to 10- membered heteroaryl, 5- to 9- membered heteroaryl, 5- to 8- membered heteroaryl, 5- to 7- membered heteroaryl or 5- to 6- membered heteroaryl. In some embodiments, Ring A is a 12-membered heteroaryl, 11-membered heteroaryl, 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl.

[0091] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring A is phenyl, pyridyl, pyrazolyl, pyrimidinyl, triazolyl, or thiadiazolyl.

[0092] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring B is heteroaryl. In some embodiments, Ring B is a 5- to 12- membered heteroaryl, 5- to 11- membered heteroaryl, 5- to 10- membered heteroaryl, 5- to 9- membered heteroaryl, 5- to 8- membered heteroaryl, 5- to 7- membered heteroaryl or 5- to 6- membered heteroaryl. In some embodiments, Ring B is a 12-membered heteroaryl, 11-membered heteroaryl, 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl or 5-membered heteroaryl.

[0093] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring B is pyridyl, pyrimidinyl, thiazolyl or imidazolyl.

[0094] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring C is aryl. In some embodiments, Ring C is a C₆₋₁₂ aryl, C₆₋₁₁ aryl, C₆₋₁₀ aryl, C₆₋₉ aryl, C₆₋₈ aryl or C₆₋₇ aryl. In some embodiments, Ring C is a C₁₂ aryl, C₁₁ aryl, C₁₀ aryl, C₉ aryl, C₈ aryl, C₇ aryl or C₆ aryl.

[0095] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), Ring C is phenyl.

[0096] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), each of L² and L³ is independently a bond, -N(R^a)-, -S(=O)₂- or -S(=O)(=NR^a)-.

[0097] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), -L²-L³- is -S(=O)₂-, -N(R^a)-S(=O)₂- or -S(=O)(=NR^a)-. In some embodiments, R^a is hydrogen or alkyl (such as C₁₋₆ (e.g., C₁₋₅, C₁₋₄, C₁₋₃ or C₁₋₂) alkyl).

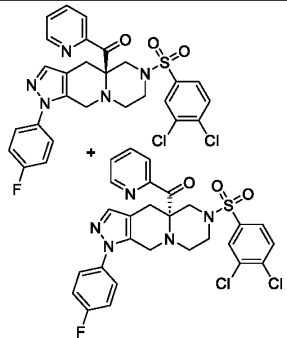
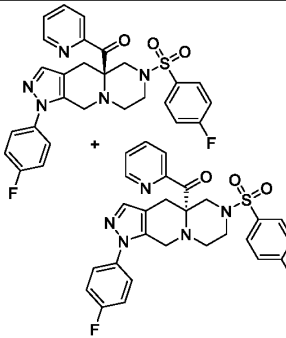
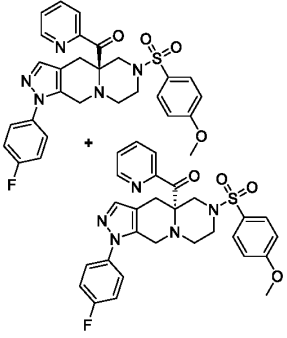
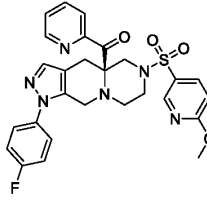
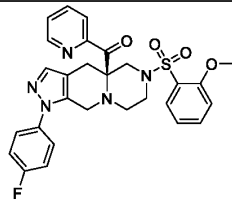
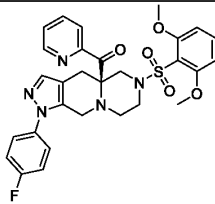
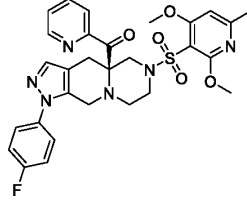
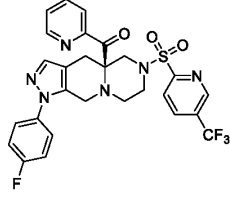
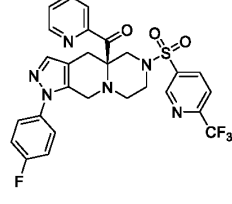
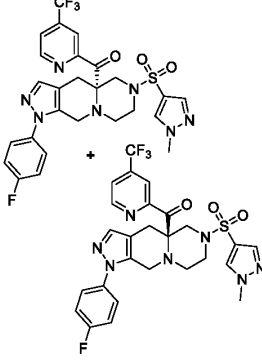
[0098] In some embodiments of Formula (Ia), Formula (Ib), Formula (Ia-1) or Formula (Ib-1), -L²-L³- is -S(=O)₂- or -S(=O)(=NH)-.

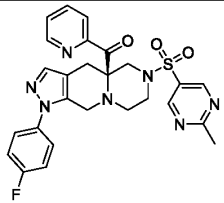
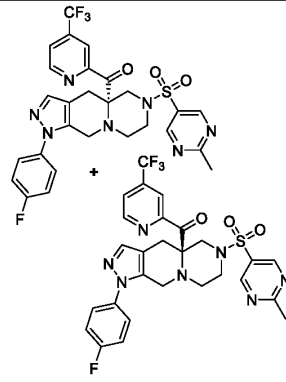
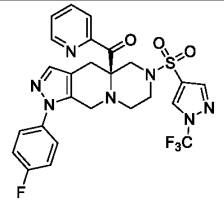
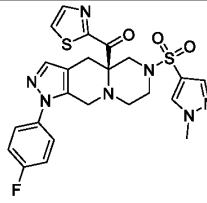
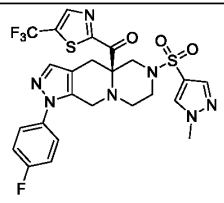
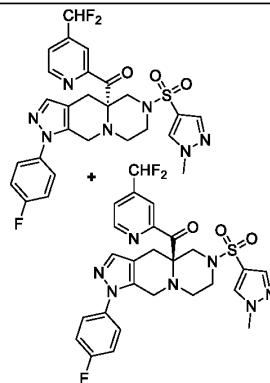
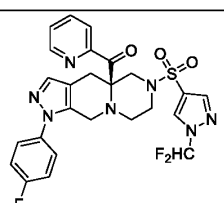
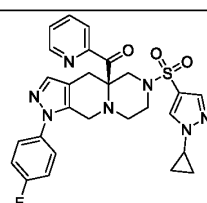
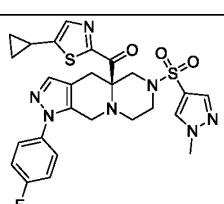
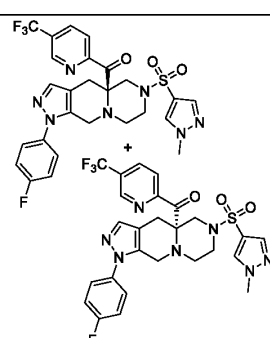
[0099] Provided herein are also compounds set forth in Table 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

TABLE 1 Exemplary Compounds

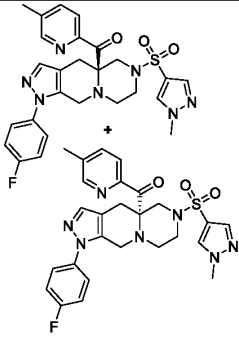
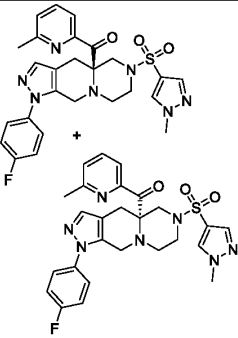
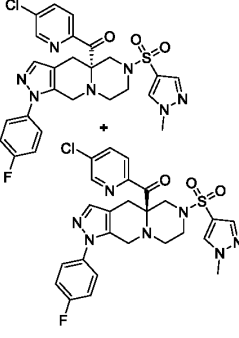
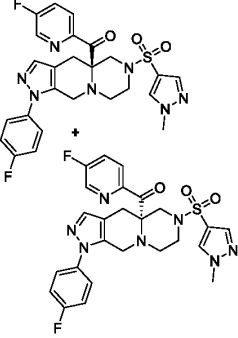
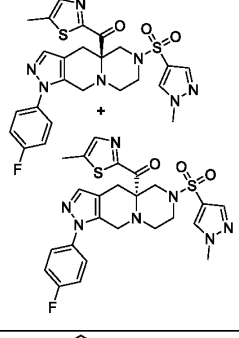
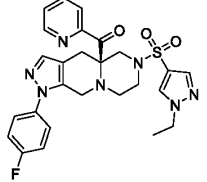
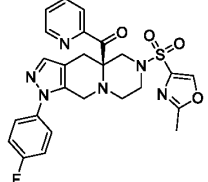
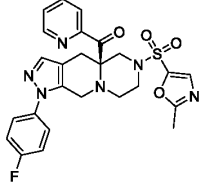
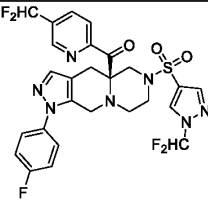
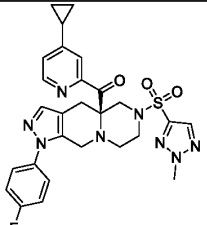
Compound	Structure	Compound	Structure
1A + 1B		2A + 2B	
3A + 3B		4A + 4B	
5A + 5B		6A + 6B	
7A + 7B		8A + 8B	

Compound	Structure	Compound	Structure
9A + 9B		10A + 10B	
11A + 11B		12A + 12B	
13A + 13B		14A + 14B	
15A + 15B		16A + 16B	

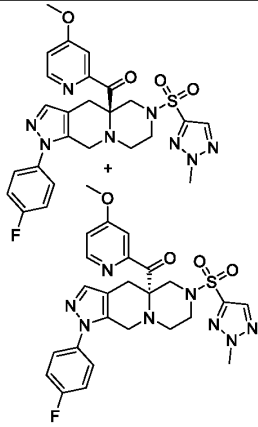
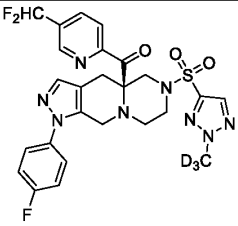
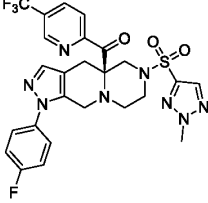
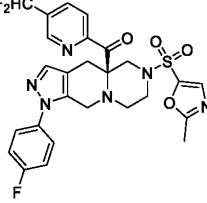
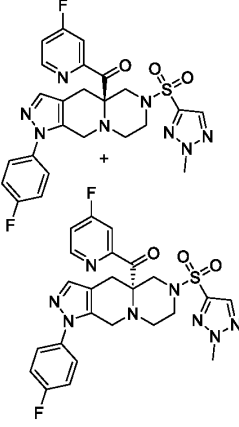
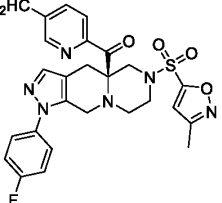
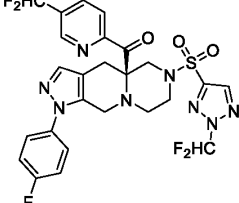
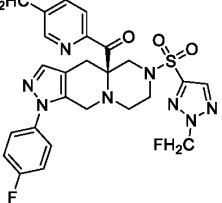
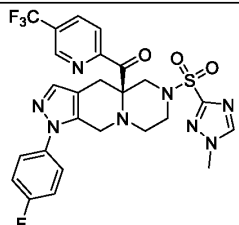
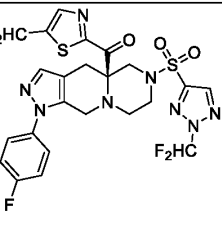
Compound	Structure	Compound	Structure
17A + 17B		18A + 18B	
19A + 19B		20A	
21A		22A	
23A		24A	
25A		26A + 26B	

Compound	Structure	Compound	Structure
27A		28A + 28B	
29A		30B	
31A		32A + 32B	
33A		34A	
35A		36A + 36B	

Compound	Structure	Compound	Structure
37A		38A + 38B	
39A		40A	
41A		42B	
43A		44A	
45A + 45B		46A	

Compound	Structure	Compound	Structure
47A + 47B		48A + 48B	
49A + 49B		50A + 50B	
51A + 51B		52A	
53A		54A	
55A		56A	

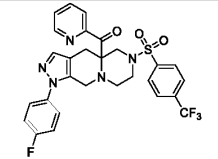
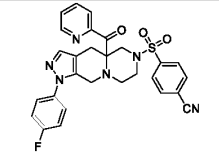
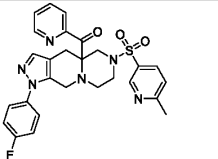
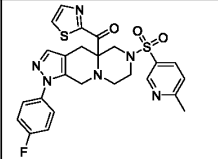
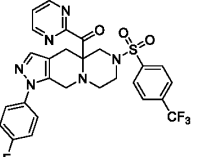
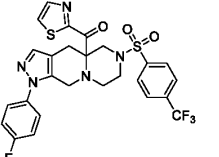
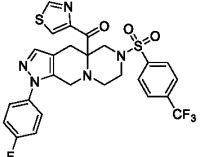
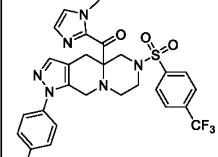
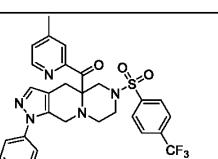
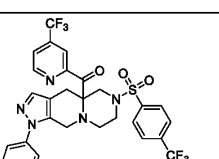
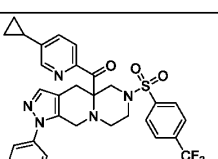
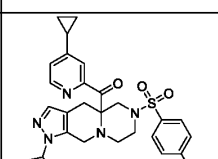
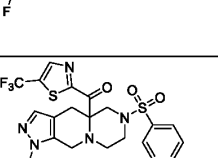
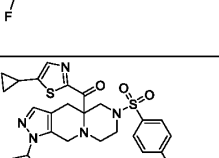
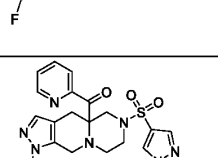
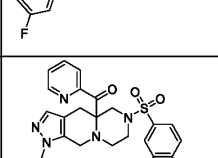
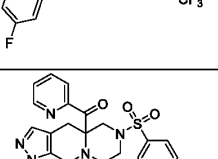
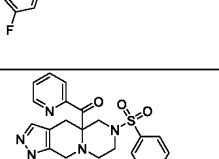
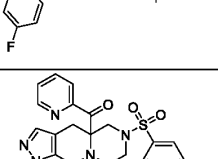
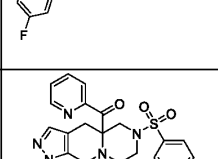
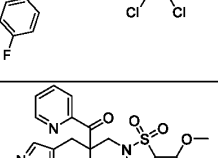
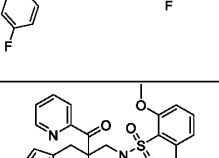
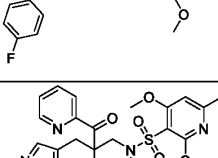
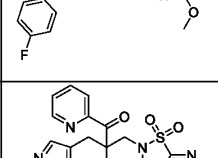
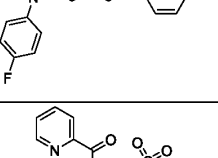
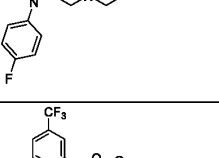
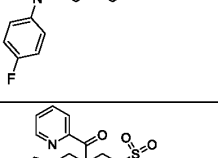
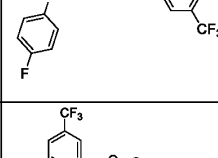
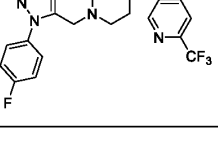
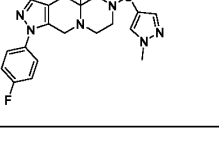
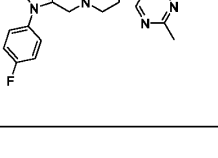
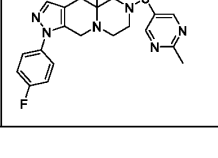
Compound	Structure	Compound	Structure
57A		58A	
59B		60A+ 60B	
61A		62A	
63A + 63B		64A	
65A		66A	

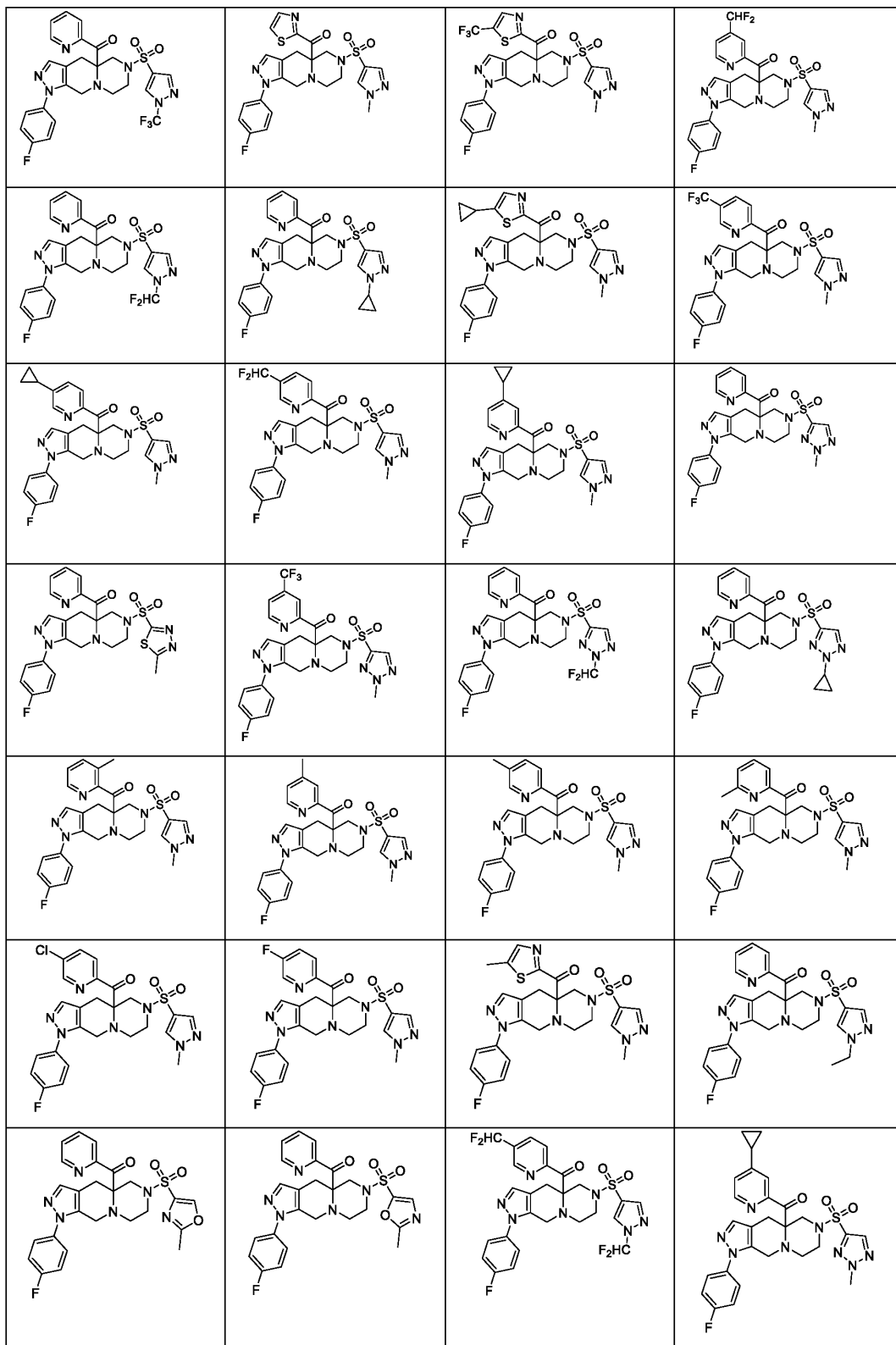
Compound	Structure	Compound	Structure
67A + 67B		68A	
69A		70A	
71A+ 71B		72A	
73A		74A	
75A		76A	

Compound	Structure	Compound	Structure
77A		78A	
79A+ 79B		80A+ 80B	
81A+ 81B		82A+ 82B	
83A+ 83B		84A+ 84B	

Compound	Structure	Compound	Structure
85A+ 85B		86A+ 86B	
87A+ 87B		88A+ 88B	
89A+ 89B		90A+ 90B	
91A+ 91B		92A+ 92B	

