

Description

Title of Invention: NOVEL COMPOUNDS AS GLP-1R AGONISTS AND USES THEREOF

FIELD OF THE DISCLOSURE

[0001] The present disclosure relates to novel compounds or pharmaceutically acceptable salts thereof, which are useful as glucagon-like peptide-1 receptor (GLP-1R) agonists. 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, such as cancer.

BACKGROUND

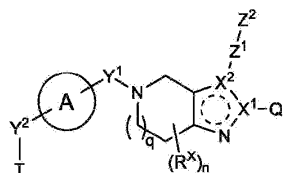
[0002] The glucagon-like peptide-1 receptor (GLP-1R) is a validated target for the treatment of diabetes and obesity. Biologics that target this receptor, such as semaglutide and liraglutide have proven clinically successful in regulating blood glucose levels, but they are not without drawbacks that include daily or weekly injections and reports of ADRs ranging from nausea and diarrhea to pancreatitis. In order to produce an orally available GLP-1R agonist, increased efforts have been directed towards the development of small molecules.

[0003] Therefore, there are still unsatisfied needs for novel compounds as GLP-1R agonists.

SUMMARY

[0004] In one aspect, the present disclosure provides a compound of Formula (I) :

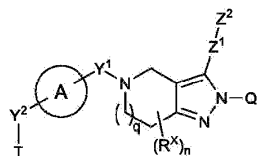
or a pharmaceutically acceptable salt thereof,



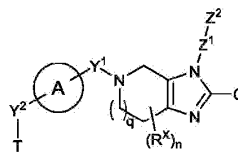
Formula (I),

as disclosed herein.

[0005] In one aspect, the present disclosure provides a compound of Formula (I-1) or Formula (I-2) :



Formula (I-1),



Formula (I-2),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

- [0006] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I) , Formula (I-1) , Formula (I-2) , or a compound set forth in Table 4.1 or Table 4.2) , or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.
- [0007] Also disclosed herein is a method of activating GLP-1R in a subject, the method comprising administering to the subject the compound disclosed herein (e.g., a compound of Formula (I) , Formula (I-1) , Formula (I-2) , or a compound set forth in Table 4.1 or Table 4.2) , or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.
- [0008] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I) , Formula (I-1) , Formula (I-2) , or a compound set forth in Table 4.1 or Table 4.2) , or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for activating GLP-1R in a subject.
- [0009] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I) , Formula (I-1) , Formula (I-2) , or a compound set forth in Table 4.1 or Table 4.2) , 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 GLP-1 associated disease or disorder.
- INCORPORATION BY REFERENCE
- [0010] 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

- [0011] 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.

- [0012] 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.
- [0013] The terms below, as used herein, have the following meanings, unless indicated otherwise.
- [0014] 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.
- [0015] 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.
- [0016] 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.

- [0017] 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.
- [0018] 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.
- [0019] "Oxo" refers to $=O$.
- [0020] "Cyano" refers to $-CN$.
- [0021] "Nitro" refers to $-NO_2$.
- [0022] "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.
- [0023] "Hydroxy" or "hydroxyl", whether as part of another term or used independently, refers to $-OH$.
- [0024] "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 " C_1-C_6 alkyl" or " C_{1-6} alkyl", 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.

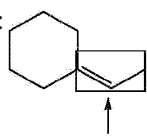
In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl 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.

[0025] “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.

[0026] “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-butenyl, 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.

[0027] “Alkylidenyl” is alkyl as defined above that is attached via the terminal divalent carbon. Exemplary alkylidenes include, but are not limited to, methylydenyl (H₂C=), ethylydenyl (CH₃CH=), propylydenyl (such as =C(CH₃)₂ and =CHCH₂CH₃), hexylydenyl (such as CH₃(CH₂)₄CH=), and the like. For example, in the compound below: the alkylidenyl group (i.e., ethylydenyl group), is enclosed by the



box which is indicated by the arrow.

[0028] “Alkoxy” or “alkoxyl”, 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, cy-

clopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalyl, 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] “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amino radicals, as defined above, e.g., aminomethyl, 2-aminoethyl, 1, 2-diaminoethyl, 1, 2-diaminopropyl, and the like.
- [0035] “Alkoxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more alkoxy radicals, as defined above. Examples of alkoxyalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH (OCH₃)₂, -CH₂CH (OCH₃)₂, -C (OCH₃)₃, -CH₂C (OCH₃)₃, and the like.
- [0036] “Haloalkoxy” refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethoxy, difluoromethoxy, fluoromethoxy, trichloromethoxy, 2, 2, 2-trifluoroethoxy, 1, 2-difluoroethoxy, 3-bromo-2-fluoropropoxy, 1, 2-dibromoethoxy, and the like.
- [0037] “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.

[0038] “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.

[0039] “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.

[0040] “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 (C_2 - C_5 heterocyclyl), or two to four carbon atoms (C_2 - C_4 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.

[0041] “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 het-

eroatoms 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, indolinyl, isoindolinyl, isoquinolyl, indoliziny, 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.

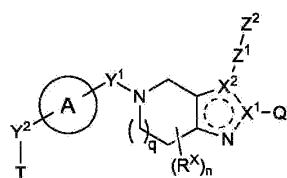
- [0042] The term “heteroarylalkyl” refers to an alkyl radical, as defined above, that is linked to an aryl radical, as defined above. In some embodiments, a heteroarylalkyl can be attached to the parent molecular moiety through heteroaryl moiety or alkyl moiety. In some embodiments, a heteroarylalkyl can be a linking substituent in the form of -heteroaryl-alkyl-or -alkyl-heteroaryl-.
- [0043] The term “heterocyclalkyl” refers to an alkyl radical, as defined above, that is linked to a heterocycl radical, as defined above. In some embodiments, a heterocyclalkyl can be attached to the parent molecular moiety through heterocycl moiety or alkyl moiety. In some embodiments, a heterocyclalkyl can be a linking substituent in the form of -heterocycl-alkyl-or -alkyl-heterocycl-.
- [0044] 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.
- [0045] 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.
- [0046] 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.

[0047] 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.

[0048] 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

[0049] Described herein are compounds, or pharmaceutically acceptable salts thereof useful as GLP-1R agonists and in the treatment of diseases or disorders, such as cancer.

[0050] In one aspect, provided herein is a compound of Formula (I) :



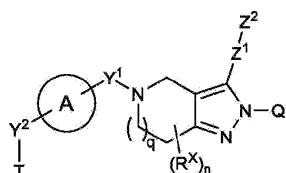
Formula (I),

of, wherein:  is heteroaryl; X¹ is N, and X² is C; or X¹ is C, and X² is N; Y¹ is -C

(=O) -, -C(R^a)₂-, or -S(=O)₂-; Ring A is heteroaryl optionally substituted with one or more R^A; each R^A is independently halogen, hydroxy, oxo, SF₅, alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the alkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more R^{A1}; each R^{A1} is independently halogen, hydroxy, oxo, alkyl or alkoxy; Y² is -Y^{2a}-Y^{2b}-Y^{2c}-; each of Y^{2a} and Y^{2c} is a bond or alkyl; Y^{2b} is alkyl, SF₅, haloalkyl or cycloalkyl, wherein the alkyl, haloalkyl and cycloalkyl are optionally substituted with one or more groups independently selected from alkyl, haloalkyl or cycloalkyl; T is -C(=O)O(R^b), -C(=O)N(R^b)-alkyl, -C(=O)N(R^b)C(=O)(R^b), -C(=O)N(R^b)-S(=O)(R^b), -C(=O)N(R^b)-S(=O)₂(R^b), heterocyclyl or heteroaryl, wherein the alkyl, heterocyclyl and heteroaryl are optionally substituted with one or more R^T; each R^X is independently halogen, hydroxyl, cyano, alkyl, SF₅, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy or alkoxyalkyl; or two R^X taken together with the intervening atom(s) form a cycloalkyl, or heterocyclyl, wherein the cycloalkyl and heterocyclyl are optionally substituted with one or more R^{XX}; each R^{XX} is independently halogen, hydroxy, oxo, alkyl, SF₅, haloalkyl, hydroxyalkyl, alkoxy or alkoxyalkyl; Q is cycloalkyl, aryl, heterocyclyl or heteroaryl, each optionally substituted with one or more R^Q; Z¹ is a bond, -N(R^c)-, -N(R^c)-alkyl-, -N(R^c)-C(=O)

-, -N(R^c) -C(=O) -N(R^c) -, heterocyclyl, heteroaryl, heterocyclyl-alkyl or heteroaryl-alkyl, wherein the alkyl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, oxo, alkyl, haloalkyl, hydroxyalkyl, or alkoxy; Z² is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, each optionally substituted with one or more R^Z; each R^T is independently halogen, hydroxy, oxo, alkyl, SF₅, haloalkyl, hydroxyalkyl, alkoxy or alkoxyalkyl; each R^Q is independently halogen, hydroxy, cyano, alkyl, SF₅, haloalkyl, hydroxyalkyl, alkoxy or cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups independently selected from halogen, haloalkyl, or alkyl; each R^Z is independently halogen, hydroxyl, cyano, oxo, alkyl, SF₅, haloalkyl, alkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, -N(R^d)₂, -C(=O)N(R^d)₂, -S(=O)(R^d), -S(=O)₂(R^d), or -P(=O)(R^d)₂, wherein the alkyl, alkoxy, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl, alkoxy, OCF₃; or two R^Z together with the same atom to which they are both attached form a C₂-C₆ alkylidenyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, SF₅, haloalkyl, alkyl or alkoxy; each of R^a, R^b and R^c is independently hydrogen or alkyl; or two R^a taken together with the same atom to which they are attached form a cycloalkyl or heterocyclyl; each R^d is independently hydrogen, alkyl, or cycloalkyl; n is any integer of 0-6; and q is any integer of 1-3.

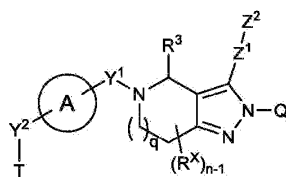
[0051] In some embodiments of Formula (I), the compound is of Formula (I-1):



Formula (I-1).