TABLE 2 Exemplary Compounds



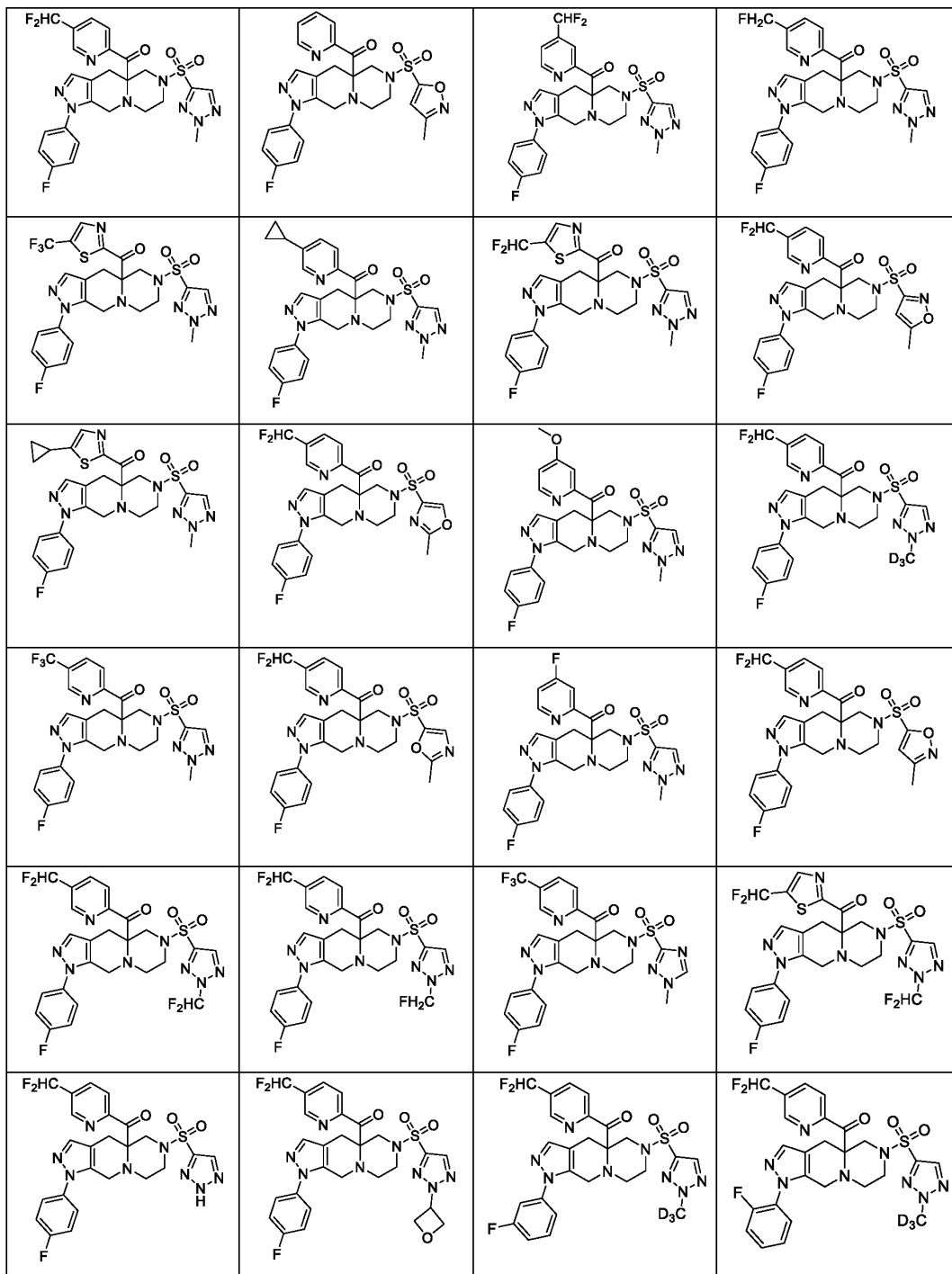
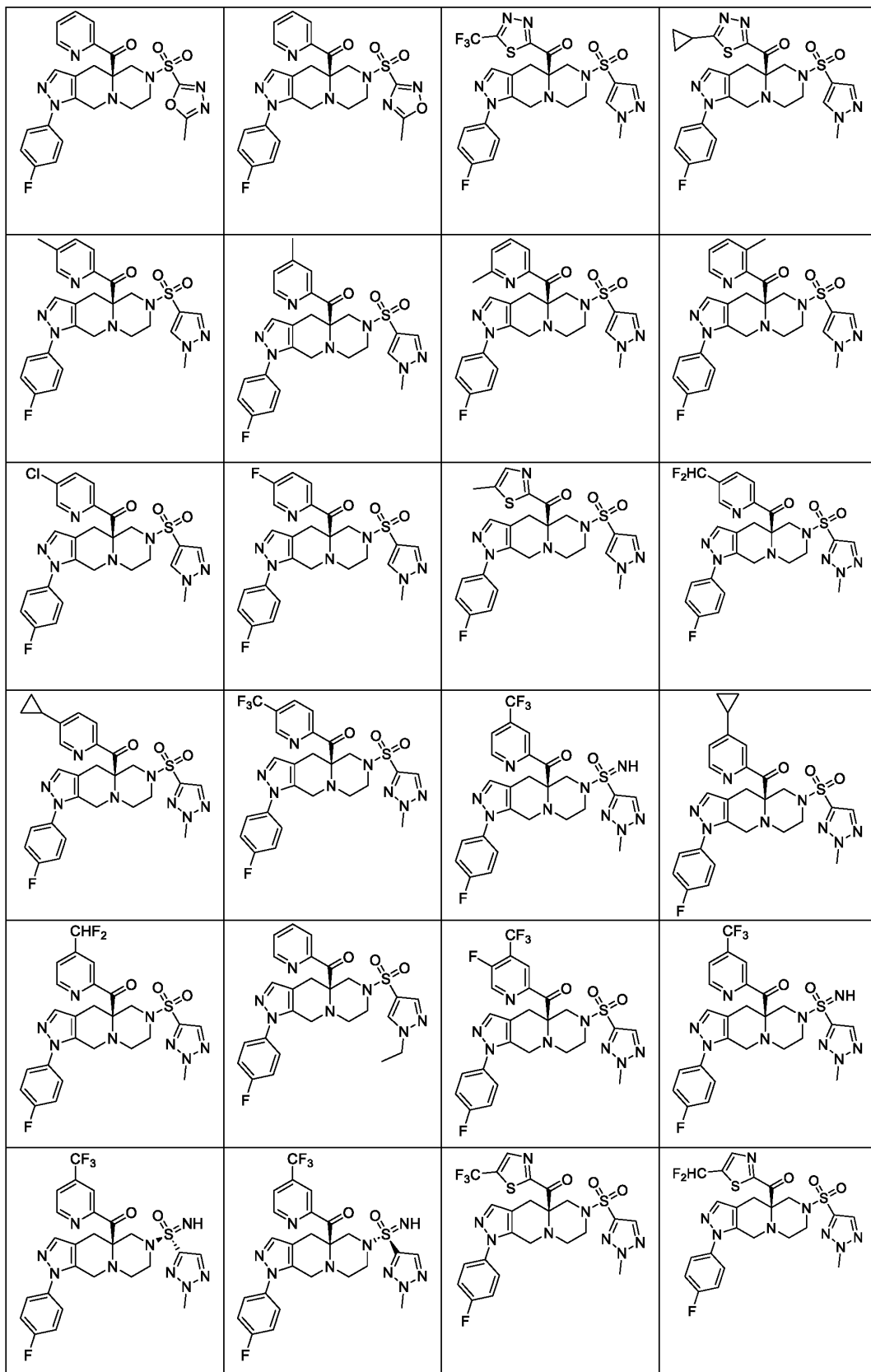
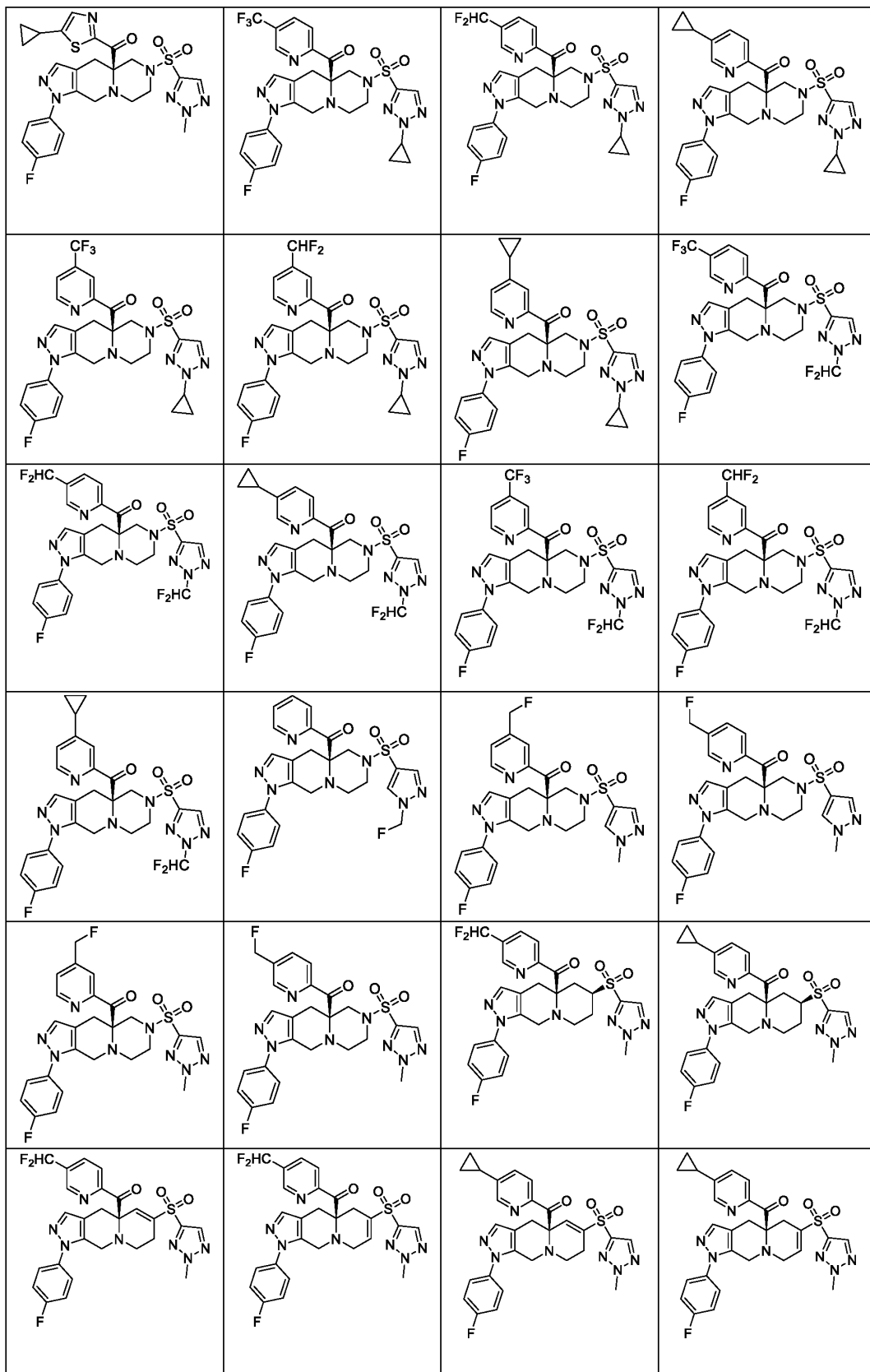
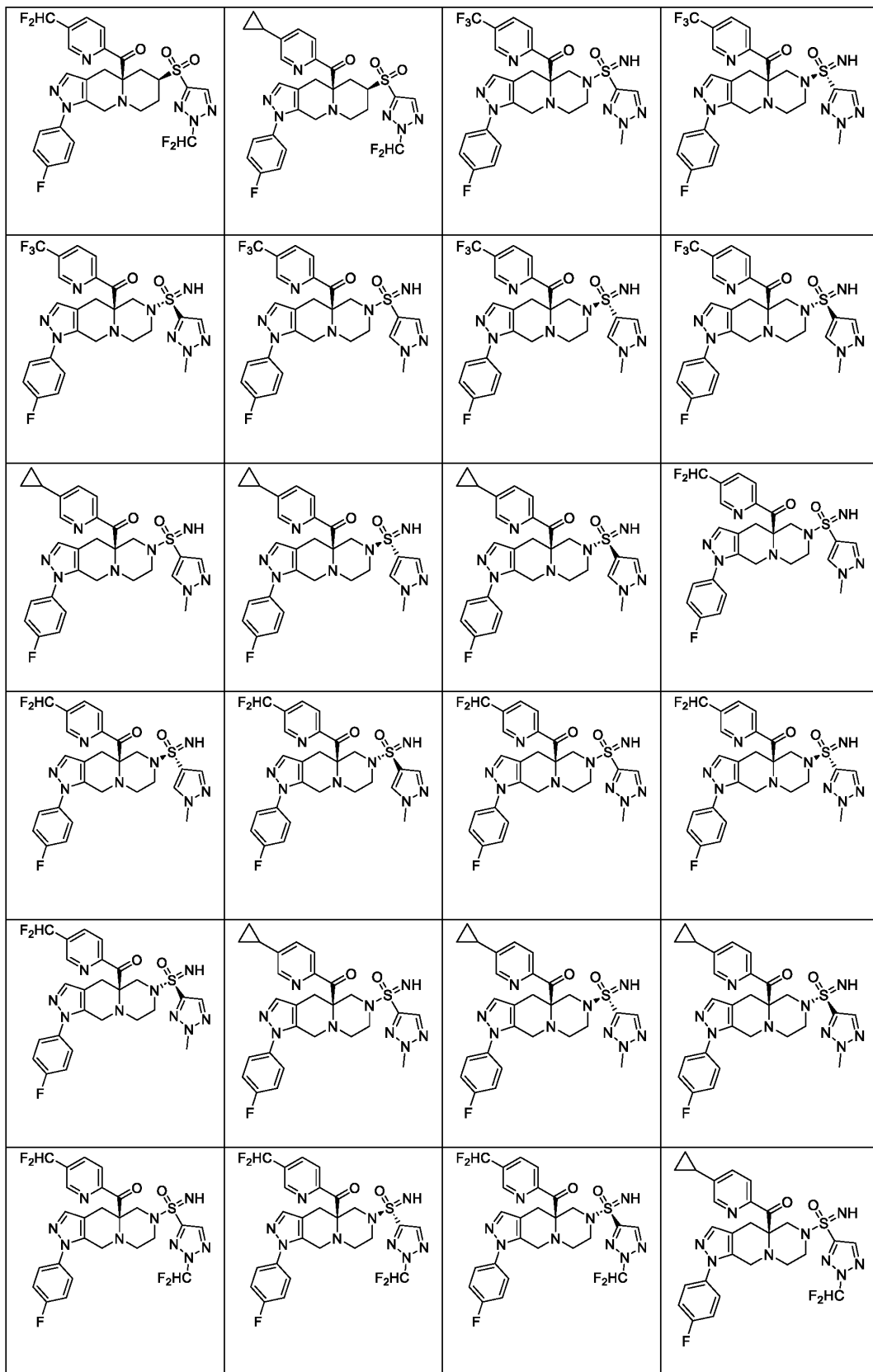
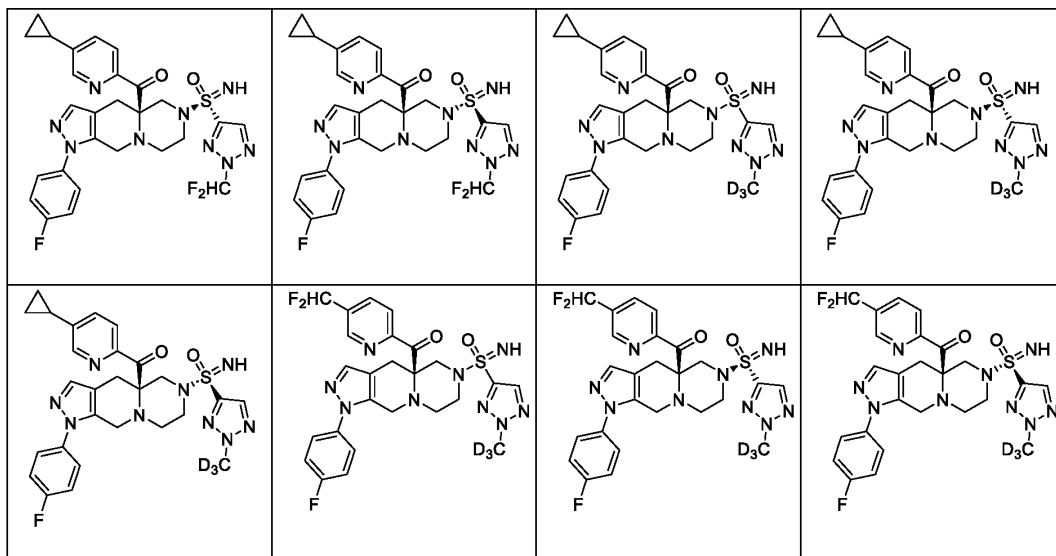


TABLE 3 Exemplary Compounds









Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[0100] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some embodiments, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Tautomers

[0101] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are

interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Isotopic form

[0102] Unless otherwise stated, compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^1H (protium), ^2H (deuterium), and ^3H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford some therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism.

[0103] For example, the compounds described herein may be artificially enriched in one or more particular isotopes. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes that are not predominantly found in nature. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes selected from deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In some embodiments, the compounds described herein are artificially enriched in one or more isotopes selected from ^2H , ^{11}C , ^{13}C , ^{14}C , ^{15}C , ^{12}N , ^{13}N , ^{15}N , ^{16}N , ^{16}O , ^{17}O , ^{14}F , ^{15}F , ^{16}F , ^{17}F , ^{18}F , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , ^{131}I , and ^{125}I . In some embodiments, the abundance of the enriched isotopes is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[0104] In some embodiments, the compound is deuterated in at least one position. In some embodiments, the compounds disclosed herein have some or all of the ^1H atoms replaced with ^2H atoms. Unless otherwise indicated, each hydrogen atom of the compounds disclosed herein is independently ^1H , ^2H (D) or ^3H (T). In some embodiments, one or more hydrogen atom of the compounds disclosed herein is ^2H (deuterium, or D).

[0105] The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997, and the following synthetic methods. For example, deuterium substituted compounds may be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**,

45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., 1981, 64(1-2), 9-32.

[0106] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

Pharmaceutically acceptable salts

[0107] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0108] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of several inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0109] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[0110] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic

acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, and their pharmaceutically acceptable acid addition salts.

[0111] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[0112] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Method of Treatment

[0113] Disclosed herein are methods of modulating glucocorticoid receptor (GR) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein.

[0114] Disclosed herein are methods of inhibiting GR in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein.

[0115] Disclosed herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein. In some embodiments, the disease or disorder is a GR associated disease or disorder.

[0116] In some embodiments, the disease or disorder is Cushing's syndrome, Addison's disease, osteoporosis, rheumatoid arthritis, asthma, rhinitis, adrenal function related diseases, human immunodeficiency virus, acquired immune deficiency syndrome, allergy or wound healing.

[0117] Also disclosed herein is use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for modulating GR, in a subject in need thereof.

[0118] Also disclosed herein is use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting GR, in a subject in need thereof.

[0119] Also disclosed herein is use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a disease or disorder, in a subject in need thereof. In some embodiments, the disease or disorder is a GR associated disease or disorder.

[0120] In some embodiments, the disease or disorder is Cushing's syndrome, Addison's disease, osteoporosis, rheumatoid arthritis, asthma, rhinitis, adrenal function related diseases, human immunodeficiency virus, acquired immune deficiency syndrome, allergy or wound healing.

Dosing

[0121] In some embodiments, the compositions containing the compound(s) described herein are administered for therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[0122] In some embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

Routes of Administration

[0123] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

Pharmaceutical Compositions/Formulations

[0124] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

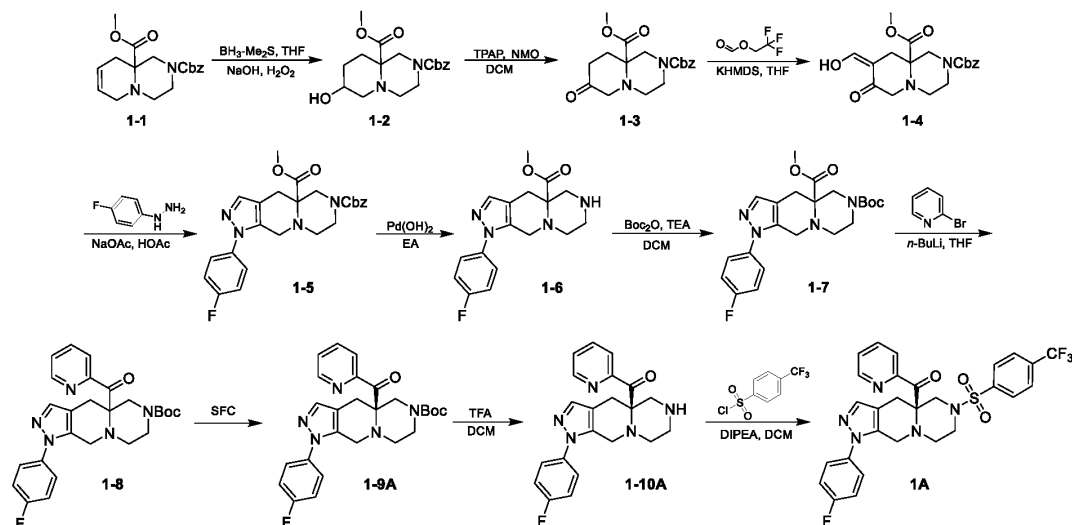
[0125] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Dekker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

Examples

[0126] For the purpose of illustration, the following examples are included. The Examples provided herein describe the synthesis of compounds disclosed herein as well as intermediates used to prepare the compounds. However, it is to be understood that these examples do not limit the present disclosure and are only meant to suggest a method of practicing the present disclosure. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds of the present disclosure, and alternative methods for preparing the compounds of the present disclosure are deemed to be within the scope of the present disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents and building blocks known in the art other than those described, and/or by making routine modifications of reaction conditions. Besides, persons skilled in the art will also understand that individual steps described herein or in the separate batches of a compound may be combined. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure. The following description is, therefore, not intended to limit the scope of the present disclosure, but rather is specified by the claims appended hereto.

Example 1: Synthesis of Exemplary Compounds

Example 1.1: Synthesis of Compound 1A



[0127] Step 1: To a solution of **Compound 1-1** (20 g, 60.61 mmol) in anhydrous tetrahydrofuran (200 mL) were slowly dropped 10 M $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (18.2 mL, 181.82 mmol) at -10°C . The mixture was heated to 25°C for 3 h. Then, the mixture was slowly added dropwise 3M NaOH (10.1 mL, 30.30 mmol) and 30% H_2O_2 (31.2 mL, 303.05 mmol) at -10°C . The mixture was heated to 25°C for 1 h. The reaction mixture was quenched with sat. Na_2SO_3 and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 1-2** (5.1 g, 24% yield) as a yellow oil. LCMS: 349.2 $[\text{M}+\text{H}]^+$.

[0128] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.43 – 7.24 (m, 5H), 5.15 – 4.94 (m, 2H), 4.21 (dd, J = 12.8, 1.6 Hz, 1H), 3.91 (d, J = 12.0 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.58 – 3.42 (m, 3H), 3.15 – 2.89 (m, 3H), 2.87 – 2.65 (m, 1H), 2.59 – 2.52 (m, 1H), 2.39 (d, J = 9.6 Hz, 1H), 1.84 – 1.48 (m, 3H), 1.38 – 1.19 (m, 1H).

[0129] Step 2: To a solution of **Compound 1-2** (5 g, 14.37 mmol) in dichloromethane (50 mL) were added 4A molecular sieves (5 g), NMO (2.5 g, 21.55 mmol) and TPAP (500 mg, 1.44 mmol) at 0°C . The reaction mixture was stirred at room temperature under N_2 atmosphere for 3 h. The mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 1-3** (3.2 g, 64% yield) as a yellow oil. LCMS: 347.1 $[\text{M}+\text{H}]^+$.

[0130] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.42 – 7.29 (m, 5H), 5.17 – 4.99 (m, 2H), 4.38 (d, J = 13.2 Hz, 1H), 3.94 (d, J = 9.6 Hz, 1H), 3.67 – 3.51 (m, 4H), 3.17 (d, J = 16.4 Hz, 1H), 3.07 – 2.77 (m, 3H), 2.61 – 2.53 (m, 1H), 2.42 – 2.33 (m, 1H), 2.30 – 2.14 (m, 2H), 1.83 – 1.70 (m, 1H).

[0131] Step 3: To a solution of **Compound 1-3** (3.2 g, 9.25 mmol) in anhydrous tetrahydrofuran (30 mL) were added KHMDS (27.7 mL, 27.75 mmol) at -78°C . The reaction mixture was stirred at

this temperature for 1 h. Then, 2,2,2-trifluoroethyl formate (7.1 g, 55.49 mmol) was added. The mixture was stirred at -78 °C under N₂ atmosphere for 1 h. The reaction mixture was quenched with 3 M HCl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide **Compound 1-4** (3 g, 87% yield) as a red oil. LCMS: 375.1 [M+H]⁺.

[0132] Step 4: To a solution of **Compound 1-4** (3 g, 8.02 mmol) in acetic acid (30 mL) were added NaOAc (986 mg, 12.03 mmol) and 4-fluorophenylhydrazine hydrochloride (1.9 g, 12.03 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 1-5** (1.5 g, 40% yield) as a red solid. LCMS: 465.2 [M+H]⁺.

[0133] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.83 – 7.70 (m, 2H), 7.42 – 7.19 (m, 7H), 5.09 (s, 2H), 4.34 (d, *J* = 13.6 Hz, 1H), 4.04 – 3.86 (m, 3H), 3.38 – 3.30 (m, 3H), 3.22 – 3.00 (m, 4H), 2.86 – 2.74 (m, 1H), 2.59 (d, *J* = 15.6 Hz, 1H).

[0134] Step 5: To a solution of **Compound 1-5** (1.5 g, 3.23 mmol) in ethyl acetate (15 mL) was added Pd(OH)₂ (633 mg, 4.52 mmol). The mixture was stirred at 25 °C under H₂ atmosphere for 2 h. The mixture was filtered. The filtrate was concentrated under reduced pressure to provide **Compound 1-6** (1.15 g, crude) as a yellow solid. LCMS: 331.1 [M+H]⁺.

[0135] Step 6: To a solution of **Compound 1-6** (1.15 g, crude) in dichloromethane (10 mL) were added di-*tert*-butyldicarbonate (2.1 g, 9.48 mmol) and TEA (957 mg, 9.48 mmol). The mixture was stirred at 25 °C under N₂ atmosphere for 1 h. The mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 1-7** (0.8 g, 57% yield) as a yellow solid. LCMS: 431.1 [M+H]⁺.

[0136] ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.35 (m, 3H), 7.22 – 7.06 (m, 2H), 4.43 (d, *J* = 12.8 Hz, 1H), 4.32 (d, *J* = 15.2 Hz, 1H), 4.08 – 3.89 (m, 1H), 3.79 (d, *J* = 15.2 Hz, 1H), 3.65 (s, 3H), 3.35 – 3.04 (m, 3H), 2.98 (d, *J* = 13.2 Hz, 1H), 2.72 (d, *J* = 9.6 Hz, 1H), 2.60 (d, *J* = 15.2 Hz, 1H), 1.45 (s, 9H).

[0137] Step 7: To a solution of 2-bromopyridine (370 mg, 3.02 mmol) in anhydrous tetrahydrofuran (15 mL) were added 1.6 M *n*-butyllithium (1.9 mL, 3.02 mmol) at -78 °C. The reaction mixture was stirred at this temperature for 1 h. Then, **Compound 1-7** (130 mg, 0.30 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched with sat. NH₄Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 1-8** (75 mg, 52% yield) as a yellow solid. LCMS: 478.2 [M+H]⁺.

[0138] ^1H NMR (400 MHz, CDCl_3) δ 8.68 (s, 1H), 7.90 – 7.70 (m, 2H), 7.49 – 7.40 (m, 3H), 7.34 – 7.30 (m, 1H), 7.20 – 7.10 (m, 2H), 5.53 (s, 1H), 4.61 (d, J = 15.2 Hz, 1H), 4.48 – 4.36 (m, 1H), 4.12 (s, 1H), 4.03 – 3.85 (m, 1H), 3.55 (s, 1H), 3.32 – 3.18 (m, 1H), 3.19 – 3.01 (m, 1H), 2.89 – 2.74 (m, 2H), 1.60 – 1.59 (m, 9H).

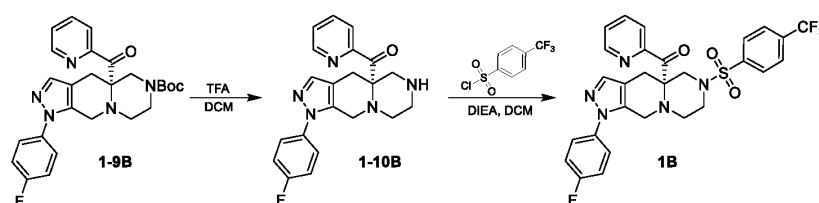
[0139] Step 8: **Compound 1-8** (75 g) was separated by SFC (column: DAICELCHIRALCEL®IG (250*25 mm, 10 μ m); mobile phase A: Supercritical CO_2 ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)) to provide **Compound 1-9A** (26 mg, 18% yield) with a retention time of 1.657 min as a white solid and **Compound 1-9B** (24 mg, 17% yield) with a retention time of 2.635 min as a white solid. LCMS: 478.2 $[\text{M}+\text{H}]^+$.

[0140] Step 9: To a solution of **Compound 1-9A** (20 mg, 0.04 mmol) in dichloromethane (2 mL) was added TFA (1 mL). The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to provide **Compound 1-10A** (14 mg, 89% yield) as a yellow solid. LCMS: 378.1 $[\text{M}+\text{H}]^+$.

[0141] Step 10: To a solution of **Compound 1-10A** (14 mg, 0.04 mmol) in dichloromethane (3 mL) were added DIPEA (14 mg, 0.11 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (9.9 mg, 0.04 mmol). The mixture was stirred at 25 °C under N_2 atmosphere for 30 min and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by Prep-HPLC to afford the corresponding **Compound 1A** (12 mg, 55% yield). LCMS: 586.2 $[\text{M}+\text{H}]^+$.

[0142] ^1H NMR (400 MHz, CDCl_3) δ 8.62 (d, J = 3.2 Hz, 1H), 7.80 (s, 4H), 7.71 (d, J = 8.4 Hz, 2H), 7.50 – 7.38 (m, 3H), 7.32 (s, 1H), 7.14 (t, J = 8.4 Hz, 2H), 5.41 (s, 1H), 4.68 (d, J = 14.0 Hz, 1H), 4.23 (d, J = 10.0 Hz, 1H), 3.95 (s, 1H), 3.76 (d, J = 9.2 Hz, 1H), 3.63 (s, 1H), 2.99 - 2.71 (m, 4H).

Example 1.2: Synthesis of Compound 1B

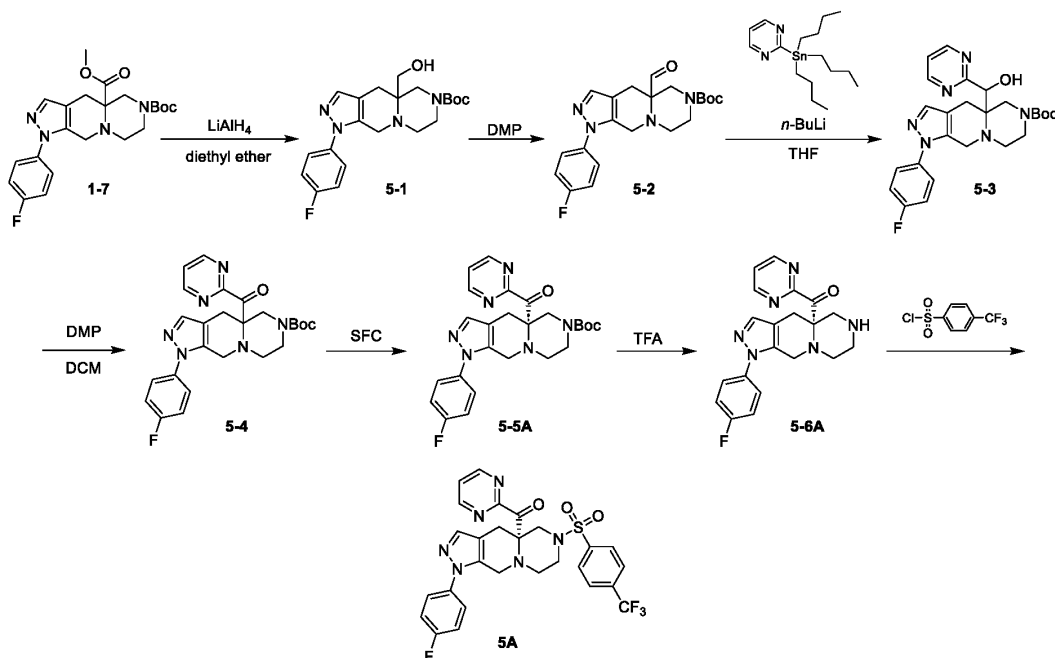


[0143] Step 1: To a solution of **Compound 1-9B** (20 mg, 0.04 mmol) in dichloromethane (2 mL) were added TFA (1 mL). The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to provide **Compound 1-10B** (13 mg, 89% yield) as a yellow solid. LCMS: 378.1 $[\text{M}+\text{H}]^+$.

[0144] Step 2: To a solution of **Compound 1-10B** (13 mg, 0.04 mmol) in dichloromethane (2 mL) were added DIPEA (14 mg, 0.11 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (9.9 mg, 0.04 mmol). The mixture was stirred at 25 °C under N_2 atmosphere for 30 min and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by Prep-HPLC to afford the corresponding **Compound 1B** (10 mg, 50% yield). LCMS: 586.2 $[\text{M}+\text{H}]^+$.

[0145] ^1H NMR (400 MHz, CDCl_3) δ 8.60 (d, J = 4.4 Hz, 1H), 7.86 – 7.76 (m, 4H), 7.70 (d, J = 8.4 Hz, 2H), 7.46 – 7.41 (m, 3H), 7.32 (s, 1H), 7.14 (t, J = 8.4 Hz, 2H), 5.39 (d, J = 11.6 Hz, 1H), 4.66 (d, J = 14.8 Hz, 1H), 4.20 (d, J = 15.6 Hz, 1H), 3.91 (d, J = 14.8 Hz, 1H), 3.74 (d, J = 11.2 Hz, 1H), 3.67 – 3.54 (m, 1H), 2.91 (d, J = 11.2 Hz, 1H), 2.82 – 2.66 (m, 3H).

Example 1.3: Synthesis of Compound 5A



[0146] Step 1: To a solution of **Compound 1-7** (801 mg, 1.86 mmol) in diethyl ether (15 ml) was added LiAlH_4 (92 mg, 2.42 mmol) at 0 °C for 10 min. The reaction mixture was at 25 °C under N_2 atmosphere for 0.5 h. The reaction was diluted with water and ethyl acetate. The organic layer was separated, washed with further brine, and concentrated in vacuo. The obtained residue was purified by flash silica gel chromatography to afford **Compound 5-1** (350 mg, 46.7 % yield) as a yellow oil. LCMS: 403.3 $[\text{M}+\text{H}]^+$.

[0147] Step 2: To a solution of **Compound 5-1** (350 mg, 0.87 mmol) in dichloromethane (10 ml) was added Dess-Martin periodinane (480 mg, 1.13 mmol). The reaction mixture was at 25 °C under N_2 atmosphere for 1 h. The reaction was diluted with water and DCM. The organic layer was separated, washed with further brine, and concentrated in vacuo. The obtained residue was purified by flash silica gel chromatography to afford **Compound 5-2** (250 mg, 71.8 % yield) as a yellow oil. LCMS: 401.2 $[\text{M}+\text{H}]^+$.

[0148] Step 3: To a solution of $n\text{-BuLi}$ (2.22 ml, 3.55 mmol, 1.6 M) in anhydrous tetrahydrofuran (15 mL) were added 2-(tributylstannyl)pyrimidine (1.31 g, 3.55 mmol) in anhydrous tetrahydrofuran (2 ml) at -78 °C. After 1.5 h, **Compound 5-2** (142 mg, 0.36 mmol) in anhydrous tetrahydrofuran (2 ml) was added into the mixture. The reaction mixture was stirred at -78 °C for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The combined organic layer

was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 5-3** (120 mg, 70.4 % yield) as a yellow solid. LCMS: 481.3 [M+H]⁺

[0149] Step 4: To a solution of **Compound 5-3** (100 mg, 0.21 mmol) in dichloromethane (5 ml) was added Dess-Martin periodinane (106 mg, 0.25 mmol) at 0 °C. Then the reaction mixture was at 25 °C under N₂ atmosphere for 12 h. The reaction was quenched with aq. Na₂SO₃, extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The obtained residue was purified by flash silica gel chromatography to afford **Compound 5-4** (60 mg, 35.2 % yield) as a white solid. LCMS: 479.3 [M+H]⁺.

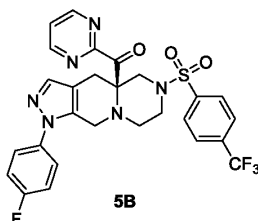
[0150] Step 5: **Compound 5-4** (60 mg) was purified by SFC (column: DAICELCHIRALCEL®IB (250*25 mm, 10μm); mobile phase A: Supercritical CO₂; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)) to afford **Compound 5-5A** (25 mg, 41.7 % yield) with a retention time of 0.896 min as a white solid and **Compound 5-5B** (19 mg, 31.7 % yield) with a retention time of 1.951 min as a white solid.

[0151] Step 6: To a solution of **Compound 5-5A** (25 mg, 0.05 mmol) in dichloromethane (2 mL) were added TFA (1 mL). The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to provide **Compound 5-6A** (24 mg, crude) as a yellow solid. LCMS: 379.1 [M+H]⁺.

[0152] Step 7: To a solution of **Compound 5-6A** (24 mg, crude) in dichloromethane (3 mL) were added DIPEA (14 mg, 0.11 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (12 mg, 0.05 mmol). The mixture was stirred at 25 °C under N₂ atmosphere for 30 min and filtered. The filtrate was concentrated under reduced pressure and then purified by Prep-HPLC to afford the corresponding **Compound 5A** (6 mg, 20% yield). LCMS: 587.3 [M+H]⁺.

[0153] ¹HNMR (400 MHz, CDCl₃): δ 8.88 (d, *J* = 4.9 Hz, 2H), 7.87 – 7.81 (m, 2H), 7.79 – 7.74 (m, 2H), 7.47 – 7.39 (m, 3H), 7.35 (s, 1H), 7.18 – 7.10 (m, 2H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H), 4.05 – 3.85 (m, 2H), 3.63 (d, *J* = 10.6 Hz, 1H), 3.56 – 3.42 (m, 1H), 2.97 – 2.82 (m, 2H), 2.80 – 2.68 (m, 2H).

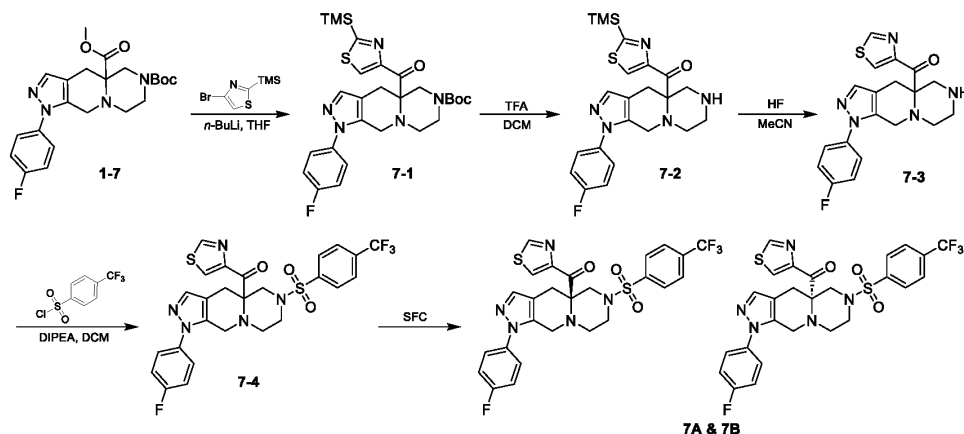
Example 1.4: Synthesis of Compound 5B



[0154] **Compound 5B** was synthesized from **Compound 5-5B** as described in **Compound 5A**. LCMS: 587.3 [M+H]⁺.

[0155] ^1H NMR (400 MHz, CDCl_3): δ 8.89 (d, J = 4.8 Hz, 2H), 7.87 - 7.73 (m, 4H), 7.50 - 7.39 (m, 3H), 7.35 (s, 1H), 7.20 - 7.09 (m, 2H), 5.19 - 4.97 (m, 1H), 4.65 (d, J = 14.8 Hz, 1H), 4.09 - 3.85 (m, 2H), 3.65 (d, J = 9.4 Hz, 2H), 3.53 (s, 2H), 3.09 - 2.65 (m, 4H).

Example 1.5: Synthesis of Compounds 7A and 7B



[0156] Step 1: To a solution of 4-bromo-2-(trimethylsilyl)thiazole (546 mg, 2.32 mmol) in anhydrous tetrahydrofuran (5 mL) were added *n*-butyllithium (1.5 mL, 2.32 mmol, 1.6 M) at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred at this temperature for 1 h. Then, **Compound 1-7** (100 mg, 0.23 mmol) was added. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography to provide **Compound 7-1** (80 mg, 63% yield) as a yellow solid. LCMS: 556.3 $[\text{M}+\text{H}]^+$.

[0157] Step 2: To a solution of **Compound 7-1** (80 mg, 0.14 mmol) in dichloromethane (1 mL) was added TFA (0.5 mL). The reaction mixture was stirred at $25\text{ }^\circ\text{C}$ for 1 h. The mixture was concentrated under reduced pressure to provide **Compound 7-2** (60 mg, 91% yield) as a yellow solid. LCMS: 456.3 $[\text{M}+\text{H}]^+$.

[0158] Step 3: To a solution of **Compound 7-2** (60 mg, 0.13 mmol) in acetonitrile (1 mL) were added 70% pyridine hydrofluoric acid solution (0.1 mL). The reaction mixture was stirred at $25\text{ }^\circ\text{C}$ for 1 h. The mixture was concentrated under reduced pressure to provide **Compound 7-3** (30 mg, 67% yield) as a yellow solid. LCMS: 384.1 $[\text{M}+\text{H}]^+$.

[0159] Step 4: To a solution of **Compound 7-3** (30 mg, 0.08 mmol) in dichloromethane (2 mL) were added DIEA (40 mg, 0.31 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (21 mg, 0.09 mmol). The mixture was stirred at $25\text{ }^\circ\text{C}$ under N_2 atmosphere for 30 min and filtered. The filtrate was concentrated under reduced pressure and then purified by Prep-HPLC to afford **Compound 7-4** (30 mg, 65% yield) as a white solid. LCMS: 592.3 $[\text{M}+\text{H}]^+$.