[0052] In some embodiments of Formula (I-1), the compound is of Formula (I-1-1):

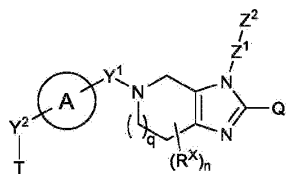
wherein R^3 is hydrogen or R^x , n-1 is any



Formula (I-1-1),

integer of 0-5. In some embodiments, R³ is methyl. In some embodiments, n-1 is 0, 1, 2, or 3.

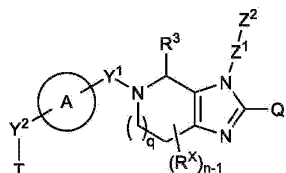
[0053] In some embodiments of Formula (I), the compound is of Formula (I-2):



Formula (I-2).

[0054] In some embodiments of Formula (I-2), the compound is of Formula (I-2-1):

wherein R^3 is hydrogen or R^X , $n-1$ is any



Formula (I-2-1),

integer of 0-5. In some embodiments, R^3 is methyl. In some embodiments, $n-1$ is 0, 1, 2, or 3.

[0055] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), one or more R^X is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, one or more R^X is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

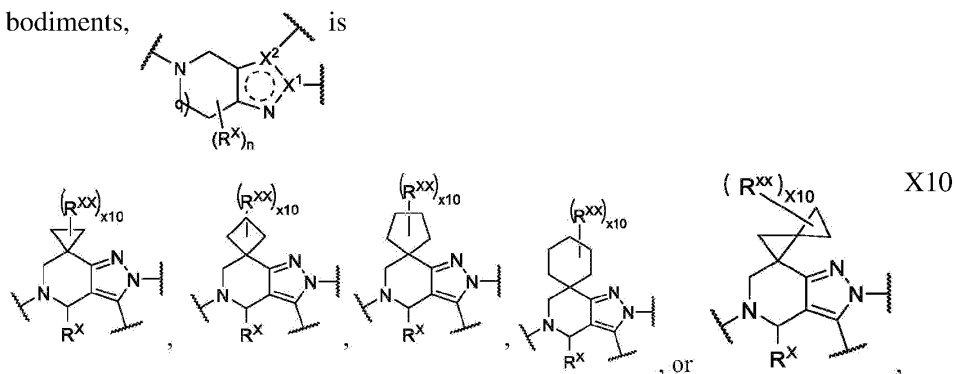
[0056] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2) or (I-2-1), two R^X taken together with the same atom to which they are attached form a C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, two R^X taken together with the same atom to which they are attached form a C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} .

[0057] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2) or (I-2-1), two R^X taken together with the adjacent atoms to which they are attached form a C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, two R^X taken together with the adjacent atoms to which they are attached form a C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} .

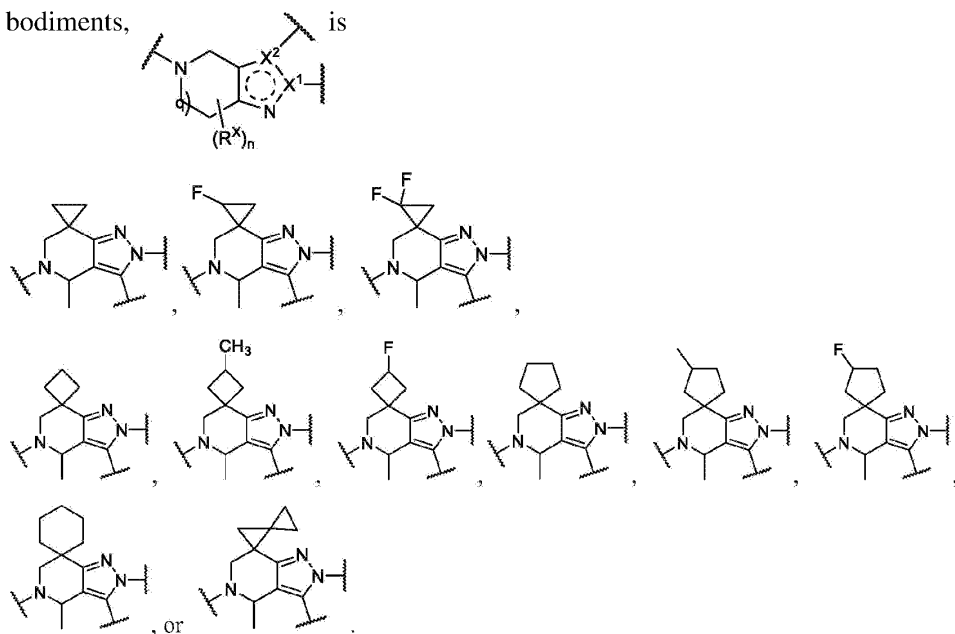
[0058] In some embodiments of Formula (I), (I-1), or (I-2), n is 1 and R^X is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, n is 1 and R^X is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0059] In some embodiments of Formula (I-1-1) or (I-2-1), $n-1$ is 1 and R^X is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, $n-1$ is 1 and R^X is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0060] In some embodiments of Formula (I), (I-1) or (I-2), n is 3, one R^X is C_{1-6} alkyl and the other two R^X taken together with the same atom to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, n is 3, one R^X is C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl and the other two R^X taken together with the same atom to which they are attached form a C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments,



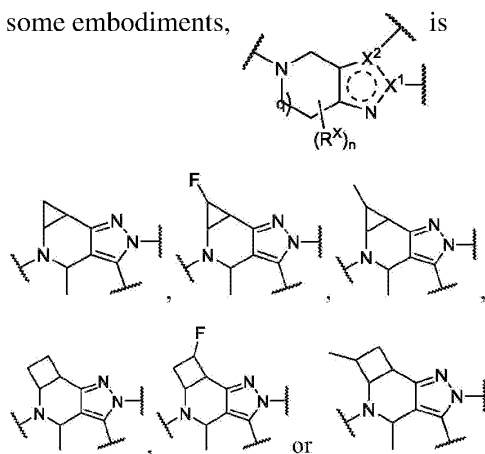
is 0, 1, 2, or 3. In some embodiments, $X10$ is 0, 1, or 2. In some embodiments, $X10$ is 0, or 1. In some embodiments, $X10$ is 0. In some embodiments, $X10$ is 1. In some embodiments,



[0061] In some embodiments of Formula (I), (I-1) or (I-2), each R^{XX} is independently halogen, hydroxy, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy or

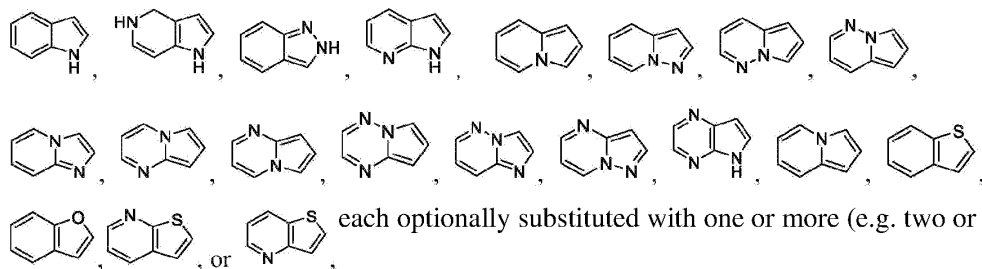
C_{1-6} alkoxy C_{1-6} alkyl. In some embodiments, each R^{xx} is independently halogen, hydroxy, oxo, or C_{1-3} alkyl.

- [0062] In some embodiments of Formula (I), (I-1) or (I-2), n is 3, one R^x is C_{1-6} alkyl and the other two R^x taken together with the adjacent atoms to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} . In some embodiments, n is 3, one R^x is C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl and the other two R^x taken together with the adjacent atoms to which they are attached form a C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} . In some embodiments,

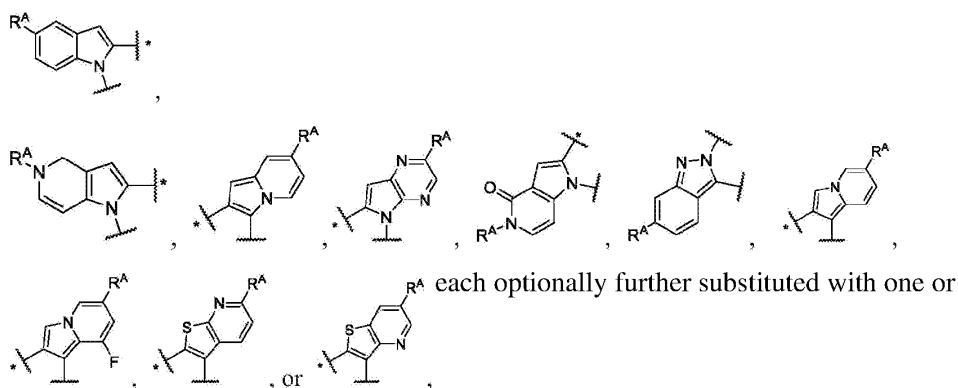


- [0063] In some embodiments of Formula (I-1-1) or (I-2-1), $n-1$ is 2, two R^x taken together with the same atom to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} . In some embodiments, $n-1$ is 2, two R^x taken together with the same atom to which they are attached form a C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} .
- [0064] In some embodiments of Formula (I-1-1) or (I-2-1), $n-1$ is 2, two R^x taken together with the adjacent atoms to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} . In some embodiments, $n-1$ is 2, two R^x taken together with the adjacent atoms to which they are attached form a C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{xx} .
- [0065] In some embodiments of Formula (I), (I-1) or (I-2), n is 0, 1, 2 or 3. In some embodiments, n is 0.
- [0066] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Ring A is a bicyclic heteroaryl optionally substituted with one or more (e.g. two or three, etc)

R^A . In some embodiments, the bicyclic heteroaryl comprises at least one N atom. In some embodiments, the bicyclic heteroaryl is fused bicyclic heteroaryl. In some embodiments, the bicyclic heteroaryl is fused bicyclic heteroaryl comprising a 5-membered ring fused with a 6-membered ring. In some embodiments, Ring A is selected from the group consisting of:



three, etc) R^A . In some embodiments, Ring A is selected from the group consisting of:

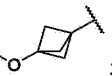


more (e.g. two or three, etc) R^A , wherein *end of Ring A is connected to Y^1 .