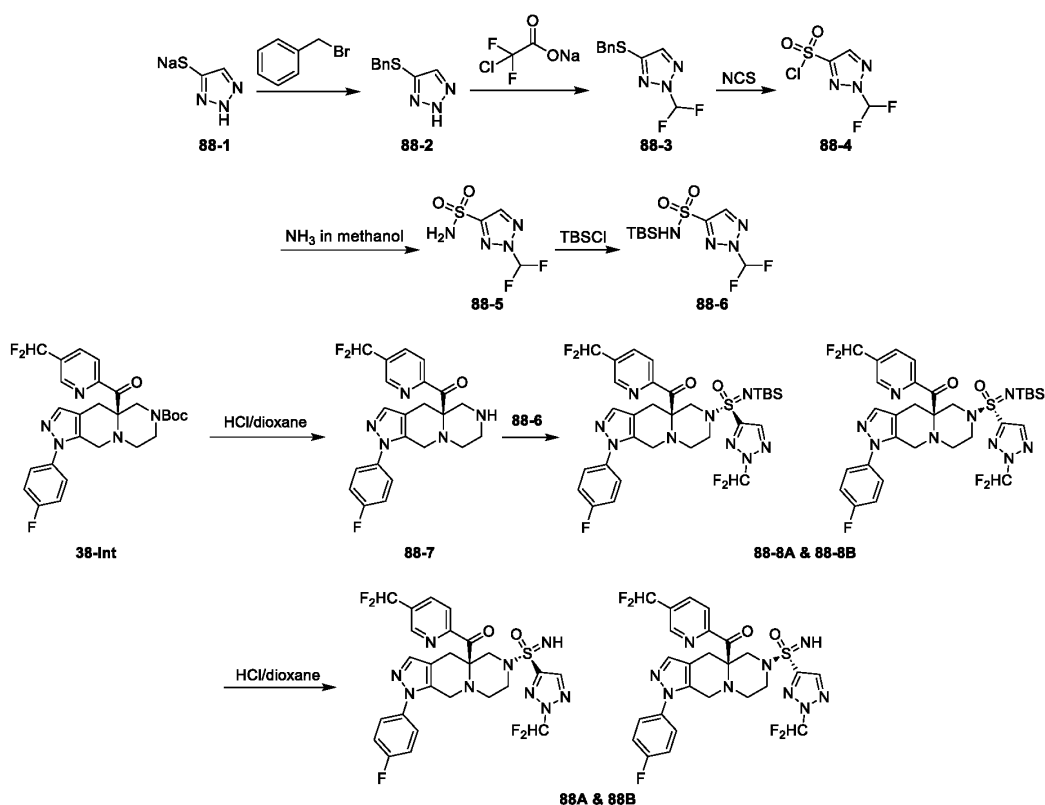
[0160] Step 5: **Compound 7-4** (30 mg) was separated by SFC (column: DAICELCHIRALCEL®AS (250*30 mm, 10 μm); mobile phase A: Supercritical CO_2 ; mobile phase

B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)) to afford **Compound 7A** (4 mg, 13% yield) with a retention time of 1.278 min and **Compound 7B** (5 mg, 17% yield) with a retention time of 2.485 min.

[0161] Compound 7A: LCMS: 592.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.8 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.35 (s, 1H), 7.18 – 7.09 (m, 2H), 5.28 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 14.8 Hz, 1H), 4.11 (d, *J* = 16.4 Hz, 1H), 4.03 – 3.90 (m, 1H), 3.81 (d, *J* = 10.4 Hz, 1H), 3.77 – 3.61 (m, 1H), 3.04 – 2.94 (m, 1H), 2.85 – 2.65 (m, 3H).

[0162] Compound 7B: LCMS: 592.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 3.2 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.34 (s, 1H), 7.18 – 7.07 (m, 2H), 5.26 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 14.8 Hz, 1H), 4.07 (d, *J* = 16.0 Hz, 1H), 3.92 (d, *J* = 14.8 Hz, 1H), 3.79 (d, *J* = 10.8 Hz, 1H), 3.71 – 3.58 (m, 1H), 3.00 – 2.87 (m, 1H), 2.84 – 2.64 (m, 3H).

Example 1.6: Synthesis of Compounds 88A and 88B



[0163] Step 1: To a solution of **Compound 88-1** (33 g, 326 mmol) in ethanol (200 mL) was added benzyl bromide (55.8 g, 326 mmol) and stirred at 25 °C under N₂ for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated to afford **Compound 88-2** (53 g, 85% yield) as a white solid. LCMS: 192.2 [M+H]⁺.

[0164] Step 2: To a solution of **Compound 88-2** (30 g, 157 mmol) in DMF (200 mL) were added sodium 2-chloro-2,2-difluoroacetate (47.8 g, 314 mmol) and cesium carbonate (102 g, 314 mmol). The reaction mixture was stirred at 70 °C under N₂ for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The obtained residue was purified by flash silica gel chromatography to afford **Compound 88-3** (5.1 g, 13% yield) as a yellow oil. LCMS: 242.1 [M+H]⁺.

[0165] Step 3: To a solution of **Compound 88-3** (5.1 g, 21 mmol) in acetic acid (48 mL) and water (24 mL) was added NCS (11.3 g, 86 mmol). The reaction mixture was stirred at 30 °C under N₂ for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The obtained residue was purified by flash silica gel chromatography to afford **Compound 88-4** (3.1 g, 68% yield) as a yellow oil. ¹HNMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 7.45 (t, *J* = 57.6 Hz, 1H).

[0166] Step 4: To a solution of **Compound 88-4** (1.9 g, 8.73 mmol) in acetonitrile (10 mL) was added 7 M ammonia in methanol (20 mL). The reaction mixture was stirred at 25 °C under N₂ for 2 h. The mixture was concentrated. The obtained residue was purified by flash silica gel chromatography to afford **Compound 88-5** (1.0 g, 58% yield) as a white solid. LCMS: 197.1 [M-H]⁻.

[0167] Step 5: To a solution of **Compound 88-5** (500 mg, 2.52 mmol) in THF (3 mL) was added NaH (202 mg, 5.05 mmol) at 0 °C and stirred for 0.5 h. Then, tert-butylchlorodimethylsilane (456 mg, 3.03 mmol) was added. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with sat. NH₄Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained residue was purified by flash silica gel chromatography to afford **Compound 88-6** (300 mg, 38% yield) as a white solid. LCMS: 311.1 [M-H]⁻.

[0168] Step 6: To a solution of **Compound 38-Int** (100 mg, 0.19 mmol) in 1,4-dioxane (1 mL) was added 4 M HCl in dioxane (1 mL). The reaction mixture was stirred at 25 °C under N₂ for 1 h. The mixture was quenched with sat. NaHCO₃. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford **Compound 88-7** (75 mg, 92% yield) as a yellow solid. LCMS: 428.1 [M+H]⁺.

[0169] Step 7: To a mixture of 4A molecular sieve (100 mg) and **Compound 88-6** (81 mg, 0.26 mmol) in dichloromethane (4 mL) was added TEA (0.12 mL, 0.86 mmol). The mixture was stirred at 25 °C for 10 min. Dichlorotriphenylphosphorane (144 mg, 0.43 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. **Compound 88-7** (50 mg, 0.12 mmol) was added to this reaction mixture at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. This reaction mixture was quenched with sat. NaHCO₃ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by Prep-HPLC to afford **Compound 88-8A** (15 mg, 17.3% yield) and **Compound 88-8B** (20 mg, 23.1 % yield). LCMS: 722.1 [M+H]⁺.

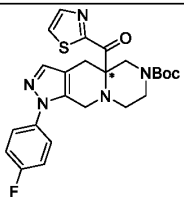
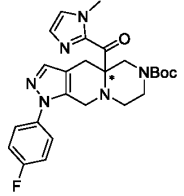
[0170] Step 8: To a solution of **Compound 88-8A** (15 mg, 0.021 mmol) in 1,4-dioxane (1 mL) was added 4 M HCl in dioxane (1 mL). The reaction mixture was stirred at 25 °C for 1 h. This mixture was quenched with sat. NaHCO₃ and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The obtained residue was purified by Prep-HPLC to afford **Compound 88A** (5.16 mg, 40.4% yield). LCMS: 608.3 [M+H]⁺.

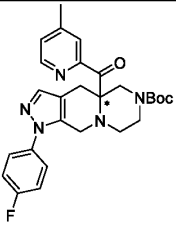
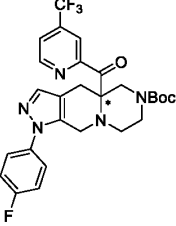
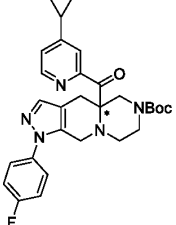
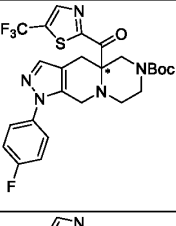
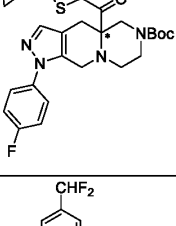
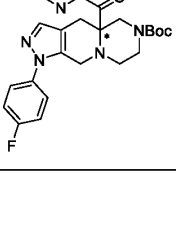
[0171] ¹H NMR (400 MHz, CDCl₃) δ 8.87 (s, 1H), 8.10 (s, 1H), 8.05 – 7.95 (m, 2H), 7.46 – 7.41 (m, 2H), 7.38 (t, *J* = 57.8 Hz, 1H), 7.35 (s, 1H), 7.20 – 7.14 (m, 2H), 6.79 (t, *J* = 55.4 Hz, 1H), 5.77 – 5.58 (m, 1H), 4.77 – 4.63 (m, 1H), 4.24 – 3.94 (m, 3H), 3.79 – 3.62 (m, 1H), 3.39 – 2.71 (m, 4H), 2.06 (brs, 1H).

[0172] Step 4: To a solution of **Compound 88-8B** (15 mg, 0.021 mmol) in 1,4-dioxane (1 mL) was added 4M HCl in dioxane (1 mL). The reaction mixture was stirred at 25 °C for 1 h. This mixture was quenched with sat. NaHCO₃ and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The obtained residue was purified by Prep-HPLC to afford **Compound 88B** (8.63 mg, 67.5 % yield). LCMS: 608.4 [M+H]⁺.

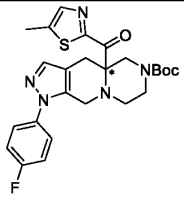
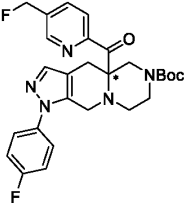
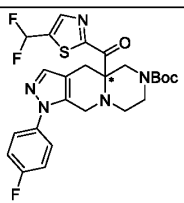
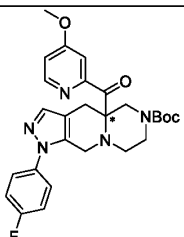
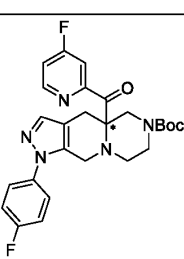
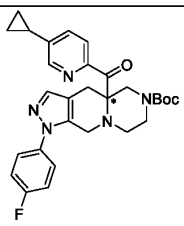
¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (s, 1H), 8.45 (s, 1H), 8.26 (t, *J* = 57.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.42 (s, 1H), 7.38 – 7.31 (m, 2H), 7.26 (t, *J* = 54.8 Hz, 1H), 5.34 – 5.20 (m, 2H), 4.42 (d, *J* = 15.2 Hz, 1H), 4.19 (d, *J* = 15.2 Hz, 1H), 4.07 (d, *J* = 16.0 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.41 – 3.35 (m, 1H), 3.02 – 2.93 (m, 1H), 2.82 – 2.70 (m, 2H), 2.69 – 2.60 (m, 1H).

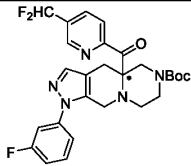
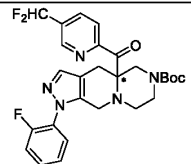
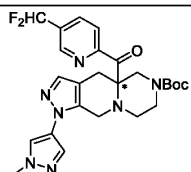
[0173] The following intermediates were prepared and separated by similar procedures as described in Example 1.1, wherein * indicates the chiral center. The enantiomeric separation conditions are shown in the table blow, and the Isomer A and Isomer B are the first eluting isomer and the second eluting isomer under the identified enantiomeric separation condition, respectively.

Intermediate	Structure	MS (ESI) [M+H] ⁺	Chiral Column and Mobile Phase
4-Int Isomer A Isomer B		484.3	DAICELCHIRALCEL®AS (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.3% 7.0mol/L Ammonia in MeOH)
8-Int Isomer A Isomer B		481.3	DAICELCHIRALCEL®OZ (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)

Intermediate	Structure	MS (ESI) [M+H] ⁺	Chiral Column and Mobile Phase
9-Int Isomer A Isomer B		492.3	DAICELCHIRALCEL®IG (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
10-Int Isomer A Isomer B		546.4	DAICELCHIRALCEL®AS (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: IPA (+0.1% 7.0mol/L Ammonia in MeOH)
12-Int Isomer A Isomer B		518.4	DAICELCHIRALCEL®IG (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
13-Int Isomer A Isomer B		552.3	DAICELCHIRALCEL®IG (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
14-Int Isomer A Isomer B		524.3	DAICELCHIRALCEL®IE (250*30 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
32-Int Isomer A Isomer B		528.4	DAICELCHIRALCEL®AS (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: EtOH (+0.1% 7.0mol/L Ammonia in MeOH)

Intermediate	Structure	MS (ESI) [M+H] ⁺	Chiral Column and Mobile Phase
36-Int Isomer A Isomer B		546.4	DAICELCHIRALCEL®IG (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
38-Int Isomer A Isomer B		528.4	DAICELCHIRALCEL®IG (250*25 mm, 10μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/L Ammonia in MeOH)
45-Int Isomer A Isomer B		492.2	DAICELCHIRALPAK®AS (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: IPA (+0.3% 7.0mol/l Ammonia in MeOH)
47-Int Isomer A Isomer B		492.2	DAICELCHIRALPAK®AD (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
48-Int Isomer A Isomer B		492.2	DAICELCHIRALPAK®IG (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
49-Int Isomer A Isomer B		512.3	DAICELCHIRALPAK®AS (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
50-Int Isomer A Isomer B		496.3	DAICELCHIRALPAK®IG (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)

Intermediate	Structure	MS (ESI) [M+H] ⁺	Chiral Column and Mobile Phase
51-Int Isomer A Isomer B		497.4	DAICELCHIRALPAK®IG (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
60-Int Isomer A Isomer B		510.3	DAICELCHIRALPAK®IG (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
63-Int Isomer A Isomer B		534.3	DAICELCHIRALPAK®IE (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
67-Int Isomer A Isomer B		508.4	DAICELCHIRALPAK®IG (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
71-Int Isomer A Isomer B		496.3	DAICELCHIRALPAK®IG (250*25 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
11-Int Isomer A Isomer B		518.4	DAICELCHIRALPAK®IG (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)

Intermediate	Structure	MS (ESI) [M+H] ⁺	Chiral Column and Mobile Phase
79-Int Isomer A Isomer B		528.5	DAICELCHIRALPAK®IG (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
80-Int Isomer A Isomer B		528.4	DAICELCHIRALPAK®IG (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
81-Int Isomer A Isomer B		514.5	DAICELCHIRALPAK®IG (250*30 mm 10 μm); mobile phase A: Supercritical CO ₂ ; mobile phase B: MeOH (+0.1% 7.0mol/l Ammonia in MeOH)

[0174] The following compounds were prepared by similar procedures as described in Examples 1.1-1.2.

Compound	Analytics	Compound	Analytics
2A	LCMS: 543.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.62 (s, 1H), 7.87 - 7.71 (m, 6H), 7.52 - 7.39 (m, 3H), 7.31 (s, 1H), 7.14 (t, <i>J</i> = 8.1 Hz, 2H), 5.41 (d, <i>J</i> = 10.0 Hz, 1H), 4.65 (d, <i>J</i> = 14.5 Hz, 1H), 4.19 (d, <i>J</i> = 15.7 Hz, 1H), 3.93 (d, <i>J</i> = 12.8 Hz, 1H), 3.75 (d, <i>J</i> = 8.5 Hz, 1H), 3.69 - 3.52 (m, 1H), 3.06 - 2.59 (m, 4H).	2B	LCMS: 543.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.63 (s, 1H), 7.88 - 7.82 (m, 2H), 7.81 - 7.78 (m, 2H), 7.77 - 7.71 (m, 2H), 7.53 - 7.46 (m, 1H), 7.45 - 7.38 (m, 2H), 7.32 (s, 1H), 7.18 - 7.10 (m, 2H), 5.58 - 5.30 (m, 1H), 4.67 (d, <i>J</i> = 14.5 Hz, 1H), 4.32 - 4.10 (m, 1H), 4.06 - 3.85 (m, 1H), 3.76 (d, <i>J</i> = 7.9 Hz, 1H), 3.69 - 3.46 (m, 1H), 3.05 - 2.54 (m, 4H).
3A	LCMS: 533.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.78 (d, <i>J</i> = 2.1 Hz, 1H), 8.65 (s, 1H), 7.90 - 7.79 (m, 3H), 7.52 - 7.40 (m, 3H), 7.34 (s, 1H), 7.23 (s, 1H), 7.19 - 7.11 (m, 2H), 5.62 - 5.26 (m, 1H), 4.79 - 4.63 (m, 1H), 4.37 - 4.15 (m, 1H), 4.08 - 3.86 (m, 1H), 3.81 - 3.55	3B	LCMS: 533.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.78 (d, <i>J</i> = 2.0 Hz, 1H), 8.63 (d, <i>J</i> = 4.2 Hz, 1H), 7.91 - 7.74 (m, 3H), 7.49 - 7.38 (m, 3H), 7.33 (s, 1H), 7.25 - 7.21 (m, 1H), 7.19 - 7.09 (m, 2H), 5.39 (d, <i>J</i> = 11.3 Hz, 1H), 4.67 (d, <i>J</i> = 14.8 Hz, 1H), 4.22 (d, <i>J</i> = 15.9 Hz,

Compound	Analytics	Compound	Analytics
	(m, 2H), 3.13 - 2.65 (m, 4H), 2.62 (s, 3H).		1H), 3.93 (d, $J = 14.4$ Hz, 1H), 3.71 (d, $J = 9.9$ Hz, 1H), 3.65 – 3.53 (m, 1H), 2.92 (d, $J = 10.6$ Hz, 1H), 2.85 – 2.66 (m, 3H), 2.62 (s, 3H).
4A	LCMS: 539.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.80 (s, 1H), 8.02 (s, 1H), 7.89 - 7.83 (m, 1H), 7.70 - 7.64 (m, 1H), 7.45 - 7.39 (m, 2H), 7.38 - 7.35 (s, 1H), 7.27 (s, 1H), 7.18 - 7.11 (m, 2H), 5.30 (d, $J = 10.8$ Hz, 1H), 4.67 (d, $J = 14.8$ Hz, 1H), 4.12 (d, $J = 15.2$ Hz, 1H), 4.04 - 3.91 (m, 1H), 3.77 (d, $J = 10.6$ Hz, 1H), 3.73 - 3.58 (m, 1H), 3.02 - 2.71 (m, 4H), 2.65 (s, 3H).	4B	LCMS: 539.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.80 (d, $J = 2.2$ Hz, 1H), 8.04 (d, $J = 2.7$ Hz, 1H), 7.88 – 7.82 (m, 1H), 7.74 – 7.66 (m, 1H), 7.46 – 7.40 (m, 2H), 7.37 (s, 1H), 7.28 (s, 1H), 7.18 – 7.11 (m, 2H), 5.43 – 5.22 (m, 1H), 4.69 (d, $J = 14.7$ Hz, 1H), 4.29 – 3.90 (m, 2H), 3.86 – 3.62 (m, 2H), 3.18 – 2.66 (m, 4H), 2.65 (s, 3H).
6A	LCMS: 592.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.04 - 7.97 (m, 1H), 7.86 - 7.81 (m, 2H), 7.77 - 7.72 (m, 2H), 7.70 - 7.63 (m, 1H), 7.45 - 7.40 (m, 2H), 7.36 (s, 1H), 7.18 - 7.12 (m, 2H), 5.31 (d, $J = 10.8$ Hz, 1H), 4.68 (d, $J = 15.0$ Hz, 1H), 4.28 - 3.95 (m, 2H), 3.89 - 3.64 (m, 2H), 3.32 - 2.52 (m, 4H).	6B	LCMS: 592.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.03 (s, 1H), 7.86 – 7.81 (m, 2H), 7.77 – 7.73 (m, 2H), 7.71 (s, 1H), 7.44 – 7.39 (m, 2H), 7.37 (s, 1H), 7.18 – 7.13 (m, 2H), 5.46 – 5.23 (m, 1H), 4.71 (d, $J = 14.8$ Hz, 1H), 4.29 – 4.01 (m, 2H), 3.91 – 3.74 (m, 2H), 3.36 – 2.66 (m, 4H).
8A	LCMS: 589.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 7.85 - 7.80 (m, 2H), 7.79 - 7.71 (m, 2H), 7.44 - 7.37 (m, 3H), 7.18 - 7.10 (m, 3H), 6.96 (s, 1H), 5.51 - 5.29 (m, 1H), 4.72 (d, $J = 12.3$ Hz, 1H), 4.48 - 4.28 (m, 1H), 4.00 - 3.69 (m, 6H), 3.20 - 2.47 (m, 4H).	8B	LCMS: 589.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 7.84 – 7.81 (m, 2H), 7.79 – 7.75 (m, 2H), 7.42 – 7.38 (m, 3H), 7.20 – 7.14 (m, 3H), 7.04 (s, 1H), 5.60 – 5.39 (m, 1H), 4.88 – 4.71 (m, 1H), 4.65 – 4.45 (m, 1H), 3.88 (s, 6H), 3.60 – 2.94 (m, 4H).
9A	LCMS: 600.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.48 (s, 1H), 7.84 - 7.79 (m, 2H), 7.74 - 7.67 (m, 3H), 7.45 - 7.40 (m, 2H), 7.32 (s, 1H), 7.27 - 7.27 (m, 1H), 7.18 - 7.13 (m, 2H), 5.80 - 5.16 (m, 1H), 4.77 - 4.63 (m, 1H), 4.41 - 4.13	9B	LCMS: 600.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.47 (s, 1H), 7.85 – 7.77 (m, 2H), 7.75 – 7.57 (m, 3H), 7.46 – 7.37 (m, 2H), 7.34 – 7.30 (m, 1H), 7.21 – 7.07 (m, 2H), 5.79 – 5.25 (m, 1H), 4.81 – 4.58 (m, 1H), 4.37 – 4.20 (m, 1H), 4.18 –

Compound	Analytics	Compound	Analytics
	(m, 1H), 4.07 - 3.47 (m, 3H), 3.42 - 2.64 (m, 3H), 2.63 - 2.18 (m, 4H).		3.61 (m, 3H), 3.53 - 2.57 (m, 4H), 2.48 - 2.31 (m, 3H).
10A	LCMS: 654.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.93 (d, <i>J</i> = 5.1 Hz, 1H), 8.20 (s, 1H), 7.83 - 7.77 (m, 5H), 7.43 - 7.38 (m, 2H), 7.36 (s, 1H), 7.21 - 7.15 (m, 2H), 5.71 - 5.44 (m, 1H), 4.77 (d, <i>J</i> = 15.0 Hz, 1H), 4.53 - 4.19 (m, 2H), 3.99 - 3.79 (m, 2H), 3.63 - 2.84 (m, 4H).	10B	LCMS: 654.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.88 (d, <i>J</i> = 4.5 Hz, 1H), 8.16 (s, 1H), 7.83 - 7.80 (m, 2H), 7.79 - 7.73 (m, 3H), 7.44 - 7.40 (m, 2H), 7.34 (s, 1H), 7.19 - 7.14 (m, 2H), 5.60 - 5.39 (m, 1H), 4.75 - 4.65 (m, 1H), 4.39 - 3.96 (m, 2H), 3.92 - 3.69 (m, 2H), 3.69 - 2.56 (m, 4H).
11A	LCMS: 626.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.44 (s, 1H), 7.83 - 7.80 (m, 2H), 7.78 - 7.70 (m, 3H), 7.43 - 7.38 (m, 2H), 7.36 - 7.30 (m, 2H), 7.15 (t, <i>J</i> = 8.2 Hz, 2H), 5.83 - 5.31 (m, 1H), 4.79 - 4.64 (m, 1H), 4.39 - 4.15 (m, 1H), 4.03 - 3.61 (m, 3H), 3.51 - 2.45 (m, 4H), 2.03 - 1.95 (m, 1H), 1.21 - 1.14 (m, 2H), 0.88 - 0.82 (m, 2H).	11B	LCMS: 626.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.46 (s, 1H), 7.83 - 7.80 (m, 2H), 7.79 - 7.68 (m, 3H), 7.42 - 7.38 (m, 2H), 7.36 - 7.32 (m, 2H), 7.15 (t, <i>J</i> = 8.4 Hz, 2H), 5.97 - 5.27 (m, 1H), 4.85 - 4.67 (m, 1H), 4.54 - 4.25 (m, 1H), 4.18 - 3.68 (m, 3H), 3.65 - 2.59 (m, 4H), 2.04 - 1.96 (m, 1H), 1.19 (d, <i>J</i> = 7.2 Hz, 2H), 0.89 - 0.83 (m, 2H).
12A	LCMS: 626.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.44 (s, 1H), 7.83 - 7.79 (m, 2H), 7.76 - 7.71 (m, 2H), 7.54 (s, 1H), 7.43 - 7.38 (m, 2H), 7.34 (s, 1H), 7.16 (t, <i>J</i> = 8.3 Hz, 3H), 5.88 - 5.29 (m, 1H), 4.82 - 4.66 (m, 1H), 4.54 - 4.24 (m, 1H), 4.09 - 3.64 (m, 3H), 3.55 - 2.63 (m, 4H), 1.95 - 1.86 (m, 1H), 1.17 - 1.11 (m, 2H), 0.87 - 0.81 (m, 2H).	12B	LCMS: 626.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.40 (s, 1H), 7.83 - 7.79 (m, 2H), 7.75 - 7.67 (m, 2H), 7.53 - 7.47 (m, 1H), 7.45 - 7.39 (m, 2H), 7.32 (s, 1H), 7.19 - 7.07 (m, 3H), 5.45 (s, 1H), 4.76 - 4.60 (m, 1H), 4.32 - 4.12 (m, 1H), 3.78 (t, <i>J</i> = 62.1 Hz, 3H), 3.10 - 2.55 (m, 4H), 1.94 - 1.85 (m, 1H), 1.17 - 1.08 (m, 2H), 0.87 - 0.80 (m, 2H).
13A	LCMS: 660.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.28 (s, 1H), 7.87 - 7.77 (m, 4H), 7.44 - 7.39 (m, 2H), 7.38 (s, 1H), 7.19 - 7.13 (m, 2H), 5.28 (d, <i>J</i> = 12.5 Hz, 1H), 4.62 (d, <i>J</i> = 14.9 Hz, 1H), 4.14 - 3.99 (m, 2H), 3.83 (d, <i>J</i> = 10.9 Hz,	13B	LCMS: 660.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.32 (s, 1H), 7.87 - 7.79 (m, 4H), 7.43 - 7.38 (m, 3H), 7.17 (t, <i>J</i> = 8.4 Hz, 2H), 5.32 (d, <i>J</i> = 12.8 Hz, 1H), 4.66 (d, <i>J</i> = 14.2 Hz, 1H), 4.20 (d, <i>J</i> = 14.6 Hz, 1H), 4.12 (d, <i>J</i> = 16.2 Hz, 1H), 3.87

Compound	Analytics	Compound	Analytics
	1H), 3.75 - 3.64 (m, 1H), 3.11 - 2.76 (m, 4H).		(d, $J = 11.3$ Hz, 1H), 3.83 - 3.72 (m, 1H), 3.23 - 2.98 (m, 4H).
14A	LCMS: 632.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 7.87 - 7.81 (m, 2H), 7.79 - 7.74 (m, 2H), 7.68 (s, 1H), 7.43 - 7.38 (m, 2H), 7.37 (s, 1H), 7.18 - 7.12 (m, 2H), 5.46 - 5.23 (m, 1H), 4.70 (d, $J = 14.0$ Hz, 1H), 4.25 - 4.02 (m, 2H), 3.92 - 3.71 (m, 2H), 3.37 - 2.72 (m, 4H), 2.21 - 2.12 (m, 1H), 1.25 - 1.17 (m, 2H), 0.89 - 0.81 (m, 2H).	14B	LCMS: 632.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 7.86 - 7.83 (m, 2H), 7.79 - 7.74 (m, 2H), 7.67 (s, 1H), 7.43 - 7.38 (m, 2H), 7.36 (s, 1H), 7.17 - 7.12 (m, 2H), 5.42 - 5.22 (m, 1H), 4.69 (d, $J = 14.0$ Hz, 1H), 4.25 - 3.96 (m, 2H), 3.87 - 3.70 (m, 2H), 3.27 - 2.65 (m, 4H), 2.20 - 2.12 (m, 1H), 1.26 - 1.19 (m, 2H), 0.87 - 0.82 (m, 2H).
15A	LCMS: 522.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.73 - 8.60 (m, 1H), 7.96 - 7.87 (m, 1H), 7.87 - 7.81 (m, 1H), 7.70 - 7.66 (m, 2H), 7.55 - 7.46 (m, 1H), 7.45 - 7.40 (m, 2H), 7.36 (s, 1H), 7.18 - 7.13 (m, 2H), 5.67 - 5.11 (m, 1H), 4.89 - 4.60 (m, 2H), 4.48 - 4.26 (m, 1H), 3.94 (s, 3H), 3.79 - 3.53 (m, 2H), 3.45 - 2.23 (m, 4H).	15B	LCMS: 522.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.67 (s, 1H), 7.92 - 7.87 (m, 1H), 7.86 - 7.80 (m, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.49 (s, 1H), 7.45 - 7.41 (m, 2H), 7.36 (s, 1H), 7.15 (t, $J = 8.2$ Hz, 2H), 5.58 - 5.19 (m, 1H), 4.74 (d, $J = 9.2$ Hz, 1H), 4.46 - 4.20 (m, 1H), 4.01 - 3.88 (m, 4H), 3.86 - 2.41 (m, 6H).
16A	LCMS: 554.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.65 (s, 1H), 7.94 - 7.78 (m, 2H), 7.53 - 7.46 (m, 3H), 7.44 - 7.40 (m, 2H), 7.34 (s, 1H), 7.27 (s, 1H), 7.15 (t, $J = 8.4$ Hz, 2H), 5.70 - 5.23 (m, 1H), 4.81 - 4.64 (m, 1H), 4.45 - 4.21 (m, 1H), 4.14 - 3.88 (m, 1H), 3.82 - 3.55 (m, 2H), 3.46 - 2.45 (m, 4H).	16B	LCMS: 554.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.65 (s, 1H), 8.04 - 7.73 (m, 2H), 7.55 - 7.45 (m, 3H), 7.45 - 7.39 (m, 2H), 7.34 (s, 1H), 7.30 (s, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.67 - 5.22 (m, 1H), 4.85 - 4.61 (m, 1H), 4.46 - 4.17 (m, 1H), 4.12 - 3.85 (m, 1H), 3.82 - 3.55 (m, 2H), 3.47 - 2.38 (m, 4H).
17A	LCMS: 586.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.60 (s, 1H), 7.89 - 7.77 (m, 2H), 7.76 - 7.68 (m, 1H), 7.51 - 7.39 (m, 5H), 7.32 (s, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.58 - 5.24 (m, 1H), 4.67 (d, $J = 13.1$ Hz, 1H), 4.37 - 4.10 (m, 1H),	17B	LCMS: 586.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.59 (s, 1H), 7.88 - 7.76 (m, 2H), 7.74 (s, 1H), 7.52 - 7.48 (m, 2H), 7.47 - 7.39 (m, 3H), 7.32 (s, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.50 - 5.26 (m, 1H), 4.67 (d, $J = 13.1$ Hz, 1H), 4.29 - 4.11 (m, 1H), 4.05 - 3.86 (m, 1H), 3.82 - 3.72 (m,

Compound	Analytics	Compound	Analytics
	4.09 - 3.85 (m, 1H), 3.85 - 3.55 (m, 2H), 3.31 - 2.45 (m, 4H).		1H), 3.69 - 3.50 (m, 1H), 3.08 - 2.64 (m, 4H).
18A	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.64 (s, 1H), 7.92 - 7.79 (m, 2H), 7.74 - 7.67 (m, 2H), 7.48 (s, 1H), 7.45 - 7.39 (m, 2H), 7.34 (s, 1H), 7.15 (t, <i>J</i> = 8.4 Hz, 4H), 5.63 - 5.20 (m, 1H), 4.71 (d, <i>J</i> = 10.5 Hz, 1H), 4.40 - 4.18 (m, 1H), 4.09 - 3.83 (m, 1H), 3.80 - 3.53 (m, 2H), 3.30 - 2.35 (m, 4H).	18B	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.61 (d, <i>J</i> = 4.4 Hz, 1H), 7.90 - 7.75 (m, 2H), 7.74 - 7.65 (m, 2H), 7.49 - 7.38 (m, 3H), 7.33 (s, 1H), 7.19 - 7.06 (m, 4H), 5.43 - 5.21 (m, 1H), 4.68 (d, <i>J</i> = 14.7 Hz, 1H), 4.24 (d, <i>J</i> = 16.0 Hz, 1H), 4.07 - 3.85 (m, 1H), 3.78 - 3.51 (m, 2H), 3.12 - 2.53 (m, 4H).
19A	LCMS: 548.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.68 (s, 1H), 7.98 - 7.77 (m, 2H), 7.64 - 7.60 (m, 2H), 7.52 (s, 1H), 7.44 - 7.39 (m, 2H), 7.35 (s, 1H), 7.16 (t, <i>J</i> = 8.3 Hz, 2H), 6.99 - 6.89 (m, 2H), 5.86 - 5.10 (m, 1H), 5.01 - 4.11 (m, 3H), 3.86 (s, 3H), 3.84 - 3.12 (m, 4H), 3.05 - 2.51 (m, 2H).	19B	LCMS: 548.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.61 (d, <i>J</i> = 4.6 Hz, 1H), 7.89 - 7.83 (m, 1H), 7.82 - 7.75 (m, 1H), 7.62 (d, <i>J</i> = 8.8 Hz, 2H), 7.48 - 7.39 (m, 3H), 7.33 (s, 1H), 7.13 (t, <i>J</i> = 8.5 Hz, 2H), 6.91 (d, <i>J</i> = 8.8 Hz, 2H), 5.27 (d, <i>J</i> = 11.5 Hz, 1H), 4.68 (d, <i>J</i> = 14.8 Hz, 1H), 4.25 (d, <i>J</i> = 16.0 Hz, 1H), 3.92 (d, <i>J</i> = 14.8 Hz, 1H), 3.85 (s, 3H), 3.65 (d, <i>J</i> = 9.6 Hz, 1H), 3.62 - 3.51 (m, 1H), 2.91 (d, <i>J</i> = 11.4 Hz, 1H), 2.80 (d, <i>J</i> = 16.0 Hz, 1H), 2.73 - 2.54 (m, 2H).
20A	LCMS: 549.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.64 (s, 1H), 8.49 (d, <i>J</i> = 2.5 Hz, 1H), 7.96 - 7.79 (m, 2H), 7.77 - 7.73 (m, 1H), 7.55 - 7.45 (m, 1H), 7.44 - 7.39 (m, 2H), 7.34 (s, 1H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 6.74 (d, <i>J</i> = 7.9 Hz, 1H), 5.88 - 5.04 (m, 1H), 4.94 - 4.59 (m, 1H), 4.51 - 4.13 (m, 1H), 4.11 - 3.92 (m, 4H), 3.92 - 2.43 (m, 6H).	21A	LCMS: 548.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.58 (s, 1H), 7.79 - 7.64 (m, 3H), 7.46 - 7.36 (m, 4H), 7.32 (s, 1H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 6.92 - 6.80 (m, 2H), 5.54 - 5.32 (m, 1H), 4.77 - 4.66 (m, 1H), 4.35 - 4.14 (m, 1H), 3.99 - 3.83 (m, 5H), 3.72 - 3.52 (m, 1H), 3.34 - 2.66 (m, 4H).
22A	LCMS: 578.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.57 (s, 1H), 7.73 (s, 2H), 7.47 - 7.31 (m,	23A	LCMS: 593.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.54 (s, 1H), 7.70 (s, 2H), 7.46 - 7.34 (m,

Compound	Analytics	Compound	Analytics
	4H), 7.15 (t, $J = 8.3$ Hz, 2H), 6.47 (d, $J = 6.9$ Hz, 2H), 5.48 - 5.23 (m, 1H), 4.72 (d, $J = 11.2$ Hz, 1H), 4.29 (d, $J = 12.6$ Hz, 1H), 4.02 - 3.81 (m, 8H), 3.66 - 3.50 (m, 1H), 3.31 - 3.03 (m, 2H), 3.02 - 2.74 (m, 2H).		3H), 7.31 (s, 1H), 7.25 (s, 1H), 7.18 - 7.10 (m, 2H), 6.18 (s, 1H), 5.58 - 5.24 (m, 1H), 4.68 (d, $J = 12.5$ Hz, 1H), 4.20 (d, $J = 15.3$ Hz, 1H), 4.08 - 3.80 (m, 9H), 3.79 - 3.51 (m, 2H), 3.27 - 3.05 (m, 2H), 2.97 - 2.71 (m, 2H), 2.31 (s, 3H).
24A	LCMS: 587.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.93 (s, 1H), 8.68 (s, 1H), 8.11 - 8.03 (m, 1H), 7.94 - 7.89 (m, 1H), 7.88 - 7.75 (m, 2H), 7.51 - 7.40 (m, 3H), 7.35 (s, 1H), 7.16 (t, $J = 8.4$ Hz, 2H), 6.00 - 5.44 (m, 1H), 5.06 - 4.44 (m, 2H), 4.42 - 4.14 (m, 1H), 4.08 - 3.82 (m, 2H), 3.78 - 3.52 (m, 1H), 3.48 - 2.68 (m, 3H).	25A	LCMS: 587.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.97 (d, $J = 2.0$ Hz, 1H), 8.62 (s, 1H), 8.15 - 8.11 (m, 1H), 7.85 - 7.79 (m, 2H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.48 (s, 1H), 7.45 - 7.40 (m, 2H), 7.32 (s, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.62 - 5.46 (m, 1H), 4.67 (d, $J = 14.2$ Hz, 1H), 4.34 - 4.12 (m, 1H), 4.10 - 3.61 (m, 3H), 3.22 - 2.54 (m, 4H).
26A	LCMS: 590.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.90 (s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.70 - 7.67 (m, 2H), 7.45 - 7.40 (m, 2H), 7.36 (s, 1H), 7.17 (t, $J = 8.5$ Hz, 2H), 5.51 - 5.31 (m, 1H), 4.73 (d, $J = 14.5$ Hz, 1H), 4.44 - 4.07 (m, 2H), 3.95 (s, 3H), 3.81 - 3.62 (m, 2H), 3.38 - 2.57 (m, 4H).	26B	LCMS: 590.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.88 (d, $J = 4.7$ Hz, 1H), 8.14 (s, 1H), 7.75 - 7.62 (m, 3H), 7.47 - 7.40 (m, 2H), 7.35 (s, 1H), 7.20 - 7.12 (m, 2H), 5.34 (s, 1H), 4.70 (d, $J = 14.4$ Hz, 1H), 4.30 - 3.97 (m, 2H), 3.94 (s, 3H), 3.74 - 3.48 (m, 2H), 3.28 - 2.30 (m, 4H).
27A	LCMS: 534.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.84 (s, 2H), 8.67 (s, 1H), 7.97 - 7.76 (m, 2H), 7.57 - 7.46 (m, 1H), 7.45 - 7.38 (m, 2H), 7.34 (s, 1H), 7.19 - 7.13 (m, 2H), 5.78 - 5.41 (m, 1H), 4.73 (d, $J = 13.5$ Hz, 1H), 4.47 - 3.95 (m, 2H), 3.91 - 3.67 (m, 2H), 3.35 - 2.85 (m, 3H), 2.81 (s, 4H).	28A	LCMS: 602.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.91 (d, $J = 4.9$ Hz, 1H), 8.85 (s, 2H), 8.16 (s, 1H), 7.76 (d, $J = 4.1$ Hz, 1H), 7.44 - 7.39 (m, 2H), 7.35 (s, 1H), 7.20 - 7.15 (m, 2H), 5.54 (d, $J = 11.6$ Hz, 1H), 4.71 (d, $J = 14.2$ Hz, 1H), 4.33 - 4.10 (m, 2H), 3.89 - 3.70 (m, 2H), 3.30 - 2.91 (m, 4H), 2.82 (s, 3H).
28B	LCMS: 602.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.91 - 8.78 (m, 3H), 8.15 - 8.05 (m, 1H), 7.76 - 7.66 (m, 1H), 7.47 - 7.38 (m,	29A	LCMS: 576.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.67 (s, 1H), 8.16 (s, 1H), 7.91 - 7.83 (m, 3H), 7.54 - 7.47 (m, 1H), 7.45 - 7.40