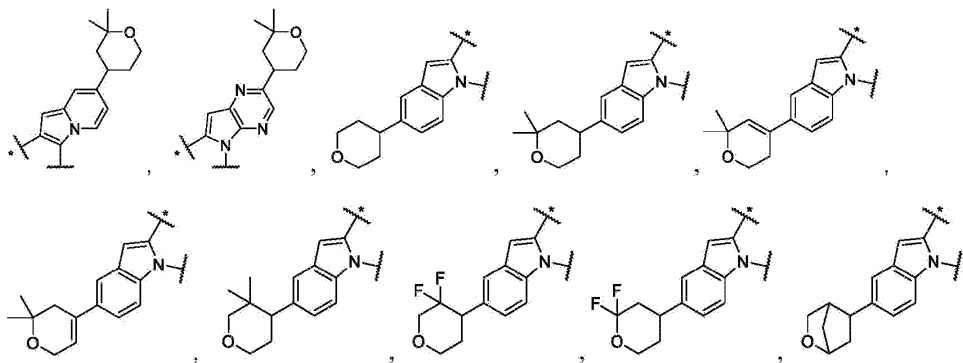
[0067] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), each R^A is independently halogen, hydroxy, oxo, cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl are optionally substituted with one or more (e.g. two or three, etc) R^{A1} . In some embodiments, one or more of R^A is oxo. In some embodiments, one or more of R^A is independently C_{3-8} cycloalkyl, C_{4-8} cycloalkyl, C_{5-8} cycloalkyl, C_{5-7} cycloalkyl or C_{5-6} cycloalkyl, each optionally substituted with one or more (e.g. two or three, etc) R^{A1} . In some embodiments, one or more of R^A is independently C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl, C_7 cycloalkyl or C_8 cycloalkyl, each optionally substituted with one or more (e.g. two or three, etc) R^{A1} . In some embodiments, one or more of R^A is independently 3-to 8-membered heterocyclyl, 4-to 8-membered heterocyclyl, 4-to 7-membered heterocyclyl or 4-to 6-membered heterocyclyl, each optionally substituted with one or more R^{A1} . In some embodiments, one or more of R^A is independently 3-membered heterocyclyl, 4-membered heterocyclyl,

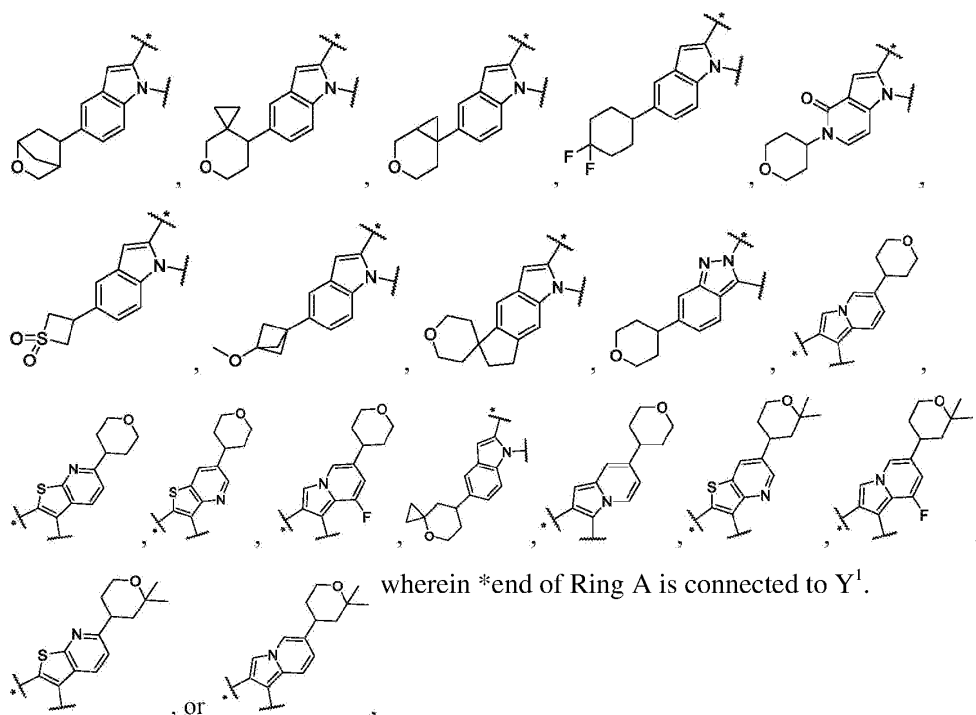
5-membered heterocyclyl, 6-membered heterocyclyl, 7-membered heterocyclyl or 8-membered heterocyclyl, each optionally substituted with one or more (e.g. two or three, etc) R^{A1} .

[0068] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), each R^{A1} is independently oxo, alkyl or alkoxy. In some embodiments, each R^{A1} is independently oxo, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , etc) alkyl or C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , etc) alkoxy. In some embodiments, each R^{A1} is independently oxo, $-CH_3$, or $-OCH_3$.

[0069] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Ring A is a bicyclic heteroaryl substituted with one or more R^A , and one R^A is  or  or Ring A is a tricyclic or tetracyclic heteroaryl optionally substituted with one or more R^A .

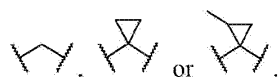
[0070] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Ring A is





[0071] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Y¹ is -C(=O)-, -C(R^a)₂-, or -S(=O)₂-. In some embodiments, Y¹ is -C(=O)-. In some embodiments, Y¹ is -C(R^a)₂-, and R^a is hydrogen or C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅, C₆, etc) alkyl. In some embodiments, Y¹ is -C(R^a)₂-, and two R^a taken together with the same atom to which they are attached form a C₃₋₆ (e.g. C₃, C₄, C₅, or C₆, etc) cycloalkyl or 3-to 6-membered (e.g. 3-, 4-, 5-, 6-, 3-to 4-, 4-to 5-, 5-to 6-membered, etc) heterocycl. In some embodiments, Y¹ is In some embodiments, Y¹ is -S(=O)₂-.

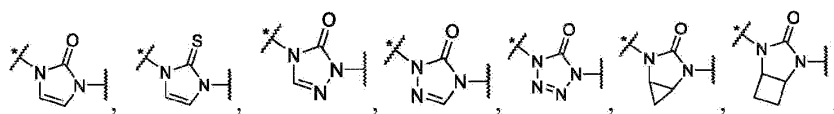
[0072] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Y² is alkyl or cycloalkyl optionally substituted with alkyl. In some embodiments, Y² is C₃₋₆ cycloalkyl, C₃₋₅ cycloalkyl or C₃₋₄ cycloalkyl, each optionally substituted with alkyl. In some embodiments, Y² is C₆ cycloalkyl, C₅ cycloalkyl, C₄ cycloalkyl, C₃ cycloalkyl, each optionally substituted with alkyl. In some embodiments, Y² is C₁₋₆ alkyl, C₁₋₅ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl or C₁₋₂ alkyl. In some embodiments, Y² is C₆ alkyl, C₅ alkyl, C₄ alkyl, C₃ alkyl or C₂ alkyl or C₁ alkyl. In some embodiments, Y² is

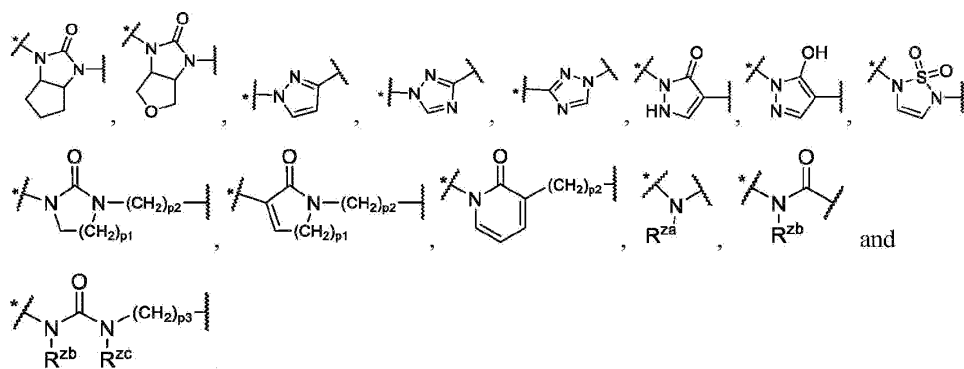


[0073] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z¹ is a bond, -N(R^c)-, -N(R^c)-C(=O)-, -N(R^c)-C(=O)-N(R^c)-, heterocycl, heteroaryl, het-

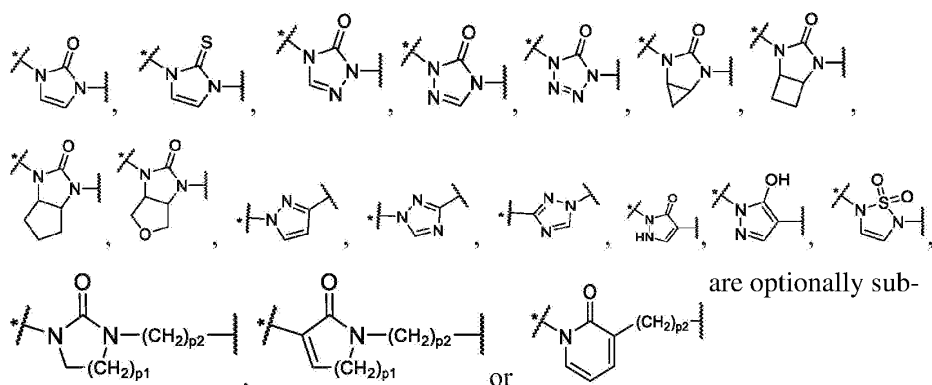
erocyclylalkyl or heteroarylalkyl, wherein the heterocyclyl or heteroaryl, heterocyclylalkyl or heteroarylalkyl are optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is a bond. In some embodiments, Z^1 is heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is a 3-to 8-membered (e.g. 3-, 4-, 5-, 6-, 7-, 8-, 4-to 8-, 4-to 7-, or 4-to 6-membered, ect) heterocyclyl, each optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is heteroaryl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is a 5-to 10-membered (e.g. 5-, 6-, 7-, 8-, 9-, 10-, 5-to 9-, 5-to 8-, 5-to 7-, or 5-to 6-membered, etc) heteroaryl, each optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is heterocyclylalkyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is a 3-to 8-membered (e.g. 3-, 4-, 5-, 6-, 7-, 8-, 4-to 8-, 4-to 7-, or 4-to 6-membered, etc) heterocyclyl- C_{1-10} (e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 , etc) alkyl, each optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is heteroarylalkyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl. In some embodiments, Z^1 is a 5-to 10-membered (e.g. 5-, 6-, 7-, 8-, 9- or 10-membered) heteroaryl- C_{1-10} (e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 , etc) alkyl, each optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl.