Compound	Analytics	Compound	Analytics
	2H), 7.36 – 7.29 (m, 1H), 7.20 – 7.10 (m, 2H), 5.55 – 5.35 (m, 1H), 4.72 – 4.54 (m, 1H), 4.20 – 3.91 (m, 2H), 3.83 – 3.57 (m, 2H), 3.05 – 2.92 (m, 1H), 2.90 – 2.68 (m, 6H).		(m, 2H), 7.36 (s, 1H), 7.19 - 7.14 (m, 2H), 5.64 - 5.36 (m, 1H), 4.80 - 4.66 (m, 1H), 4.42 - 4.23 (m, 1H), 4.16 - 3.91 (m, 1H), 3.85 - 3.64 (m, 2H), 3.30 - 2.48 (m, 4H).
30B	LCMS: 528.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.07 (s, 1H), 7.72 (s, 2H), 7.69 (s, 1H), 7.45 – 7.40 (m, 2H), 7.39 (s, 1H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 5.45 – 5.19 (m, 1H), 4.73 (d, <i>J</i> = 13.6 Hz, 1H), 4.37 – 4.02 (m, 2H), 3.98 – 3.91 (m, 3H), 3.86 – 3.64 (m, 2H), 3.33 – 2.37 (m, 4H).	31A	LCMS: 596.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.29 (s, 1H), 7.74 – 7.69 (m, 2H), 7.44 – 7.38 (m, 3H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 5.22 (d, <i>J</i> = 11.4 Hz, 1H), 4.65 (d, <i>J</i> = 14.8 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.96 (s, 3H), 3.76 – 3.64 (m, 2H), 3.15 – 2.72 (m, 4H).
32A	LCMS: 572.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.89 (d, <i>J</i> = 4.9 Hz, 1H), 8.12 (s, 1H), 7.74 - 7.67 (m, 3H), 7.44 - 7.37 (m, 3H), 7.22 - 7.16 (m, 2H), 6.69 (t, <i>J</i> = 55.3 Hz, 1H), 5.60 (d, <i>J</i> = 10.1 Hz, 1H), 4.85 (d, <i>J</i> = 13.9 Hz, 1H), 4.67 - 4.43 (m, 2H), 4.08 - 3.93 (m, 4H), 3.87 - 3.78 (m, 1H), 3.70 - 3.27 (m, 4H).	32B	LCMS: 572.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.89 – 8.78 (m, 1H), 8.11 – 7.96 (m, 1H), 7.70 (s, 1H), 7.69 – 7.62 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 (s, 1H), 7.17 (t, <i>J</i> = 8.4 Hz, 2H), 6.68 (t, <i>J</i> = 55.4 Hz, 1H), 5.64 – 5.23 (m, 1H), 4.85 – 4.66 (m, 1H), 4.46 – 4.20 (m, 1H), 4.00 – 3.83 (m, 4H), 3.83 – 3.60 (m, 2H), 3.55 – 2.43 (m, 4H).
33A	LCMS: 558.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.70 - 8.64 (m, 1H), 8.15 (s, 1H), 7.90 - 7.80 (m, 3H), 7.51 - 7.46 (m, 1H), 7.45 - 7.41 (m, 2H), 7.36 (s, 1H), 7.19 (t, <i>J</i> = 60.4 Hz, 1H), 7.18 - 7.13 (m, 2H), 5.45 (s, 1H), 4.72 (d, <i>J</i> = 13.7 Hz, 1H), 4.40 - 4.21 (m, 1H), 4.08 - 3.87 (m, 1H), 3.77 - 3.59 (m, 2H), 3.12 - 2.56 (m, 4H) .	34A	LCMS: 548.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.67 (s, 1H), 7.91 – 7.79 (m, 2H), 7.77 (s, 1H), 7.64 (s, 1H), 7.51 – 7.40 (m, 3H), 7.36 (s, 1H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 5.45 – 5.17 (m, 1H), 5.04 – 4.57 (m, 2H), 4.40 – 4.17 (m, 1H), 4.06 – 3.81 (m, 1H), 3.74 – 3.48 (m, 3H), 3.02 – 2.53 (m, 3H), 1.19 – 1.06 (m, 4H).
35A	LCMS: 568.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 7.71 (s, 1H), 7.68 (s, 2H), 7.43 – 7.40 (m, 2H), 7.37 (s, 1H), 7.16 – 7.12 (m, 2H), 5.29 – 5.15 (m, 1H), 4.68 (d, <i>J</i>	36A	LCMS: 590.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.95 (s, 1H), 8.12 – 7.99 (m, 2H), 7.71 (s, 1H), 7.67 (s, 1H), 7.47 – 7.40 (m, 2H), 7.37 (s, 1H), 7.16 (t, <i>J</i> = 8.5 Hz,

Compound	Analytics	Compound	Analytics
	= 15.1 Hz, 1H), 4.18 – 3.99 (m, 2H), 3.95 (s, 3H), 3.72 – 3.65 (m, 2H), 2.99 – 2.62 (m, 4H), 2.18 – 2.12 (m, 1H), 1.20 – 1.17 (m, 2H), 0.85 – 0.83 (m, 2H).		2H), 5.41 – 5.18 (m, 1H), 4.70 (d, J = 14.3 Hz, 1H), 4.49 – 4.00 (m, 2H), 3.95 (s, 3H), 3.77 – 3.54 (m, 2H), 3.31 – 2.30 (m, 4H).
36B	LCMS: 590.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.93 (s, 1H), 8.10 - 8.04 (m, 1H), 8.01 - 7.95 (m, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 7.47 - 7.41 (m, 2H), 7.35 (s, 1H), 7.19 - 7.11 (m, 2H), 5.23 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 14.7 Hz, 1H), 4.17 (d, J = 16.0 Hz, 1H), 4.04 - 3.91 (m, 4H), 3.70 - 3.54 (m, 2H), 3.01 - 2.81 (m, 2H), 2.73 - 2.56 (m, 2H).	37A	LCMS: 562.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.46 (s, 1H), 7.82 (s, 1H), 7.72 – 7.65 (m, 2H), 7.44 – 7.34 (m, 4H), 7.16 (t, J = 8.3 Hz, 2H), 5.80 – 5.24 (m, 1H), 4.90 – 4.67 (m, 1H), 4.65 – 4.02 (m, 2H), 3.94 (s, 3H), 3.83 – 2.54 (m, 6H), 2.02 – 1.94 (m, 1H), 1.23 – 1.13 (m, 2H), 0.88 – 0.80 (m, 2H).
38A	LCMS: 572.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.82 (s, 1H), 7.98 (s, 2H), 7.70 (s, 1H), 7.67 (s, 1H), 7.45 - 7.41 (m, 2H), 7.36 (s, 1H), 7.19 - 7.13 (m, 2H), 6.79 (t, J = 55.6 Hz, 1H), 5.50 - 5.19 (m, 1H), 4.71 (d, J = 13.0 Hz, 1H), 4.38 - 4.18 (m, 1H), 4.07 - 3.90 (m, 4H), 3.75 - 3.57 (m, 2H), 3.23 - 2.35 (m, 4H).	38B	LCMS: 572.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.84 (s, 1H), 8.00 (s, 2H), 7.71 (s, 1H), 7.67 (s, 1H), 7.45 – 7.40 (m, 2H), 7.37 (s, 1H), 7.17 (t, J = 8.5 Hz, 2H), 6.80 (t, J = 55.5 Hz, 1H), 5.64 – 5.19 (m, 1H), 4.83 – 4.69 (m, 1H), 4.43 – 4.22 (m, 1H), 4.11 – 3.89 (m, 4H), 3.84 – 3.60 (m, 2H), 3.56 – 2.37 (m, 4H).
39A	LCMS: 562.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.47 (s, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.58 – 7.49 (m, 1H), 7.45 – 7.40 (m, 2H), 7.35 (s, 1H), 7.15 (t, J = 8.2 Hz, 3H), 5.47 – 4.43 (m, 2H), 4.40 – 4.03 (m, 1H), 3.93 (s, 4H), 3.78 – 3.38 (m, 3H), 3.14 – 2.48 (m, 3H), 1.93 – 1.87 (m, 1H), 1.15 – 1.10 (m, 2H), 0.85 – 0.82 (m, 2H).	40A	LCMS: 523.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.69 (s, 1H), 7.91 - 7.86 (m, 1H), 7.85 - 7.81 (m, 2H), 7.49 - 7.42 (m, 3H), 7.36 (s, 1H), 7.18 - 7.13 (m, 2H), 5.59 - 5.38 (m, 1H), 4.74 (d, J = 12.2 Hz, 1H), 4.33 - 4.24 (m, 4H), 4.06 - 3.88 (m, 1H), 3.83 - 3.73 (m, 1H), 3.68 - 3.53 (m, 1H), 3.12 - 2.69 (m, 4H).
41A	LCMS: 540.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.66 (d, J = 4.5 Hz, 1H), 7.90 - 7.77 (m,	42B	LCMS: 591.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.89 (d, J = 4.9 Hz, 1H), 8.13 (s, 1H), 7.85

Compound	Analytics	Compound	Analytics
	2H), 7.51 - 7.41 (m, 3H), 7.36 (s, 1H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.66 (d, $J = 11.9$ Hz, 1H), 4.72 (d, $J = 14.7$ Hz, 1H), 4.31 (d, $J = 15.9$ Hz, 1H), 4.01 (d, $J = 13.3$ Hz, 1H), 3.88 (d, $J = 11.2$ Hz, 1H), 3.74 - 3.58 (m, 1H), 3.42 - 3.20 (m, 2H), 3.05 - 2.81 (m, 5H).		(s, 1H), 7.70 (d, $J = 4.7$ Hz, 1H), 7.47 - 7.42 (m, 2H), 7.35 (s, 1H), 7.19 - 7.13 (m, 2H), 5.48 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 14.6$ Hz, 1H), 4.27 (s, 3H), 4.23 - 4.13 (m, 1H), 4.04 - 3.89 (m, 1H), 3.77 (d, $J = 10.6$ Hz, 1H), 3.67 - 3.53 (m, 1H), 3.03 - 2.75 (m, 4H).
43A	LCMS: 559.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.77 - 8.68 (m, 1H), 8.03 (s, 1H), 7.95 - 7.84 (m, 2H), 7.56 - 7.51 (m, 1H), 7.44 - 7.38 (m, 3H), 7.39 (t, $J = 57.6$ Hz, 1H), 7.20 - 7.15 (m, 2H), 5.89 - 5.60 (m, 1H), 4.80 (d, $J = 13.2$ Hz, 1H), 4.54 - 4.40 (m, 1H), 3.99 - 3.83 (m, 2H), 3.71 - 2.96 (m, 4H).	44A	LCMS: 549.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃): δ 8.68 (d, $J = 3.7$ Hz, 1H), 7.90 - 7.78 (m, 3H), 7.51 - 7.41 (m, 3H), 7.36 (s, 1H), 7.18 - 7.12 (m, 2H), 5.61 - 5.34 (m, 1H), 4.74 (d, $J = 14.0$ Hz, 1H), 4.43 - 4.22 (m, 1H), 4.13 - 4.07 (m, 1H), 4.04 - 3.87 (m, 1H), 3.81 - 3.73 (m, 1H), 3.69 - 3.52 (m, 1H), 3.22 - 2.65 (m, 4H), 1.45 - 1.39 (m, 2H), 1.21 - 1.14 (m, 2H).
45A	LCMS: 536.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.47 (s, 1H), 7.68 (d, $J = 5.2$ Hz, 2H), 7.62 - 7.53 (m, 1H), 7.47 - 7.30 (m, 4H), 7.17 (t, $J = 8.5$ Hz, 2H), 4.81 - 4.36 (m, 2H), 4.31 - 3.87 (m, 2H), 3.93 (s, 3H), 3.75 - 3.47 (m, 2H), 3.38 - 2.51 (m, 4H), 2.25 (s, 3H).	45B	LCMS: 536.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.45 (s, 1H), 7.68 (d, $J = 5.1$ Hz, 2H), 7.61 - 7.51 (m, 1H), 7.47 - 7.29 (m, 4H), 7.16 (t, $J = 8.4$ Hz, 2H), 4.76 - 4.38 (m, 2H), 4.16 - 3.85 (m, 2H), 3.93 (s, 3H), 3.69 - 3.42 (m, 2H), 3.20 - 2.47 (m, 4H), 2.22 (s, 3H).
46A	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.53 (s, 1H), 7.76 - 7.66 (m, 3H), 7.44 - 7.40 (m, 2H), 7.36 (s, 1H), 7.31 (s, 1H), 7.16 (t, $J = 8.4$ Hz, 2H), 5.80 - 5.14 (m, 1H), 4.89 - 4.68 (m, 1H), 4.61 - 4.21 (m, 1H), 4.02 - 3.86 (m, 1H), 3.94 (s, 3H), 3.81 - 3.33 (m, 3H), 3.16 - 2.26 (m, 3H), 2.40 (s, 3H).	47A	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 7.83 (s, 1H), 7.69 (d, $J = 10.5$ Hz, 2H), 7.66 - 7.59 (m, 1H), 7.45 - 7.40 (m, 2H), 7.35 (s, 1H), 7.16 (t, $J = 8.3$ Hz, 2H), 5.79 - 5.22 (m, 1H), 4.88 - 4.68 (m, 1H), 4.60 - 4.25 (m, 1H), 4.02 - 3.86 (m, 1H), 3.94 (s, 3H), 3.81 - 3.34 (m, 3H), 3.18 - 2.48 (m, 3H), 2.43 (s, 3H).

Compound	Analytics	Compound	Analytics
47B	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.53 (s, 1H), 8.32 (s, 1H), 7.80 – 7.75 (m, 1H), 7.75 – 7.68 (m, 2H), 7.60 – 7.53 (m, 2H), 7.39 (s, 1H), 7.34 (t, <i>J</i> = 8.8 Hz, 2H), 5.19 (d, <i>J</i> = 11.5 Hz, 1H), 4.44 (d, <i>J</i> = 15.0 Hz, 1H), 4.22 – 4.06 (m, 2H), 3.88 (s, 3H), 3.48 (d, <i>J</i> = 10.6 Hz, 1H), 3.44 – 3.39 (m, 1H), 2.95 (d, <i>J</i> = 10.7 Hz, 1H), 2.75 (d, <i>J</i> = 15.8 Hz, 1H), 2.48 – 2.42 (m, 2H), 2.40 (s, 3H).	48A	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.28 (s, 1H), 7.83 (t, <i>J</i> = 7.8 Hz, 1H), 7.72 (s, 1H), 7.62 – 7.54 (m, 3H), 7.49 (d, <i>J</i> = 7.7 Hz, 1H), 7.42 (s, 1H), 7.39 – 7.30 (m, 2H), 5.27 (d, <i>J</i> = 11.4 Hz, 1H), 4.43 (d, <i>J</i> = 15.1 Hz, 1H), 4.14 (d, <i>J</i> = 15.1 Hz, 1H), 4.02 (d, <i>J</i> = 15.8 Hz, 1H), 3.87 (s, 3H), 3.46 (d, <i>J</i> = 10.8 Hz, 1H), 3.38 – 3.34 (m, 2H), 3.00 – 2.91 (m, 1H), 2.77 (d, <i>J</i> = 16.0 Hz, 1H), 2.59 (s, 3H), 2.48 – 2.44 (m, 1H).
48B	LCMS: 536.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 7.73 – 7.64 (m, 4H), 7.48 – 7.40 (m, 2H), 7.39 – 7.29 (m, 2H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 5.53 – 5.18 (m, 1H), 4.91 – 4.58 (m, 1H), 4.37 – 4.14 (m, 1H), 4.06 – 3.86 (m, 1H), 3.92 (s, 3H), 3.73 – 3.46 (m, 2H), 3.16 – 2.42 (m, 4H), 2.66 (s, 3H).	49A	LCMS: 556.0 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (dd, <i>J</i> = 4.6, 1.2 Hz, 1H), 7.86 (dd, <i>J</i> = 8.3, 1.2 Hz, 1H), 7.69 (d, <i>J</i> = 7.8 Hz, 2H), 7.51 – 7.45 (m, 1H), 7.44 – 7.38 (m, 3H), 7.22 – 7.17 (m, 2H), 5.00 – 4.74 (m, 2H), 4.65 – 4.50 (m, 1H), 4.29 – 4.16 (m, 1H), 4.01 – 3.91 (m, 1H), 3.96 (s, 3H), 3.88 – 3.81 (m, 1H), 3.59 – 3.31 (m, 4H).
49B	LCMS: 556.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (d, <i>J</i> = 4.1 Hz, 1H), 7.77 (d, <i>J</i> = 8.2 Hz, 1H), 7.69 (d, <i>J</i> = 6.0 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.40 – 7.33 (m, 2H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 4.63 (d, <i>J</i> = 14.9 Hz, 1H), 4.42 – 4.15 (m, 1H), 4.01 – 3.88 (m, 1H), 3.94 (s, 3H), 3.88 – 3.69 (m, 1H), 3.67 – 3.37 (m, 2H), 3.12 – 2.63 (m, 4H).	50A	LCMS: 540.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.47 (s, 1H), 7.68 (d, <i>J</i> = 9.1 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.45 – 7.40 (m, 3H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 4.91 – 4.57 (m, 2H), 4.23 – 3.88 (m, 2H), 3.94 (s, 3H), 3.74 – 3.44 (m, 2H), 3.32 – 2.36 (m, 4H).
50B	LCMS: 540.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.47 (s, 1H), 7.68 (d, <i>J</i> = 9.1 Hz, 2H), 7.58 – 7.48 (m, 2H), 7.48 – 7.38 (m, 3H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 4.91 – 4.57 (m, 2H), 4.37 – 3.97 (m, 2H),	51A	LCMS: 542.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 7.72 (s, 1H), 7.69 (s, 2H), 7.46 – 7.40 (m, 2H), 7.37 (s, 1H), 7.14 (t, <i>J</i> = 8.5 Hz, 2H), 5.36 – 5.12 (m, 1H), 4.69 (d, <i>J</i> = 14.5 Hz, 1H), 4.20 – 4.05 (m, 1H),

Compound	Analytics	Compound	Analytics
	3.94 (s, 3H), 3.77 – 3.44 (m, 2H), 3.35 – 2.39 (m, 4H).		4.04 – 3.84 (m, 1H), 3.95 (s, 3H), 3.80 – 3.58 (m, 2H), 3.08 – 2.49 (m, 4H), 2.55 (s, 3H).
51B	LCMS: 542.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 7.72 (s, 1H), 7.68 (s, 2H), 7.46 – 7.40 (m, 2H), 7.37 (s, 1H), 7.14 (t, <i>J</i> = 8.5 Hz, 2H), 5.35 – 5.13 (m, 1H), 4.68 (d, <i>J</i> = 14.6 Hz, 1H), 4.20 – 4.07 (m, 1H), 4.04 – 3.84 (m, 1H), 3.95 (s, 3H), 3.77 – 3.57 (m, 2H), 3.06 – 2.49 (m, 4H), 2.55 (s, 3H).	52A	LCMS: 536.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.67 (s, 1H), 7.93 – 7.79 (m, 2H), 7.72 (s, 1H), 7.68 (s, 1H), 7.50 – 7.41 (m, 3H), 7.36 (s, 1H), 7.15 (t, <i>J</i> = 8.5 Hz, 2H), 5.44 – 5.20 (m, 1H), 4.73 (d, <i>J</i> = 13.3 Hz, 1H), 4.42 – 4.25 (m, 1H), 4.19 (q, <i>J</i> = 7.3 Hz, 2H), 4.07 – 3.82 (m, 1H), 3.73 – 3.53 (m, 2H), 3.23 – 2.39 (m, 4H), 1.52 (t, <i>J</i> = 7.2 Hz, 3H).
53A	LCMS: 523.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.69 (s, 1H), 8.00 – 7.69 (m, 2H), 7.93 (s, 1H), 7.55 – 7.39 (m, 3H), 7.37 (s, 1H), 7.16 (t, <i>J</i> = 8.4 Hz, 2H), 5.86 – 5.31 (m, 1H), 4.97 – 4.17 (m, 3H), 4.12 – 3.36 (m, 4H), 3.21 – 2.76 (m, 2H), 2.51 (s, 3H).	54A	LCMS: 523.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.69 (s, 1H), 7.92 – 7.77 (m, 2H), 7.55 – 7.47 (m, 1H), 7.46 – 7.41 (m, 2H), 7.36 (d, <i>J</i> = 5.4 Hz, 2H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 5.71 – 5.47 (m, 1H), 4.80 – 4.66 (m, 1H), 4.42 – 4.18 (m, 1H), 4.14 – 2.75 (m, 7H), 2.52 (s, 3H).
55A	LCMS: 608.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.83 (s, 1H), 8.17 (s, 1H), 8.00 (s, 2H), 7.80 (s, 1H), 7.47 – 7.40 (m, 2H), 7.36 (s, 1H), 7.19 (t, <i>J</i> = 60.0 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.79 (t, <i>J</i> = 55.5 Hz, 1H), 5.63 – 5.32 (m, 1H), 4.82 – 4.63 (m, 1H), 4.43 – 3.97 (m, 2H), 3.86 – 3.69 (m, 2H), 3.45 – 2.46 (m, 4H).	56A	LCMS: 563.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.49 (s, 1H), 7.84 (s, 1H), 7.62 – 7.50 (m, 1H), 7.45 – 7.40 (m, 2H), 7.37 (s, 1H), 7.22 – 7.05 (m, 3H), 6.02 – 5.26 (m, 1H), 4.88 – 4.70 (m, 1H), 4.38 – 4.22 (m, 1H), 4.28 (s, 3H), 4.12 – 3.33 (m, 5H), 3.12 – 2.70 (m, 2H), 1.95 – 1.87 (m, 1H), 1.20 – 1.04 (m, 2H), 0.87 – 0.82 (m, 2H).
57A	LCMS: 573.4 [M+H] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.25 (s, 1H), 8.21 – 8.17 (m, 1H), 7.91 (d, <i>J</i> = 8.2 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.42 (s, 1H), 7.38 – 7.31 (m, 2H), 7.27 (t, <i>J</i> = 54.8 Hz, 1H), 5.20 (dd, <i>J</i> = 12.1,	58A	LCMS: 523.3 [M+H] ⁺ ¹ H NMR (400 MHz, CDCl ₃) δ 8.69 (d, <i>J</i> = 4.2 Hz, 1H), 7.97 – 7.77 (m, 2H), 7.54 – 7.40 (m, 3H), 7.36 (s, 1H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 6.53 (s, 1H), 5.78 – 5.45 (m, 1H), 4.87 – 4.61 (m, 1H), 4.45 – 4.25 (m, 1H), 4.22 –