[0074] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^1 is selected from the group consisting of: a bond,

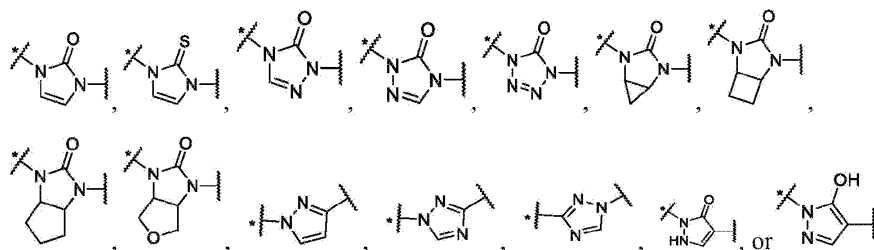




wherein the



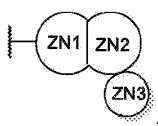
stituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl, p_1 is any integer of 1-3; p_2 is any integer of 0-10; p_3 is any integer of 0-10; R^{Za} is hydrogen, C_{1-6} alkyl, or (C_{1-6} alkyl) carbonyl; R^{Zb} and R^{Zc} are independently hydrogen or C_{1-6} alkyl; and *end of Z^1 is connected to X^2 . In some embodiments, Z^1 is selected from the group consisting of: a bond,



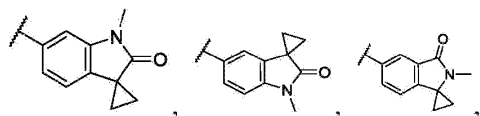
[0075] In some embodiments, p_1 is 1, 2, or 3. In some embodiments, p_2 is 0, 1, 2, 3, or 4. In some embodiments, p_3 is 0, 1, 2, 3, or 4. In some embodiments, R^{Za} is hydrogen, C_{1-3} alkyl, or (C_{1-3} alkyl) carbonyl. In some embodiments, R^{Zb} and R^{Zc} are independently hydrogen or C_{1-3} alkyl.

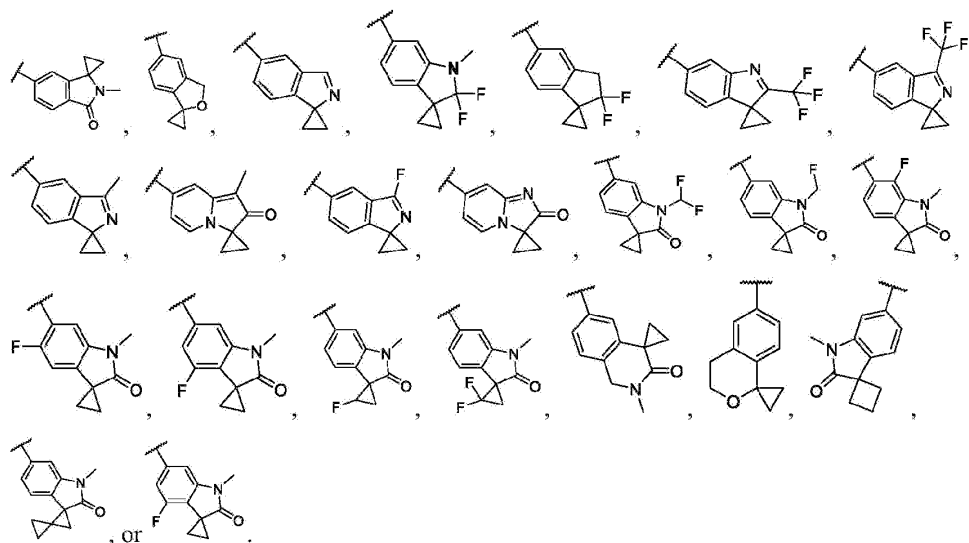
[0076] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is aryl or heteroaryl, each optionally substituted with one or more R^Z .

- [0077] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is C_{6-12} (e.g. C_{12} , C_{11} , C_{10} , C_9 , C_8 , C_7 , or C_6) aryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .
- [0078] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is 5-to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heteroaryl, 6-to 14-membered heteroaryl, 7-to 14-membered heteroaryl, 8-to 14-membered heteroaryl, 8-to 13-membered heteroaryl, 8-to 12-membered heteroaryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .
- [0079] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is tricyclic aryl or tricyclic heteroaryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z . In some embodiments, Z^2 is spiro-system containing tricyclic aryl or spiro-system containing tricyclic heteroaryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .
- [0080] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is aryl or heteroaryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z . In some embodiments, Z^2 is

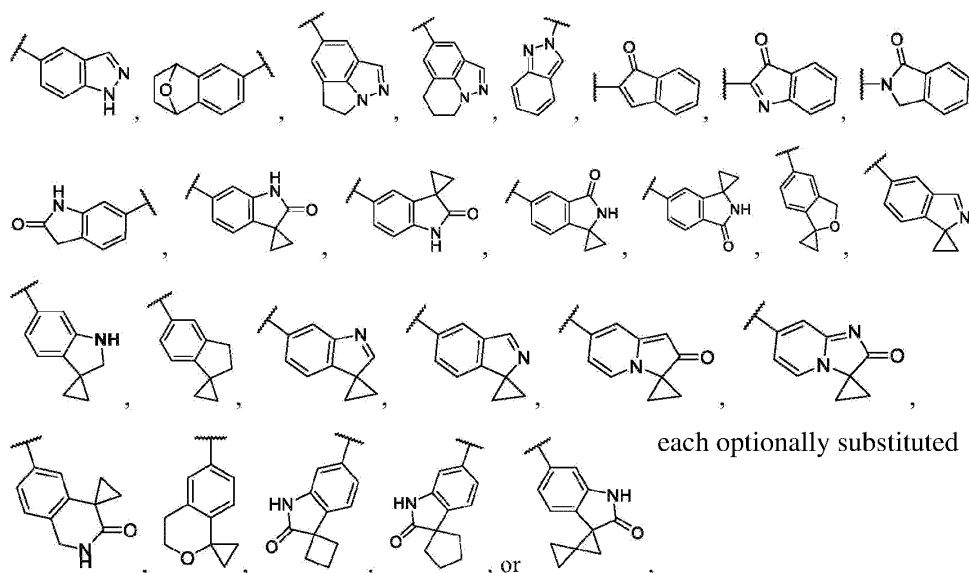


wherein ring ZN1 is aryl or heteroaryl, ring ZN2 is cycloalkyl or heterocyclyl, ring ZN3 is cycloalkyl or heterocyclyl, each of ring ZN1, ring ZN2 and ring ZN3 is independently optionally substituted with one or more (e.g. two or three, etc) R^Z . In some embodiments, ring ZN1 is phenyl or 5-to 6-membered heteroaryl, ring ZN2 is C_{4-6} cycloalkyl, or 4-to -6 heterocyclyl, ring ZN3 is C_{3-6} cycloalkyl, 3-to 6-membered heterocyclyl, each of ring ZN1, ring ZN2 and ring ZN3 is independently optionally substituted with one or more (e.g. two or three, etc) R^Z . In some embodiments, each R^Z is independently halogen, or C_{1-6} alkyl (such as methyl, etc) , or C_{1-6} haloalkyl such as $-CF_3$, etc) . In some embodiments, Z^2 is





[0081] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is phenyl, indazolyl,



with one or more (e.g. two or three, etc) R^Z .

[0082] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is cycloalkyl or heterocyclyl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .

[0083] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is C_{6-12} (e.g. C_{12} , C_{11} , C_{10} , C_9 , C_8 , C_7 , or C_6) cycloalkyl, C_{6-11} cycloalkyl, C_{6-10} cycloalkyl, C_{6-9} cycloalkyl or C_{6-8} cycloalkyl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .

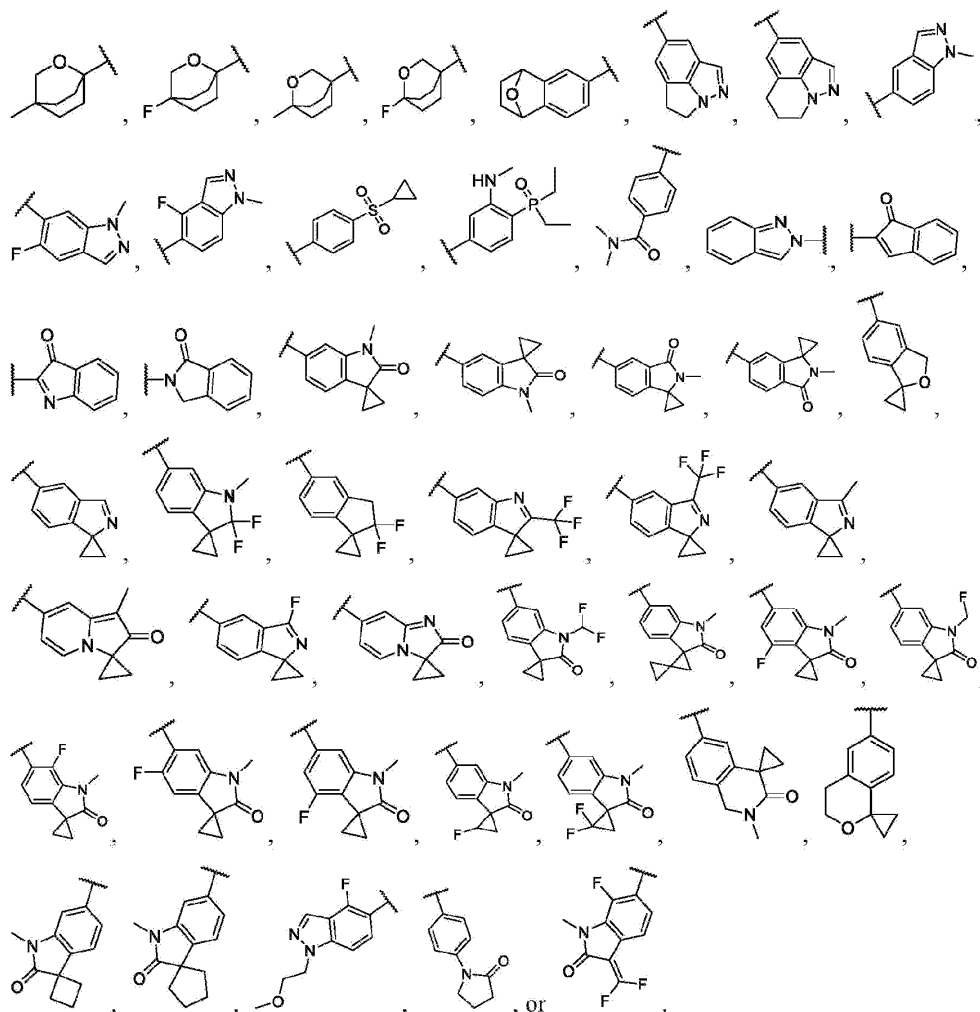
[0084] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is 5-to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heterocyclyl, 6-to 14-membered heterocyclyl, 7-to 14-membered heterocyclyl, 8-to 14-membered heterocyclyl, 8-to 13-membered heterocyclyl or 8-to 12-membered heterocyclyl, each optionally substituted with one or more (e.g. two or three, etc) R^Z . In some embodiments, Z^2 is  or , each optionally substituted with one or more (e.g. two or three, etc) R^Z .

[0085] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), each R^Z is independently halogen, alkyl, oxo, haloalkyl, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)_2(R^d)$, $-P(=O)(R^d)_2$ or heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy. In some embodiments, each R^Z is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, 5-to 6-membered heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy, $-N(R^d)_2$, $-S(=O)_2(R^d)$, or $-P(=O)(R^d)_2$. In some embodiments, each R^Z is independently  methyl, F, oxo,

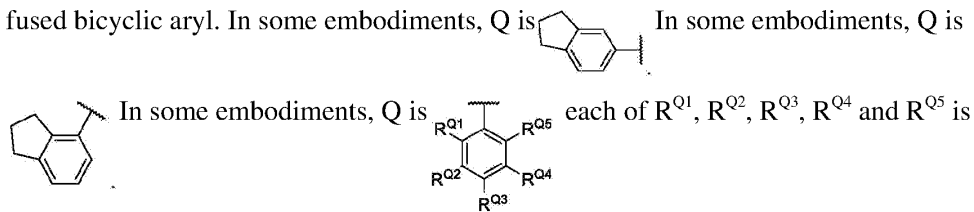
$-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CH_2OCH_3$, $-NH(CH_3)$, $-C(=O)N(CH_3)_2$, $-S(=O)_2$ (cyclopropyl) or $-P(=O)(CH_2CH_3)_2$. In some embodiments, two R^Z together with the same atom to which they are both attached form a C_2-C_6 alkylidenyl optionally substituted with one or more R. In some embodiments, two R^Z together with the same atom to which they are both attached form a C_2-C_6 alkylidenyl optionally substituted with one or more halogen. In some embodiments, two R^Z together with the same atom to which they are both attached form a C_2-C_4 alkylidenyl optionally substituted with one or more halogen. In some embodiments, two R^Z together with the same atom to which they are both attached form a  optionally substituted with one or more

halogen. In some embodiments, two R^Z together with the same atom to which they are both attached form a .

[0086] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Z^2 is selected from

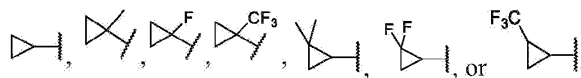


[0087] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is aryl optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is C_{6-12} (e.g. C_{12} , C_{11} , C_{10} , C_9 , C_8 , C_7 , or C_6) aryl, each optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is phenyl optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is fused bicyclic aryl. In some embodiments, Q is



independently hydrogen or R^Q . In some embodiments, each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, cyano, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl substituted

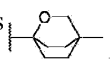
with one or more groups independently selected from halogen or haloalkyl. In some embodiments, each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, cyano, F, Cl, Br, I, $-CH_3$,

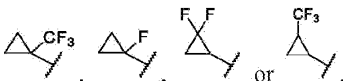
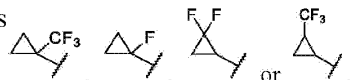


bodiments, R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with intervening atoms form a cycloalkyl, aryl, heterocyclyl or heteroaryl, each optionally substituted with one or more group independently selected from halogen, hydroxy, alkyl, haloalkyl, alkoxy or cycloalkyl. In some embodiments, R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with intervening atoms form a C_{3-6} (e.g. C_3 , C_4 , C_5 , C_6 , or, C_{5-6} , etc) cycloalkyl optionally substituted with one or more group independently selected from halogen, hydroxy, alkyl, haloalkyl, alkoxy or cycloalkyl. In some embodiments, R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with intervening atoms form a phenyl optionally substituted with one or more group independently selected from halogen, hydroxy, alkyl, haloalkyl, alkoxy or cycloalkyl. In some embodiments, R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with intervening atoms form a 3-to 6- (e.g. 3-, 4-, 5-, 6-, 5-to 6-, etc) membered heterocyclyl optionally substituted with one or more group independently selected from halogen, hydroxy, alkyl, haloalkyl, alkoxy or cycloalkyl. In some embodiments, R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with intervening atoms form a 3-to 6- (e.g. 3-, 4-, 5-, 6-, 5-to 6-, etc) membered heteroaryl optionally substituted with one or more group independently selected from halogen, hydroxy, alkyl, haloalkyl, alkoxy or cycloalkyl.

[0088] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is cycloalkyl or heterocyclyl, each are optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is cycloalkyl optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is C_{6-12} (e.g. C_{12} , C_{11} , C_{10} , C_9 , C_8 , C_7 , or C_6) cycloalkyl, C_{6-11} cycloalkyl, C_{6-10} cycloalkyl, C_{6-9} cycloalkyl or C_{6-8} cycloalkyl, each optionally substituted with one or more R^Q .

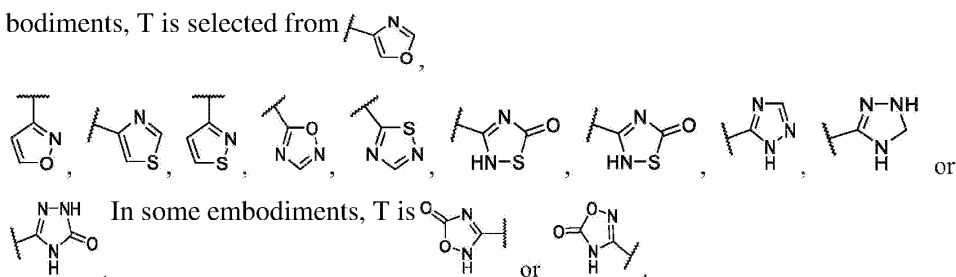
[0089] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is heterocyclyl optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is 5-to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heterocyclyl, 6-to 14-membered heterocyclyl, 7-to 14-membered heterocyclyl, 8-to 14-membered heterocyclyl, 8-to 13-membered heterocyclyl or 8-to 12-membered heterocyclyl, each optionally substituted with one or more R^Q . In some embodiments, Q is



- [0090] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is aryl substituted with one or more R^Q , and one R^Q is cycloalkyl substituted with one or more groups independently selected from halogen or haloalkyl.
- [0091] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is aryl substituted with one or more R^Q , and one R^Q is C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, each substituted with one or more groups independently selected from halogen or haloalkyl. In some embodiments of, Q is aryl substituted with one or more R^Q , and one R^Q is C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl, each substituted with one or more groups independently selected from halogen or haloalkyl.
- [0092] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), Q is aryl substituted with one or more R^Q , and one R^Q is .
- [0093] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), each R^Q is independently halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxy or cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more (e.g. two or three, etc) groups independently selected from halogen, haloalkyl, or alkyl. In some embodiments, each R^Q is independently halogen (e.g. F, Cl, Br, I), alkyl, or cycloalkyl, wherein the alkyl or cycloalkyl is optionally substituted with one or more groups independently selected from halogen, haloalkyl, or alkyl. In some embodiments, R^Q is cycloalkyl substituted with one or more groups independently selected from halogen or haloalkyl. In some embodiments, R^Q is C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, each substituted with one or more groups independently selected from halogen or haloalkyl. In some embodiments, R^Q is C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl, each substituted with one or more groups independently selected from halogen or haloalkyl. In some embodiments, R^Q is . In some embodiments, R^Q is alkyl optionally substituted with one or more groups independently selected from halogen or haloalkyl. In some embodiments, R^Q is C_{1-6} alkyl (e.g., C_1 alkyl, C_2 alkyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, or C_6 alkyl) optionally substituted with one or more groups independently selected from halogen or haloalkyl.
- [0094] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), T is heterocyclyl or heteroaryl, each optionally substituted with one or more R^T . In some embodiments, T is heterocyclyl. In some embodiments, T is 5-to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heterocyclyl, 6-to 14-membered heterocyclyl, 7-to 14-membered heterocyclyl, 8-to 14-membered heterocyclyl, 8-to 13-

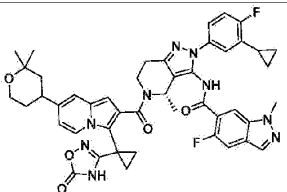
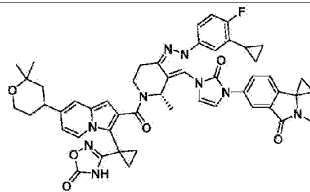
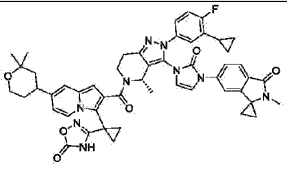
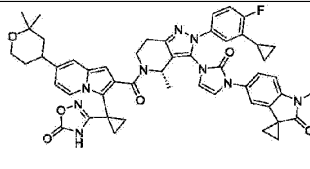
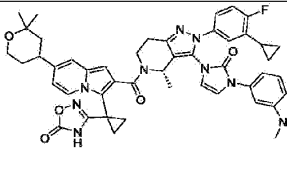
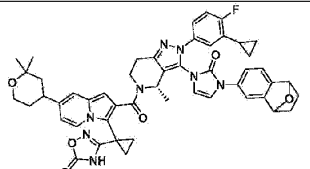
membered heterocyclyl or 8-to 12-membered heterocyclyl, each optionally substituted with one or more R^T . In some embodiments, T is heteroaryl. In some embodiments, T is 5-to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heteroaryl, 6-to 14-membered heteroaryl, 7-to 14-membered heteroaryl, 8-to 14-membered heteroaryl, 8-to 13-membered heteroaryl or 8-to 12-membered heteroaryl, each optionally substituted with one or more R^T . In some embodiments, each R^T is independently oxo, halogen or alkyl.