Compound	Analytics	Compound	Analytics
	1.4 Hz, 1H), 4.42 (d, $J = 15.3$ Hz, 1H), 4.26 (s, 3H), 4.20 (d, $J = 15.1$ Hz, 1H), 4.04 (d, $J = 15.9$ Hz, 1H), 3.65 – 3.56 (m, 1H), 3.41 – 3.34 (m, 1H), 3.03 – 2.96 (m, 1H), 2.84 – 2.69 (m, 3H).		3.93 (m, 1H), 3.88 – 3.59 (m, 2H), 3.40 – 2.80 (m, 4H), 2.36 (s, 3H).
59B	LCMS: 573.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (d, $J = 4.5$ Hz, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.64 (s, 1H), 7.46 – 7.40 (m, 2H), 7.36 (s, 1H), 7.17 (t, $J = 8.4$ Hz, 2H), 6.67 (t, $J = 55.4$ Hz, 1H), 5.77 – 5.33 (m, 1H), 4.90 – 4.63 (m, 1H), 4.49 – 4.16 (m, 1H), 4.28 (s, 3H), 3.97 – 3.48 (m, 3H), 3.38 – 2.52 (m, 4H).	60A	LCMS: 555.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.70 (s, 1H), 7.97 – 7.80 (m, 3H), 7.46 – 7.41 (m, 2H), 7.37 (s, 1H), 7.16 (t, $J = 8.5$ Hz, 2H), 5.67 – 5.41 (m, 1H), 5.52 (d, $J = 46.8$ Hz, 2H), 4.84 – 4.68 (m, 1H), 4.39 – 4.22 (m, 1H), 4.28 (s, 3H), 4.11 – 3.41 (m, 4H), 3.26 – 2.67 (m, 3H).
60B	LCMS: 555.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.72 (s, 1H), 8.06 – 7.92 (m, 1H), 7.90 – 7.82 (m, 2H), 7.45 – 7.40 (m, 2H), 7.38 (s, 1H), 7.18 (t, $J = 8.4$ Hz, 2H), 5.84 – 5.47 (m, 1H), 5.53 (d, $J = 46.4$ Hz, 2H), 4.88 – 4.74 (m, 1H), 4.67 – 4.27 (m, 2H), 4.29 (s, 3H), 3.98 – 3.74 (m, 2H), 3.71 – 2.50 (m, 4H).	61A	LCMS: 597.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.30 (s, 1H), 7.88 (s, 1H), 7.47 – 7.37 (m, 3H), 7.20 – 7.12 (m, 2H), 5.37 (d, $J = 12.0$ Hz, 1H), 4.66 (d, $J = 14.8$ Hz, 1H), 4.28 (s, 3H), 4.16 – 4.00 (m, 2H), 3.84 (d, $J = 10.9$ Hz, 1H), 3.77 – 3.62 (m, 1H), 3.29 – 2.77 (m, 4H).
62A	LCMS: 563.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.48 (s, 1H), 7.85 (s, 1H), 7.45 – 7.34 (m, 5H), 7.17 (t, $J = 8.5$ Hz, 2H), 5.93 – 5.43 (m, 1H), 4.93 – 4.70 (m, 1H), 4.66 – 4.44 (m, 1H), 4.35 – 4.23 (m, 1H), 4.29 (s, 3H), 4.01 – 3.38 (m, 5H), 3.07 – 2.78 (m, 1H), 2.04 – 1.94 (m, 1H), 1.22 – 1.13 (m, 2H), 0.89 – 0.82 (m, 2H).	63A	LCMS: 579.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.17 (s, 1H), 7.87 (s, 1H), 7.45 – 7.39 (m, 3H), 7.20 – 7.14 (m, 2H), 6.94 (t, $J = 55.1$ Hz, 1H), 5.40 (d, $J = 12.2$ Hz, 1H), 4.68 (d, $J = 14.8$ Hz, 1H), 4.28 (s, 3H), 4.17 – 3.97 (m, 2H), 3.84 (d, $J = 10.6$ Hz, 1H), 3.80 – 3.66 (m, 1H), 3.27 – 2.87 (m, 4H).
63B	LCMS: 579.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.20 (s, 1H), 7.88 (s, 1H), 7.45 – 7.39 (m,	64A	LCMS: 573.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.81 (s, 1H), 7.97 (s, 2H), 7.48 – 7.41 (m,

Compound	Analytics	Compound	Analytics
	3H), 7.21 – 7.15 (m, 2H), 6.95 (t, J = 55.0 Hz, 1H), 5.44 (d, J = 12.7 Hz, 1H), 4.72 (d, J = 14.7 Hz, 1H), 4.29 (s, 3H), 4.27 – 4.11 (m, 2H), 3.92 – 3.74 (m, 2H), 3.42 – 3.03 (m, 4H).		2H), 7.36 (s, 1H), 7.19 – 7.13 (m, 2H), 6.77 (t, J = 55.5 Hz, 1H), 6.23 (d, J = 0.8 Hz, 1H), 5.60 – 5.43 (m, 1H), 4.71 (d, J = 14.6 Hz, 1H), 4.26 (d, J = 15.4 Hz, 1H), 4.17 – 3.94 (m, 1H), 3.82 (d, J = 10.2 Hz, 1H), 3.73 – 3.56 (m, 1H), 3.41 – 2.74 (m, 4H), 2.50 (s, 3H).
65A	LCMS: 569.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 7.86 (s, 1H), 7.72 (s, 1H), 7.44 – 7.40 (m, 2H), 7.38 (s, 1H), 7.15 (t, J = 8.5 Hz, 2H), 5.66 – 5.20 (m, 1H), 4.80 – 4.66 (m, 1H), 4.39 – 4.05 (m, 2H), 4.28 (s, 3H), 3.90 – 3.66 (m, 2H), 3.54 – 2.64 (m, 4H), 2.20 – 2.12 (m, 1H), 1.24 – 1.15 (m, 2H), 0.89 – 0.81 (m, 2H).	66A	LCMS: 573.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (s, 1H), 8.07 – 7.88 (m, 3H), 7.49 – 7.40 (m, 2H), 7.37 (s, 1H), 7.20 – 7.11 (m, 2H), 6.77 (t, J = 55.5 Hz, 1H), 5.74 – 5.27 (m, 1H), 4.71 (d, J = 13.8 Hz, 1H), 4.46 – 3.91 (m, 2H), 3.87 – 3.51 (m, 2H), 3.34 – 2.67 (m, 4H), 2.51 (s, 3H).
67A	LCMS: 553.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.49 (s, 1H), 7.84 (s, 1H), 7.47 – 7.34 (m, 4H), 7.16 (t, J = 8.4 Hz, 2H), 7.02 – 6.90 (m, 1H), 5.81 – 5.27 (m, 1H), 4.89 – 4.64 (m, 1H), 4.49 – 4.32 (m, 1H), 4.27 (s, 3H), 4.10 – 3.47 (m, 4H), 3.88 (s, 3H), 3.15 – 2.62 (m, 3H).	67B	LCMS: 553.2 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (d, J = 5.4 Hz, 1H), 7.85 (s, 1H), 7.47 – 7.40 (m, 3H), 7.38 (s, 1H), 7.16 (t, J = 8.5 Hz, 2H), 7.02 – 6.96 (m, 1H), 5.85 – 5.45 (m, 1H), 4.77 (d, J = 13.9 Hz, 1H), 4.56 – 4.36 (m, 1H), 4.34 – 4.08 (m, 1H), 4.28 (s, 3H), 3.96 – 3.58 (m, 3H), 3.88 (s, 3H), 3.30 – 2.84 (m, 3H).
68A	LCMS: 576.4 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.25 (s, 1H), 8.22 – 8.17 (m, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.42 (s, 1H), 7.38 – 7.31 (m, 2H), 7.27 (t, J = 54.8 Hz, 1H), 5.20 (dd, J = 12.0, 1.5 Hz, 1H), 4.42 (d, J = 15.1 Hz, 1H), 4.20 (d, J = 15.1 Hz, 1H), 4.04 (d, J = 15.9 Hz, 1H), 3.66 – 3.57 (m,	69A	LCMS: 591.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.98 (s, 1H), 8.12 – 8.00 (m, 2H), 7.86 (s, 1H), 7.46 – 7.41 (m, 2H), 7.38 (s, 1H), 7.17 (t, J = 8.5 Hz, 2H), 5.56 – 5.38 (m, 1H), 4.72 (d, J = 12.5 Hz, 1H), 4.37 – 4.21 (m, 2H), 4.28 (s, 3H), 3.84 – 3.78 (m, 1H), 3.75 – 3.59 (m, 1H), 3.30 – 2.69 (m, 4H).

Compound	Analytics	Compound	Analytics
	¹ H), 3.42 – 3.34 (m, 1H), 3.05 – 2.95 (m, 1H), 2.85 – 2.69 (m, 3H).		
70A	LCMS: 573.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (s, 1H), 8.00 – 7.90 (m, 2H), 7.47 – 7.41 (m, 2H), 7.38 (s, 1H), 7.35 (s, 1H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 6.78 (t, <i>J</i> = 55.5 Hz, 1H), 5.50 (d, <i>J</i> = 9.7 Hz, 1H), 4.68 (d, <i>J</i> = 14.6 Hz, 1H), 4.20 (d, <i>J</i> = 15.3 Hz, 1H), 4.11 – 3.91 (m, 1H), 3.80 (d, <i>J</i> = 10.0 Hz, 1H), 3.70 – 3.55 (m, 1H), 3.19 – 2.74 (m, 4H), 2.53 (s, 3H).	71A	LCMS: 541.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.77 – 8.65 (m, 1H), 7.85 (s, 1H), 7.67 (d, <i>J</i> = 7.8 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.31 – 7.27 (m, 1H), 7.21 – 7.14 (m, 2H), 5.84 – 5.40 (m, 1H), 4.91 – 4.66 (m, 1H), 4.62 – 4.22 (m, 2H), 4.29 (s, 3H), 3.99 – 3.73 (m, 2H), 3.69 – 2.75 (m, 4H).
71B	LCMS: 541.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.68 (t, 1H), 7.85 (s, 1H), 7.63 (d, <i>J</i> = 8.2 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.37 (s, 1H), 7.25 – 7.20 (m, 1H), 7.16 (t, <i>J</i> = 8.5 Hz, 2H), 5.71 – 5.31 (m, 1H), 4.78 – 4.64 (m, 1H), 4.37 – 4.23 (m, 1H), 4.28 (s, 3H), 4.07 – 3.74 (m, 2H), 3.72 – 2.45 (m, 5H).	72A	LCMS: 573.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 7.99 (s, 2H), 7.49 – 7.40 (m, 2H), 7.36 (s, 1H), 7.17 (t, <i>J</i> = 8.5 Hz, 2H), 6.79 (t, <i>J</i> = 55.4 Hz, 1H), 6.56 (s, 1H), 5.61 (d, <i>J</i> = 10.3 Hz, 1H), 4.72 (d, <i>J</i> = 14.5 Hz, 1H), 4.46 – 4.07 (m, 2H), 3.93 – 3.64 (m, 2H), 3.52 – 2.84 (m, 4H), 2.37 (s, 3H).
73A	LCMS: 609.4 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.71 (s, 1H), 8.29 (t, <i>J</i> = 56.8 Hz, 1H), 8.19 (d, <i>J</i> = 8.3 Hz, 1H), 7.91 (d, <i>J</i> = 8.2 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.42 (s, 1H), 7.38 – 7.32 (m, 2H), 7.26 (t, <i>J</i> = 54.8 Hz, 1H), 5.26 (d, <i>J</i> = 12.1 Hz, 1H), 4.42 (d, <i>J</i> = 15.1 Hz, 1H), 4.21 (d, <i>J</i> = 15.1 Hz, 1H), 4.03 (d, <i>J</i> = 15.9 Hz, 1H), 3.67 (d, <i>J</i> = 11.5 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.04 – 2.78 (m, 4H).	74A	LCMS: 591.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 7.99 (s, 3H), 7.48 – 7.40 (m, 2H), 7.36 (s, 1H), 7.17 (t, <i>J</i> = 8.5 Hz, 2H), 6.79 (t, <i>J</i> = 55.5 Hz, 1H), 6.29 (d, <i>J</i> = 50.4 Hz, 2H), 5.73 – 5.42 (m, 1H), 4.72 (d, <i>J</i> = 14.5 Hz, 1H), 4.42 – 3.98 (m, 2H), 3.92 – 3.60 (m, 2H), 3.52 – 2.68 (m, 4H).
75A	LCMS: 591.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.99 (s, 1H), 8.15 (s, 1H), 8.13 – 8.01 (m, 2H), 7.45 – 7.40 (m, 2H), 7.39 (s,	76A	LCMS: 615.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.20 (s, 1H), 8.08 (s, 1H), 7.44 – 7.41 (m, 3H), 7.40 (t, <i>J</i> = 57.6 Hz, 1H), 7.18 (t,

Compound	Analytics	Compound	Analytics
	¹ H, 7.18 (t, <i>J</i> = 8.5 Hz, 2H), 5.74 – 5.44 (m, 1H), 4.77 (d, <i>J</i> = 12.7 Hz, 1H), 4.55 – 4.09 (m, 2H), 4.03 (s, 3H), 3.98 – 3.58 (m, 3H), 3.54 – 2.81 (m, 3H).		<i>J</i> = 8.5 Hz, 2H), 6.96 (t, <i>J</i> = 55.0 Hz, 1H), 5.51 (d, <i>J</i> = 12.8 Hz, 1H), 4.73 (d, <i>J</i> = 14.5 Hz, 1H), 4.38 – 4.16 (m, 2H), 4.02 – 3.78 (m, 2H), 3.61 – 3.19 (m, 4H).
77A	LCMS: 559.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 13.34 (brs, 1H), 8.84 (s, 1H), 8.38 (s, 1H), 8.13 - 7.99 (m, 2H), 7.46 - 7.39 (m, 3H), 7.23 - 7.15 (m, 2H), 6.80 (t, <i>J</i> = 55.4 Hz, 1H), 6.09 - 5.42 (m, 1H), 5.06 - 4.26 (m, 3H), 4.18 - 3.07 (m, 6H).	78A	LCMS: 615.5 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 7.98 (s, 2H), 7.95 (s, 1H), 7.47 – 7.41 (m, 2H), 7.36 (s, 1H), 7.20 – 7.13 (m, 2H), 6.79 (t, <i>J</i> = 55.5 Hz, 1H), 5.87 – 5.79 (m, 1H), 5.61 – 5.44 (m, 1H), 5.20 – 5.08 (m, 4H), 4.81 – 4.63 (m, 1H), 4.34 – 3.92 (m, 2H), 3.86 – 2.68 (m, 6H).
79A	LCMS: 576.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (s, 1H), 7.97 (s, 2H), 7.85 (s, 1H), 7.46 – 7.38 (m, 2H), 7.31 – 7.27 (m, 2H), 7.08 – 7.00 (m, 1H), 6.78 (t, <i>J</i> = 55.5 Hz, 1H), 5.52 – 5.36 (m, 1H), 4.83 – 4.70 (m, 1H), 4.31 – 4.17 (m, 1H), 4.16 – 3.98 (m, 1H), 3.84 – 3.73 (m, 1H), 3.72 – 3.55 (m, 1H), 3.15 – 2.69 (m, 4H).	79B	LCMS: 576.5 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.25 (s, 1H), 8.21 – 8.16 (m, 1H), 7.95 – 7.87 (m, 1H), 7.60 – 7.51 (m, 1H), 7.47 (s, 1H), 7.45 – 7.38 (m, 2H), 7.26 (t, <i>J</i> = 54.8 Hz, 1H), 7.24 – 7.17 (m, 1H), 5.19 (d, <i>J</i> = 12.0 Hz, 1H), 4.47 (d, <i>J</i> = 15.6 Hz, 1H), 4.31 (d, <i>J</i> = 15.6 Hz, 1H), 4.04 (d, <i>J</i> = 16.0 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.42 – 3.37 (m, 1H), 3.07 – 2.97 (m, 1H), 2.85 – 2.69 (m, 3H).
80A	LCMS: 576.5 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.82 (s, 1H), 8.01 – 7.89 (m, 2H), 7.85 (s, 1H), 7.48 – 7.35 (m, 3H), 7.27 (s, 1H), 7.25 – 7.20 (m, 1H), 6.78 (t, <i>J</i> = 55.5 Hz, 1H), 5.51 – 5.27 (m, 1H), 4.56 – 4.37 (m, 1H), 4.31 – 4.13 (m, 1H), 3.97 – 3.79 (m, 1H), 3.77 – 3.67 (m, 1H), 3.60 – 3.41 (m, 1H), 3.26 – 2.58 (m, 4H).	80B	LCMS: 576.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 7.99 (s, 2H), 7.85 (s, 1H), 7.49 - 7.38 (m, 3H), 7.31 - 7.27 (m, 1H), 7.26 - 7.21 (m, 1H), 6.79 (t, <i>J</i> = 55.5 Hz, 1H), 5.71 - 5.32 (m, 1H), 4.73 - 4.46 (m, 1H), 4.41 - 4.21 (m, 1H), 4.09 - 3.56 (m, 3H), 3.48 - 2.61 (m, 4H).
81A	LCMS: 562.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.81 (s, 1H), 7.94 (s, 2H), 7.85 (s, 1H),	81B	LCMS: 562.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.84 (s, 1H), 7.98 (s, 2H), 7.85 (s, 1H), 7.61

Compound	Analytics	Compound	Analytics
	7.61 (s, 1H), 7.60 (s, 1H), 7.29 (s, 1H), 6.77 (t, $J = 55.5$ Hz, 1H), 5.49 – 5.40 (m, 1H), 4.65 – 4.54 (m, 1H), 4.25 – 4.10 (m, 1H), 4.04 – 3.90 (m, 1H), 3.94 (s, 3H), 3.82 – 3.74 (m, 1H), 3.69 – 3.53 (m, 1H), 3.14 – 2.66 (m, 4H).		(s, 2H), 7.30 (s, 1H), 6.78 (t, $J = 55.5$ Hz, 1H), 5.71 – 5.37 (m, 1H), 4.75 – 4.57 (m, 1H), 4.45 – 4.06 (m, 2H), 3.95 (m, 3H), 3.88 – 3.64 (m, 2H), 3.47 – 2.65 (m, 4H).

[0175] The following compounds were prepared by similar procedures as described in Example 1.6.

Compound	Analytics	Compound	Analytics
82A	LCMS: 590.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.98 – 8.89 (m, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.79 – 7.71 (m, 1H), 7.46 – 7.41 (m, 2H), 7.35 (s, 1H), 7.19 – 7.14 (m, 2H), 5.75 – 5.51 (m, 1H), 4.78 – 4.64 (m, 1H), 4.28 (s, 3H), 4.19 – 3.85 (m, 3H), 3.78 – 3.56 (m, 1H), 3.28 – 2.58 (m, 4H), 1.89 (brs, 1H).	82B	LCMS: 590.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.93 – 8.90 (m, 1H), 8.13 (s, 1H), 7.87 (s, 1H), 7.71 (s, 1H), 7.46 – 7.41 (m, 2H), 7.35 (s, 1H), 7.19 – 7.13 (m, 2H), 5.85 – 5.44 (m, 1H), 4.75 – 4.63 (m, 1H), 4.32 – 4.17 (m, 1H), 4.27 (s, 3H), 4.07 – 3.77 (m, 2H), 3.72 – 3.50 (m, 1H), 3.44 – 2.28 (m, 5H).
83A	LCMS: 590.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 9.02 (s, 1H), 8.15 – 8.09 (m, 1H), 8.07 – 7.96 (m, 1H), 7.89 (s, 1H), 7.45 – 7.40 (m, 2H), 7.36 (s, 1H), 7.21 – 7.14 (m, 2H), 5.77 – 5.47 (m, 1H), 4.80 – 4.62 (m, 1H), 4.39 – 4.09 (m, 2H), 4.29 (s, 3H), 4.00 – 3.89 (m, 1H), 3.84 – 3.63 (m, 1H), 3.52 – 2.49 (m, 4H), 1.99 (brs, 1H).	83B	LCMS: 590.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 9.02 (s, 1H), 8.15 – 8.03 (m, 2H), 7.87 (s, 1H), 7.44 – 7.40 (m, 2H), 7.38 (s, 1H), 7.21 – 7.15 (m, 2H), 5.79 – 5.58 (m, 1H), 4.80 – 4.69 (m, 1H), 4.59 – 4.33 (m, 2H), 4.29 (s, 3H), 4.04 – 3.78 (m, 2H), 3.67 – 2.95 (m, 4H), 2.00 (brs, 1H).
84A	LCMS: 589.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 9.02 (s, 1H), 8.17 – 8.01 (m, 2H), 7.78 – 7.71 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 (s, 1H), 7.20 – 7.14 (m, 2H), 5.66 – 5.35 (m, 1H), 4.78 – 4.66 (m, 1H), 4.47 – 4.05 (m, 2H), 3.96 (s,	84B	LCMS: 589.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.98 (s, 1H), 8.13 – 7.95 (m, 2H), 7.74 (s, 1H), 7.70 (s, 1H), 7.46 – 7.40 (m, 2H), 7.35 (s, 1H), 7.19 – 7.13 (m, 2H), 5.62 – 5.18 (m, 1H), 4.79 – 4.59 (m, 1H), 4.37 – 4.18 (m, 2H), 3.94 (s,

Compound	Analytics	Compound	Analytics
	3H), 3.90 – 3.69 (m, 2H), 3.52 – 2.55 (m, 4H).		3H), 3.87 – 3.60 (m, 2H), 3.37 – 2.40 (m, 4H).
85A	LCMS: 561.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.49 (s, 1H), 7.85 – 7.76 (m, 1H), 7.76 – 7.73 (m, 2H), 7.46 – 7.40 (m, 2H), 7.40 – 7.34 (m, 2H), 7.18 – 7.12 (m, 2H), 5.74 – 5.38 (m, 1H), 4.82 – 4.64 (m, 1H), 4.27 – 4.08 (m, 1H), 4.04 – 3.89 (m, 4H), 3.83 – 3.51 (m, 2H), 3.21 – 2.14 (m, 4H), 2.03 – 1.92 (m, 1H), 1.20 – 1.13 (m, 2H), 0.87 – 0.82 (m, 2H).	85B	LCMS: 561.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.48 (s, 1H), 7.87 – 7.76 (m, 1H), 7.74 – 7.70 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.19 – 7.12 (m, 2H), 5.97 – 5.17 (m, 1H), 4.86 – 4.65 (m, 1H), 4.56 – 4.23 (m, 1H), 4.07 – 3.86 (m, 4H), 3.82 – 3.44 (m, 2H), 3.31 – 2.14 (m, 4H), 2.03 – 1.92 (m, 1H), 1.20 – 1.10 (m, 2H), 0.90 – 0.80 (m, 2H).
86A	LCMS: 571.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.85 (s, 1H), 8.02 – 7.91 (m, 2H), 7.73 (s, 1H), 7.70 (s, 1H), 7.46 – 7.40 (m, 2H), 7.35 (s, 1H), 7.20 – 7.13 (m, 2H), 6.79 (t, <i>J</i> = 55.5 Hz, 1H), 5.62 – 5.28 (m, 1H), 4.78 – 4.62 (m, 1H), 4.41 – 4.23 (m, 1H), 4.06 – 3.87 (m, 4H), 3.86 – 3.64 (m, 2H), 3.37 – 2.48 (m, 4H), 1.40 – 1.26 (m, 1H).	86B	LCMS: 571.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (s, 1H), 8.07 – 7.96 (m, 2H), 7.75 (s, 1H), 7.73 (s, 1H), 7.47 – 7.40 (m, 2H), 7.36 (s, 1H), 7.20 – 7.14 (m, 2H), 6.80 (t, <i>J</i> = 55.4 Hz, 1H), 5.67 – 5.36 (m, 1H), 4.80 – 4.62 (m, 1H), 4.31 – 4.01 (m, 2H), 3.99 – 3.94 (m, 3H), 3.87 – 3.58 (m, 2H), 3.40 – 2.39 (m, 4H), 1.43 – 1.28 (m, 1H).
87A	LCMS: 572.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.87 (s, 1H), 8.07 – 7.94 (m, 2H), 7.89 (s, 1H), 7.47 – 7.40 (m, 2H), 7.36 (s, 1H), 7.20 – 7.13 (m, 2H), 6.79 (t, <i>J</i> = 55.4 Hz, 1H), 5.75 – 5.45 (m, 1H), 4.80 – 4.61 (m, 1H), 4.44 – 4.18 (m, 4H), 4.18 – 3.75 (m, 3H), 3.73 – 3.50 (m, 1H), 3.20 – 2.55 (m, 3H), 1.85 (brs, 1H).	87B	LCMS: 572.3 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.86 (s, 1H), 7.99 (s, 2H), 7.87 (s, 1H), 7.45 – 7.41 (m, 2H), 7.36 (s, 1H), 7.19 – 7.14 (m, 2H), 6.78 (t, <i>J</i> = 55.5 Hz, 1H), 5.86 – 5.44 (m, 1H), 4.78 – 4.65 (m, 1H), 4.38 – 4.24 (m, 4H), 4.14 – 3.83 (m, 2H), 3.82 – 3.63 (m, 1H), 3.62 – 2.37 (m, 5H).
89A	LCMS: 575.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.88 (s, 1H), 8.06 – 7.93 (m, 2H), 7.89 (s, 1H), 7.46 – 7.40 (m, 2H), 7.36 (s, 1H), 7.20 – 7.13 (m, 2H), 6.79 (t, <i>J</i> = 55.4 Hz, 1H), 5.86 – 5.42 (m, 1H),	89B	LCMS: 575.5 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.85 (s, 1H), 8.06 – 7.92 (m, 2H), 7.87 (s, 1H), 7.46 – 7.40 (m, 2H), 7.35 (s, 1H), 7.19 – 7.13 (m, 2H), 6.78 (t, <i>J</i> = 55.5 Hz, 1H), 5.91 – 5.35 (m, 1H),

Compound	Analytics	Compound	Analytics
	4.82 – 4.61 (m, 1H), 4.35 – 2.60 (m, 8H), 1.97 – 1.70 (m, 1H).		4.83 – 4.60 (m, 1H), 4.55 – 3.85 (m, 3H), 3.83 – 3.26 (m, 2H), 3.24 – 2.39 (m, 4H).
90A	LCMS: 562.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 7.90 (s, 1H), 7.86 – 7.72 (m, 1H), 7.47 – 7.34 (m, 4H), 7.20 – 7.12 (m, 2H), 5.84 – 5.48 (m, 1H), 4.84 – 4.66 (m, 1H), 4.27 (s, 3H), 4.22 – 3.39 (m, 5H), 3.02 – 2.59 (m, 3H), 2.03 – 1.95 (m, 1H), 1.78 (brs, 1H), 1.23 – 1.13 (m, 2H), 0.90 – 0.81 (m, 2H).	90B	LCMS: 562.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.47 (s, 1H), 7.87 (s, 1H), 7.85 – 7.68 (m, 1H), 7.46 – 7.39 (m, 2H), 7.38 – 7.29 (m, 2H), 7.19 – 7.10 (m, 2H), 6.03 – 5.46 (m, 1H), 4.84 – 4.64 (m, 1H), 4.44 – 4.15 (m, 4H), 4.09 – 3.33 (m, 4H), 3.29 – 2.71 (m, 3H), 2.69 – 2.52 (m, 1H), 2.02 – 1.92 (m, 1H), 1.21 – 1.07 (m, 2H), 0.92 – 0.77 (m, 2H).
91A	LCMS: 598.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 8.10 (s, 1H), 7.85 – 7.76 (m, 1H), 7.45 – 7.40 (m, 3H), 7.38 (t, <i>J</i> = 58.2 Hz, 1H), 7.35 (s, 1H), 7.19 – 7.13 (m, 2H), 5.90 – 5.60 (m, 1H), 4.82 – 4.66 (m, 1H), 4.43 – 3.48 (m, 5H), 3.28 – 2.62 (m, 3H), 2.03 – 1.96 (m, 1H), 1.22 – 1.15 (m, 2H), 0.88 – 0.83 (m, 2H).	91B	LCMS: 598.4 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 8.05 (s, 1H), 7.84 – 7.75 (m, 1H), 7.44 – 7.40 (m, 2H), 7.38 (t, <i>J</i> = 57.8 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.19 – 7.13 (m, 2H), 6.04 – 5.66 (m, 1H), 4.83 – 4.68 (m, 1H), 4.53 – 4.31 (m, 1H), 4.18 – 3.66 (m, 3H), 3.51 – 2.68 (m, 4H), 2.02 – 1.95 (m, 1H), 1.21 – 1.12 (m, 2H), 0.91 – 0.81 (m, 2H).
92A	LCMS: 565.5 [M+H] ⁺ . ¹ H NMR (400 MHz, CDCl ₃) δ 8.50 (s, 1H), 7.90 (s, 1H), 7.87 – 7.72 (m, 1H), 7.47 – 7.34 (m, 4H), 7.20 – 7.12 (m, 2H), 5.80 – 5.52 (m, 1H), 4.87 – 4.63 (m, 1H), 4.31 – 3.37 (m, 5H), 3.08 – 2.55 (m, 3H), 2.03 – 1.94 (m, 1H), 1.77 (brs, 1H), 1.25 – 1.08 (m, 2H), 0.93 – 0.77 (m, 2H).	92B	LCMS: 565.4 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 – 8.50 (m, 1H), 8.00 (s, 1H), 7.70 – 7.64 (m, 1H), 7.59 – 7.50 (m, 3H), 7.40 – 7.30 (m, 3H), 5.42 – 5.32 (m, 1H), 4.83 (s, 1H), 4.48 – 4.39 (m, 1H), 4.18 – 4.08 (m, 2H), 3.71 – 3.61 (m, 1H), 3.47 – 3.37 (m, 1H), 2.96 – 2.89 (m, 1H), 2.74 – 2.66 (m, 1H), 2.63 – 2.56 (m, 1H), 2.56 – 2.51 (m, 1H), 2.12 – 2.03 (m, 1H), 1.15 – 1.08 (m, 2H), 0.91 – 0.82 (m, 2H).

Example 2: Biological Evaluation**[0176] In Vitro GR Reporter Gene Assay:**

- [0177] Cell Line: HEK293T
- [0178] Plasmid: pGL4.35 [luc2P/9XGAL4 UAS/Hygro]
- [0179] Culture Media: DMEM (with phenol red) + 10% FBS
- [0180] Assay Media: DMEM (without phenol red) + 10% FBS
- [0181] Culture HEK293T cells in T175 flasks in Culture Media at conditions less than 90% confluence.
- [0182] HEK293T cells were assayed in exponential growth phase.
- [0183] Seeded 6×10^6 HEK293T cells into a 100mm dish.
- [0184] Cells were incubated for 16h at 37°C under 5% CO₂ atmosphere.
- [0185] Transfection of plasmids into cells and incubated for 5-6h at 37°C under 5% CO₂ atmosphere.
- [0186] Control and test compounds were 3-fold serial diluted from 1 mM for 10 doses in DMSO.
- [0187] Transfer 75nl compound dilutions into 384 well assay plates using Echo655.
- [0188] Seeded HEK293T cells at 17,000 cells /well into 384 well assay plate with 5nM Dexamethasone.
- [0189] Cells were incubated for 18-20 hours at 37°C under 5% CO₂ atmosphere.
- [0190] Add 25µl britelite plus Luciferase Assay Reagent into each well of 384-well assay plate.
- [0191] Record the luminescence value on Envision 2105 plate reader.
- [0192] RLU signal is calculated for each well.
- [0193] Analyzed the raw data using the equation (V. Data analysis).
- [0194] The GR antagonist activity of the compounds disclosed herein was measured with GR reporter gene assay and the IC₅₀ value was determined. Table 4 provided the IC₅₀ of exemplary compounds for inhibiting GR.

TABLE 4 IC₅₀ of Exemplary Compounds For Inhibiting GR

Compound No.	GR IC ₅₀ (nM)	Compound No.	GR IC ₅₀ (nM)	Compound No.	GR IC ₅₀ (nM)
1A	A	2A	A	2B	D
3A	A	3B	D	4A	D
4B	B	5A	D	5B	B
6A	D	6B	A	7A	A
7B	D	8A	D	8B	B
9A	D	9B	A	10A	D
10B	A	11A	A	11B	D
12A	A	12B	D	13A	A
13B	D	14A	A	14B	D
15A	A	15B	D	16A	A
16B	D	17A	A	17B	D

18A	A	18B	D	19A	A
19B	D	20A	A	21A	B
22A	C	23A	C	24A	A
25A	A	26A	D	26B	A
27A	B	28A	D	28B	A
29A	A	30B	B	31A	A
32A	C	32B	A	33A	A
34A	A	35A	A	36A	A
36B	C	37A	A	38A	A
38B	C	39A	A	40A	A
41A	A	42B	A	43A	A
44A	A	45A	D	45B	C
46A	A	47A	A	47B	D
48A	B	48B	D	49A	D
49B	C	50A	B	50B	D
51A	A	51B	D	52A	A
53A	A	54A	A	55A	A
56A	A	57A	A	58A	A
59B	A	60A	A	60B	C
61A	A	62A	A	63A	A
63B	C	64A	A	65A	A
66A	A	67A	A	67B	C
68A	A	69A	A	70A	A
71A	A	71B	D	72A	A
73A	A	74A	A	75A	B
76A	A	77A	C	78A	A
79A	A	79B	C	80A	A
80B	C	81A	A	81B	C
82A	A	82B	A	83A	B
83B	A	84A	B	84B	B
85A	B	85B	A	86A	A
86B	B	87A	A	87B	A
88A	A	88B	A	89A	A
89B	A	90A	A	90B	A
91A	A	91B	A	92A	A
92B	A				

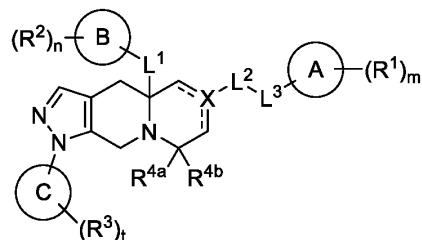
IC₅₀ (nM): $0 < A \leq 20$ nM; 20 nM $< B \leq 100$ nM; 100 nM $< C \leq 1000$ nM; 1000 nM $< D$

[0195] Other compounds disclosed herein also show GR antagonist activity.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof,

wherein:

each $\equiv$ is independently a single bond or double bond;

X is N, C or CH;

L^1 is $-C(=O)-$, $-C(=O)O-$, $-C(=O)N(R^a)-$, $-C(R^a)_2-$, $-N(R^a)-$, $-O-$, $-S-$, $S(=O)$ or $-S(=O)_2-$;

each of L^2 and L^3 is independently a bond, $-N(R^a)-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)N(R^a)-$, $-O-$, $-S-$, $S(=O)$, $-S(=O)_2-$, $-S(=O)(=NR^a)-$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, or oxo;

each of Ring A, Ring B and Ring C is independently cycloalkyl, aryl, heterocyclyl or heteroaryl;

each of R^1 , R^2 and R^3 is independently halogen, hydroxy, cyano, $-OR^b$, $-N(R^b)_2$, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)N(R^b)_2$, $-S(=O)R^b$, $-S(=O)_2R^b$, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, alkoxy, cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the alkyl, haloalkyl, hydroxyalkyl, alkoxy, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, oxo, alkyl, alkenyl, alkynyl, haloalkyl, or hydroxyalkyl;

each of R^{4a} and R^{4b} is independently hydrogen, halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxyalkyl or alkoxy;

or R^{4a} and R^{4b} together with the carbon atom to which they are attached form a cycloalkyl or heterocyclyl, each optionally substituted with one or more groups independently selected from halogen, hydroxyl, amino or alkyl;

each of R^a and R^b is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

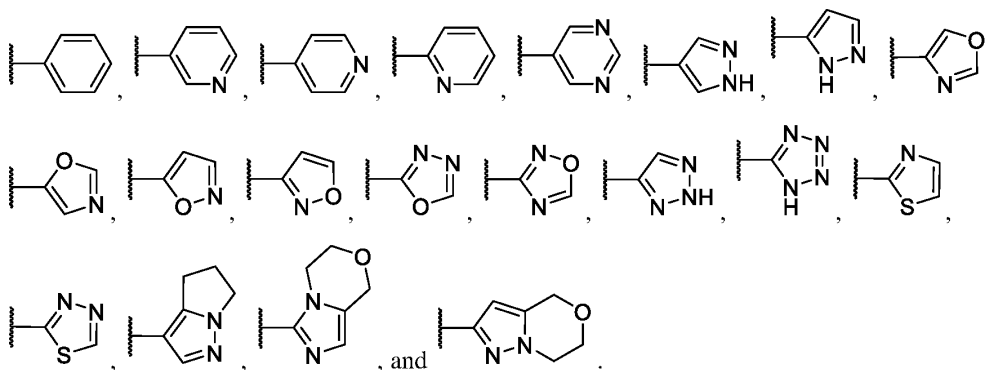
or two R^b together with the nitrogen atom to which they are attached form a heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxyl, amino or alkyl;

n is any integer of 0-5;

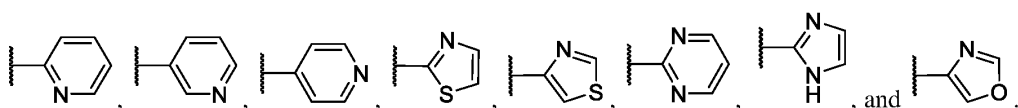
m is any integer of 0-5; and

t is any integer of 0-5.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L¹ is -C(=O)-.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein L² is a bond, -N(R^a)- or alkyl and L³ is -S(=O)₂- or -S(=O)(=NR^a)-; or L² is -S(=O)₂- or -S(=O)(=NR^a)- and L³ is a bond, -N(R^a)- or alkyl.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein -L²-L³- is -S(=O)₂-, -N(R^a)-S(=O)₂- or -S(=O)(=NR^a)-.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Ring A is aryl or heteroaryl.
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenyl, pyridyl, pyrazolyl, pyrimidinyl, triazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, tetrazolyl, dihydropyrrolopyrazolyl, dihydroimidazooxazinyl, or dihydropyrazoloxazinyl.
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from the group consisting of:

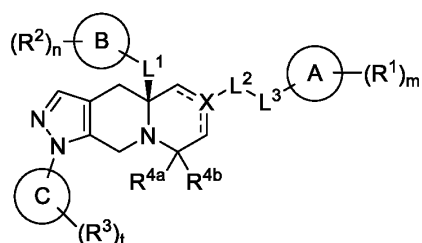


8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently halogen, cyano, $-OR^b$, alkyl, haloalkyl, cycloalkyl or heterocyclyl.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently $-F$, $-Cl$, cyano, $-OCH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl or .
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein Ring B is heteroaryl.
11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein Ring B is pyridyl, thiazolyl, pyrimidinyl, imidazolyl or oxazolyl.
12. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein Ring B is selected from the group consisting of:

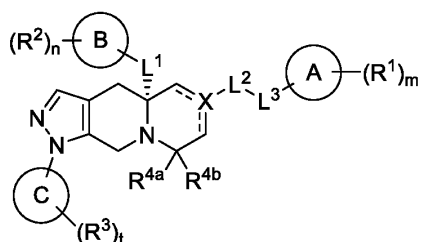


13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently halogen, alkyl, haloalkyl or cycloalkyl.
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently $-CH_3$, $-F$, $-Cl$, $-CH_2F$, $-CHF_2$, $-CF_3$ or cyclopropyl.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein Ring C is aryl.
16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein Ring C is phenyl.
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently halogen, alkyl, or haloalkyl.

18. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein each R^3 is -F, -CH₃, -CH₂F, -CHF₂, or -CF₃.
19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is hydrogen or alkyl.
20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is hydrogen or alkyl.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein both R^{4a} and R^{4b} are hydrogen.
22. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} together with the carbon atom to which they are attached form cyclopropyl.
23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (Ia) or Formula (Ib):

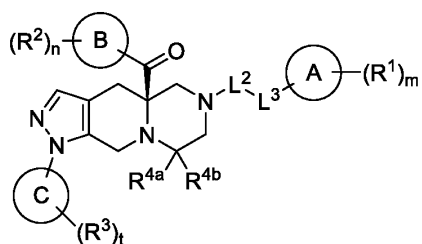


Formula (Ia),

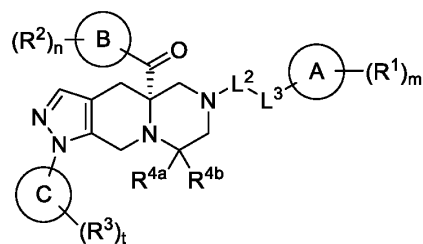


Formula (Ib).

24. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula selected from:



Formula (Ia-1)



Formula (Ib-1).

25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein Ring A is aryl or heteroaryl, optionally Ring A is phenyl, pyridyl, pyrazolyl, pyrimidinyl, triazolyl, or thiadiazolyl.
26. The compound of claim 24 or 25, or a pharmaceutically acceptable salt thereof, wherein Ring B is heteroaryl, optionally Ring B is pyridyl, pyrimidinyl, thiazolyl or imidazolyl.
27. The compound of any one of claims 24-26, or a pharmaceutically acceptable salt thereof, wherein Ring C is aryl, optionally Ring C is phenyl.
28. The compound of any one of claims 24-27, or a pharmaceutically acceptable salt thereof, wherein each of L^2 and L^3 is independently a bond, $-N(R^a)-$, $-S(=O)_2-$ or $-S(=O)(=NR^a)-$, optionally $-L^2-L^3-$ is $-S(=O)_2-$, $-N(R^a)-S(=O)_2-$ or $-S(=O)(=NR^a)-$, optionally R^a is hydrogen or alkyl.
29. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from any compound set forth in Table 1, 2 or 3.
30. A pharmaceutical composition comprising the compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
31. A method of modulating a glucocorticoid receptor, in a subject in need thereof, comprising administering to the subject an effective amount of the compound of any one of claims 1-29 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 30.
32. A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of the compound of any one of claims 1-29 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 30.
33. The method of claim 32, wherein the disease or disorder is Cushing's syndrome, Addison's disease, osteoporosis, rheumatoid arthritis, asthma, rhinitis, adrenal function related diseases, human immunodeficiency virus, acquired immune deficiency syndrome, allergy, or wound healing.