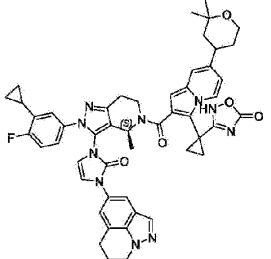
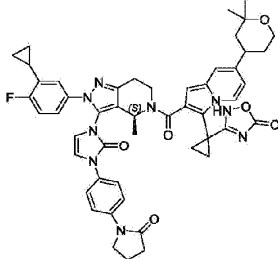
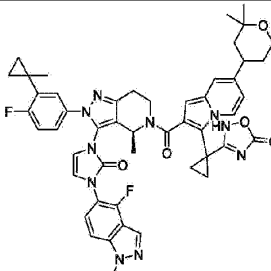
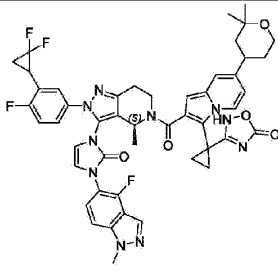
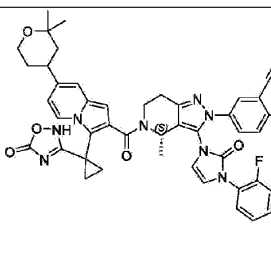
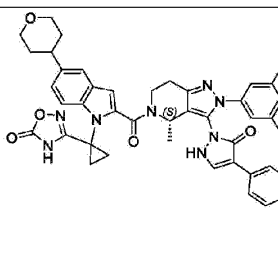
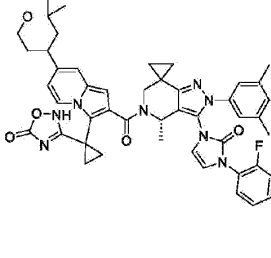
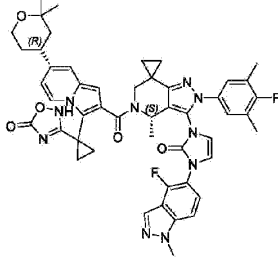
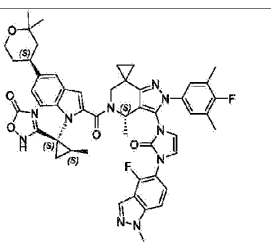
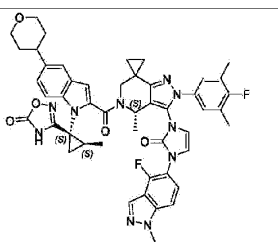
[0095] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), T is selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, oxadiazolonyl, thiadiazolonyl, triazolyl, dihydrotriazolyl, or dihydrotriazolonyl. In some embodiments, T is selected from

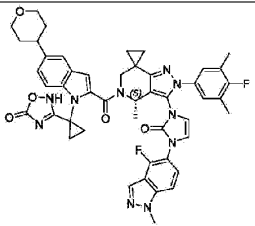
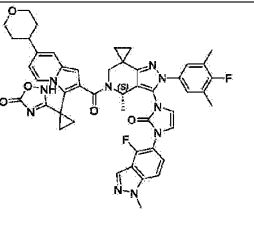
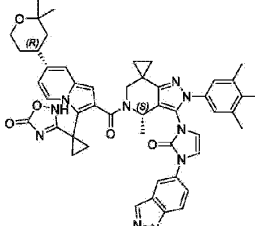
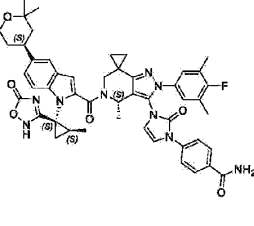
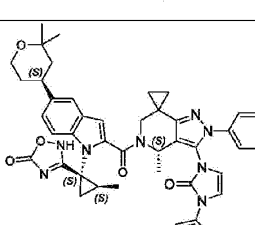
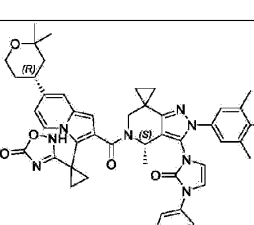
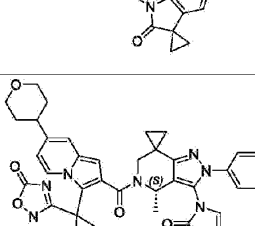
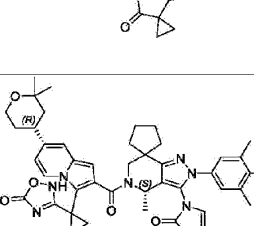
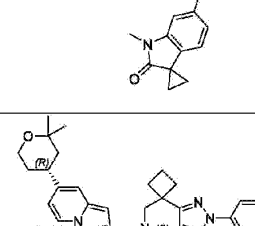
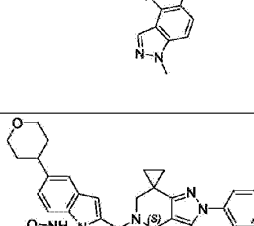


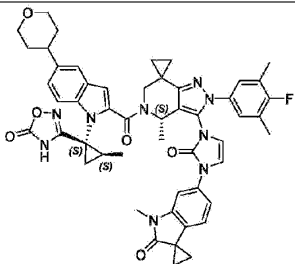
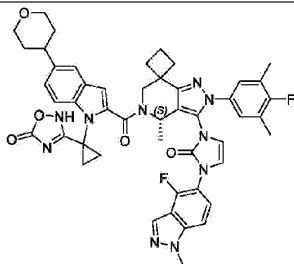
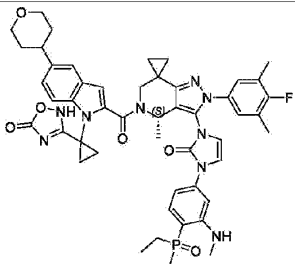
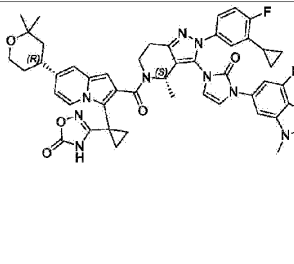
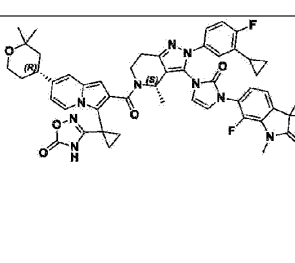
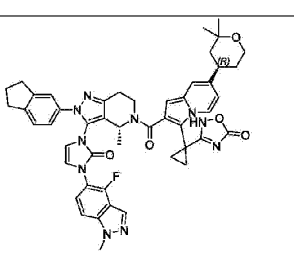
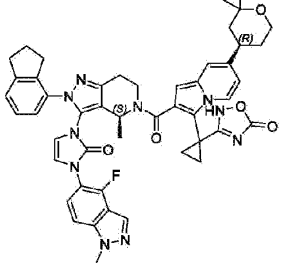
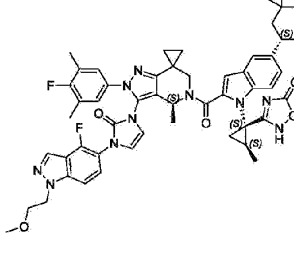
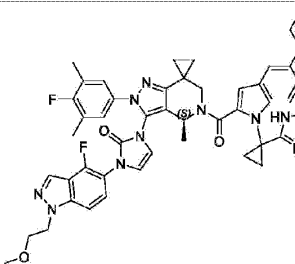
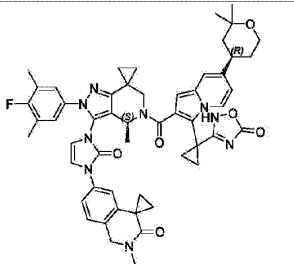
[0096] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), q is 1, 2 or 3. In some embodiments, q is 1. In some embodiments, q is 2 or 3.

[0097] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 4.1 or Table 4.2. TABLE 4.1 Exemplary Compounds

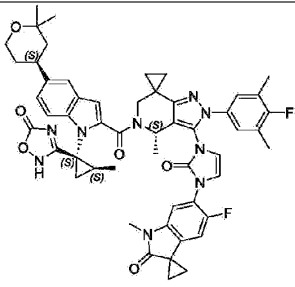
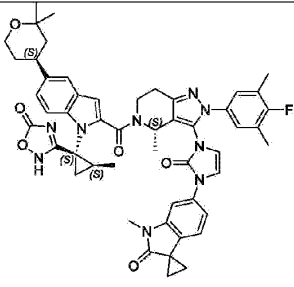
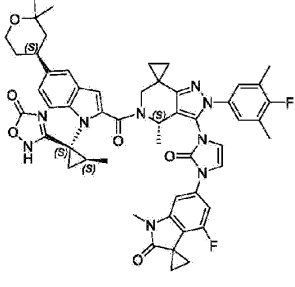
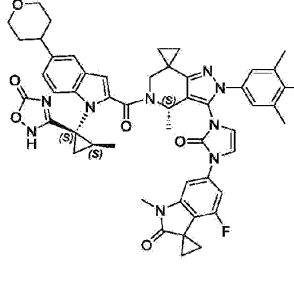
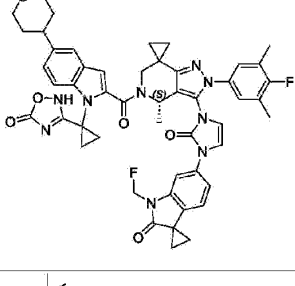
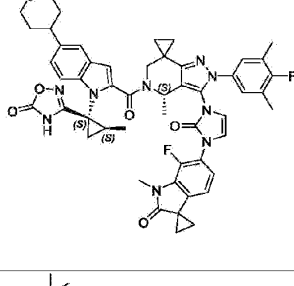
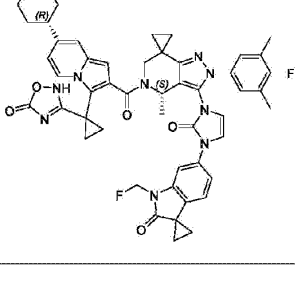
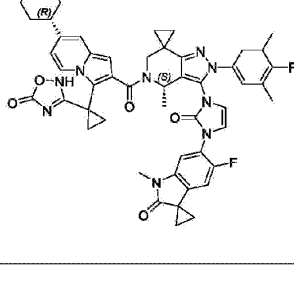
Compound No.	Structure	Compound No.	Structure
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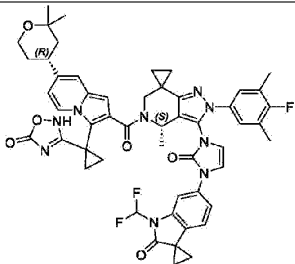
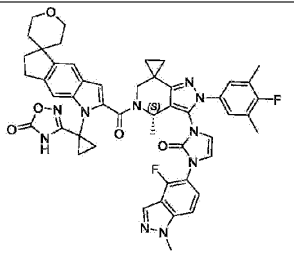
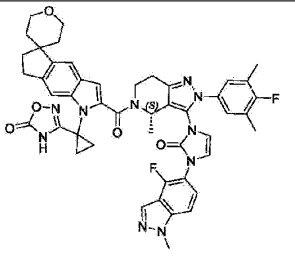
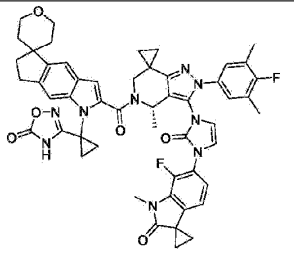
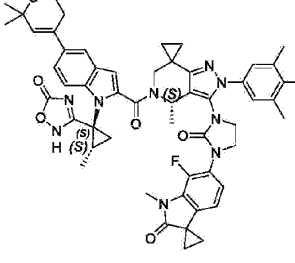
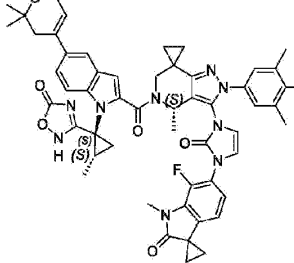
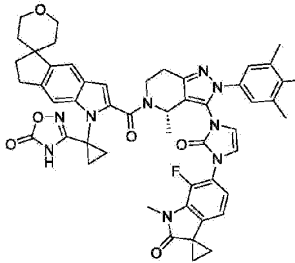
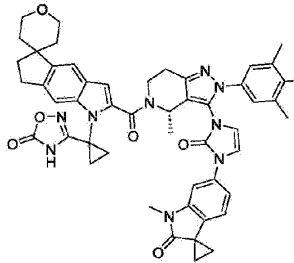
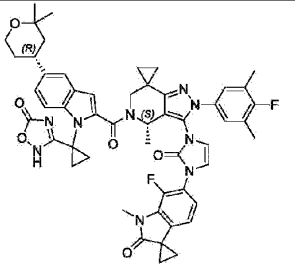
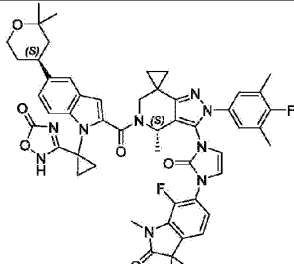
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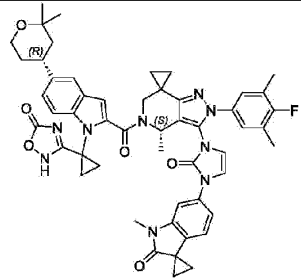
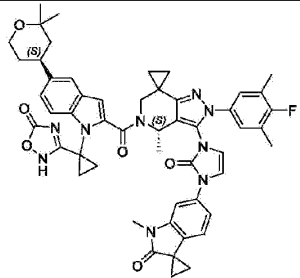
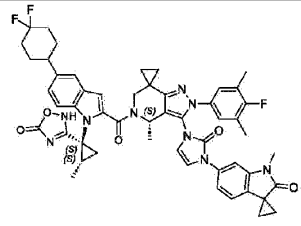
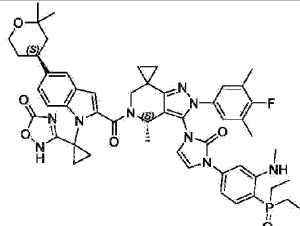
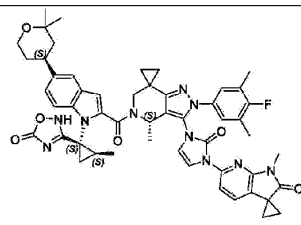
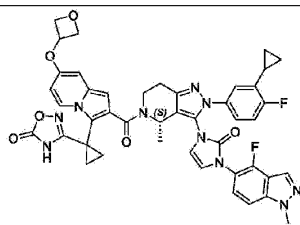
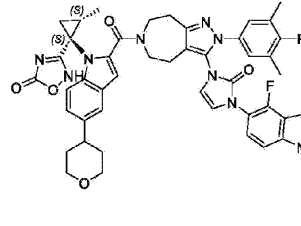
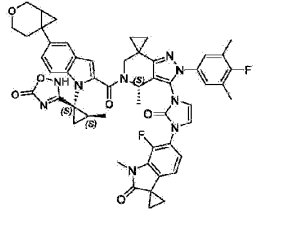
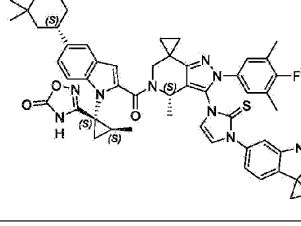
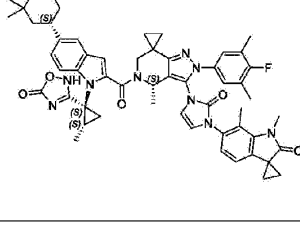
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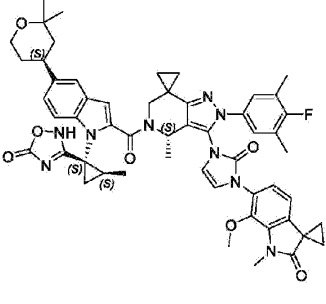
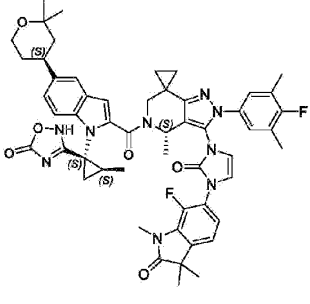
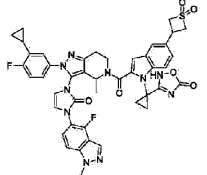
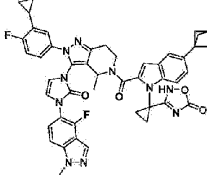
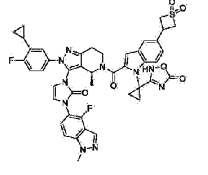
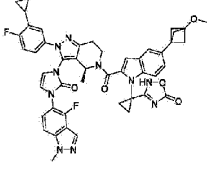
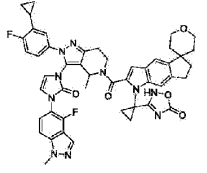
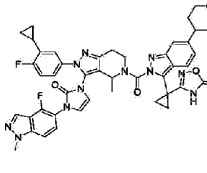
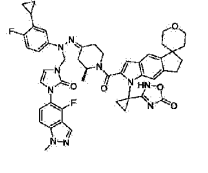
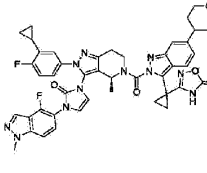
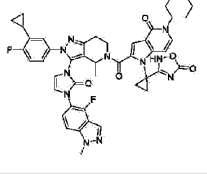
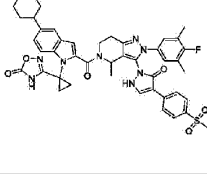
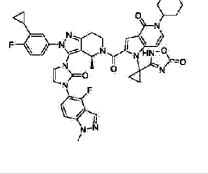
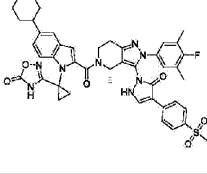
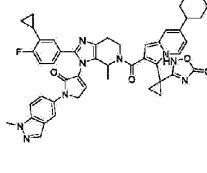
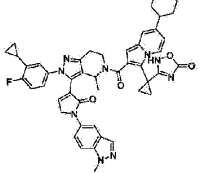
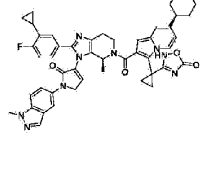
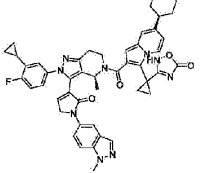
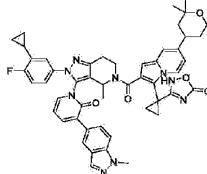
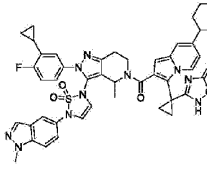
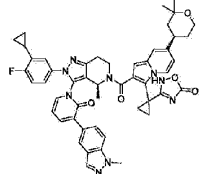
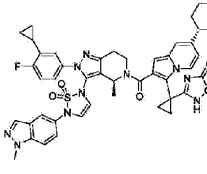
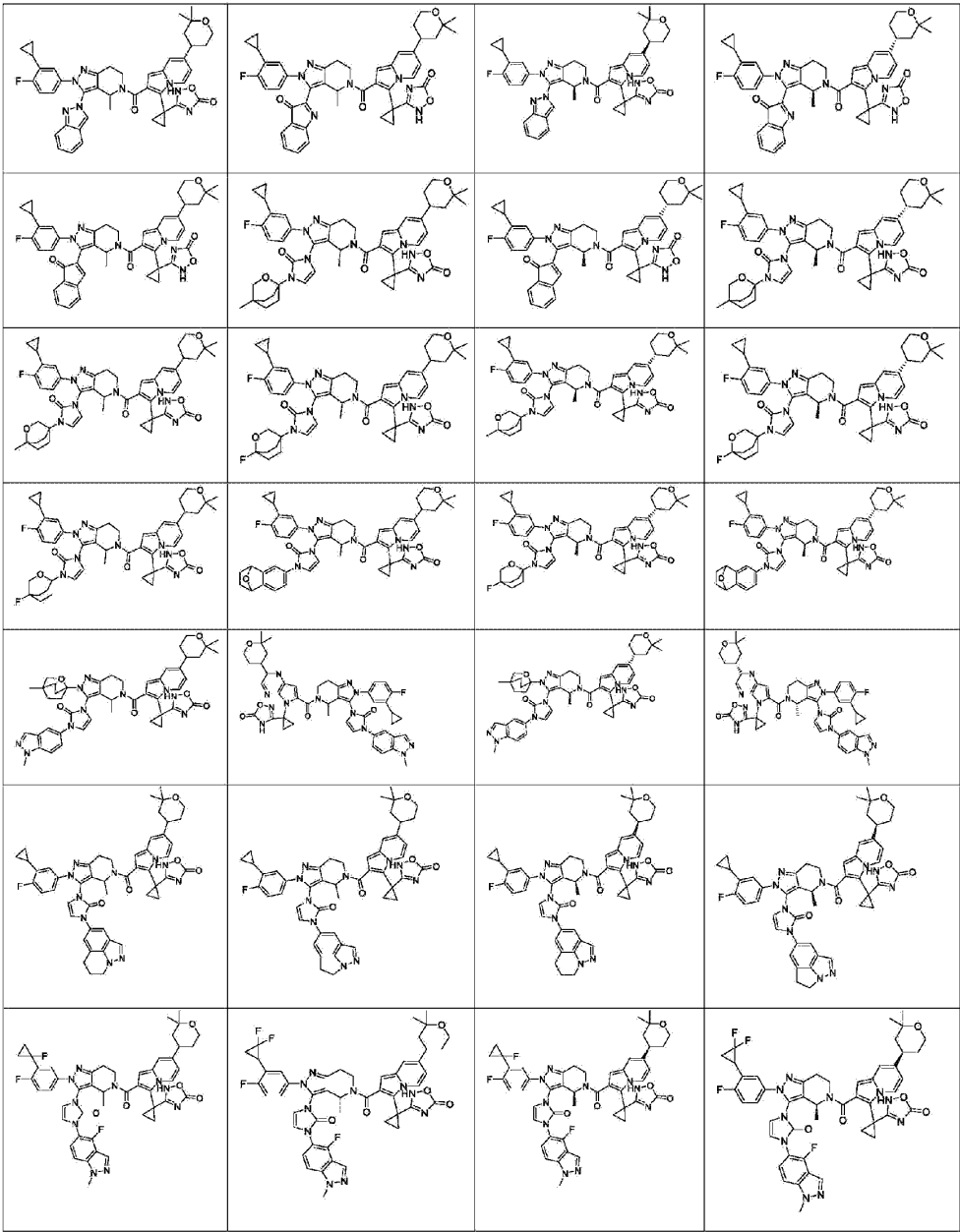
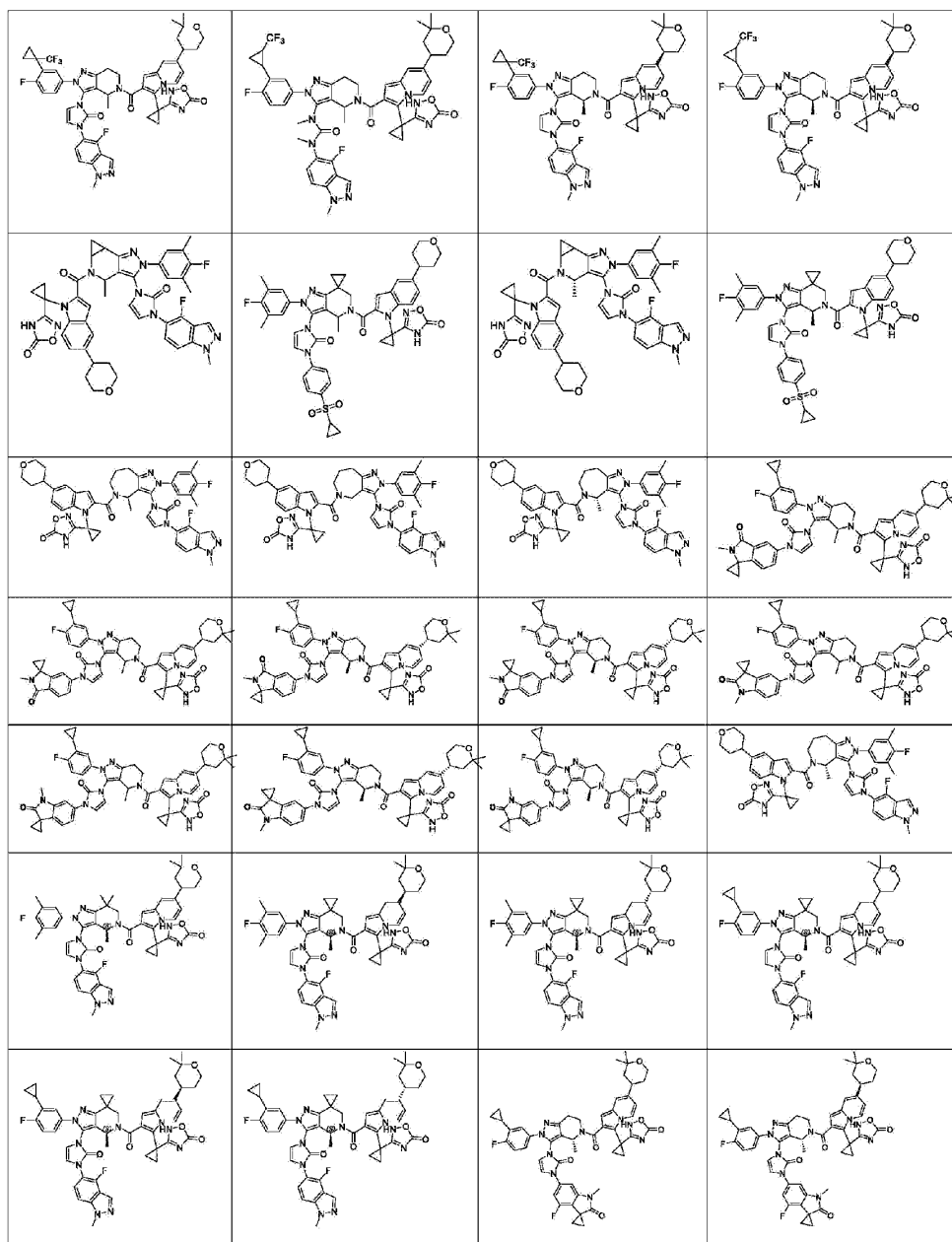
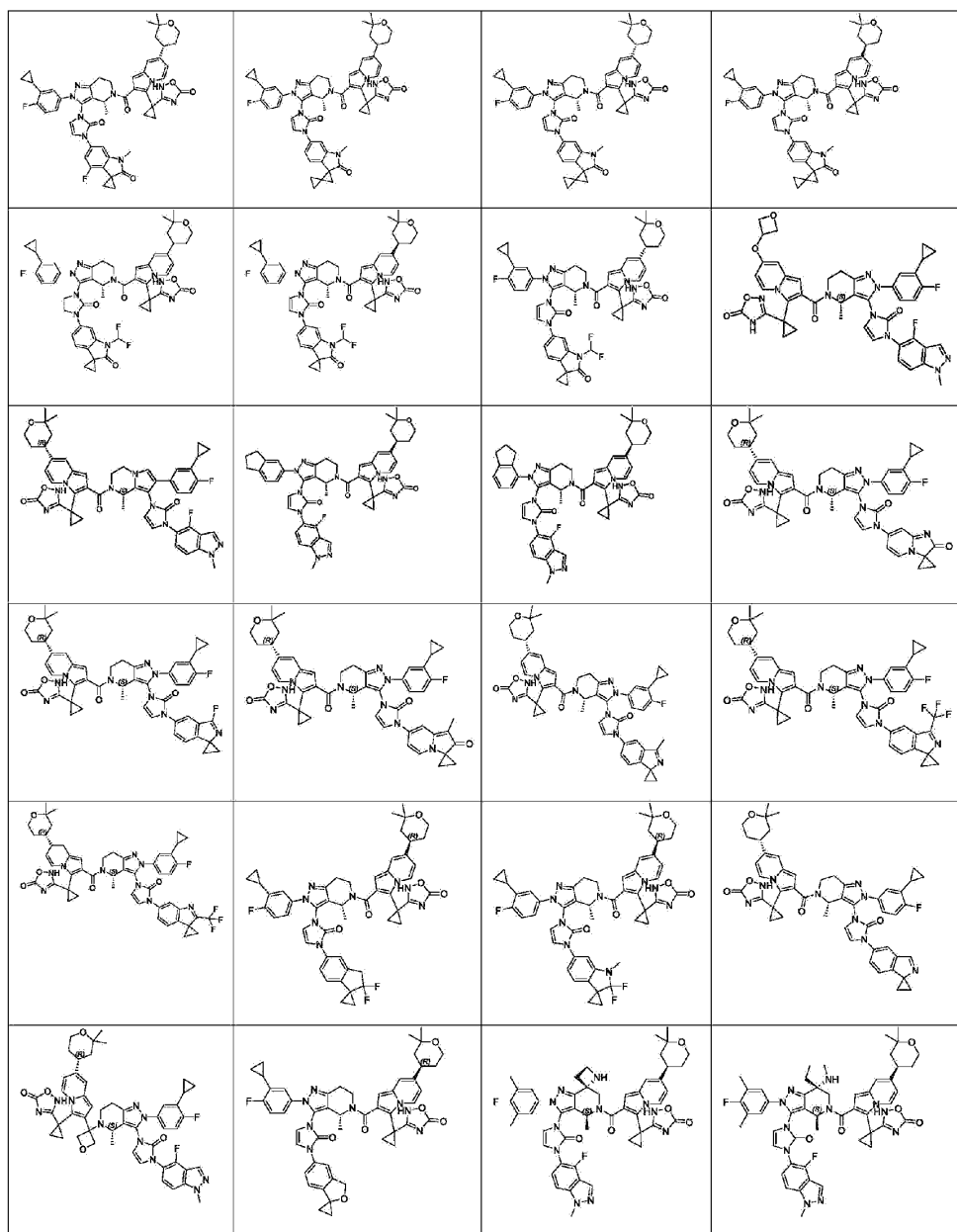
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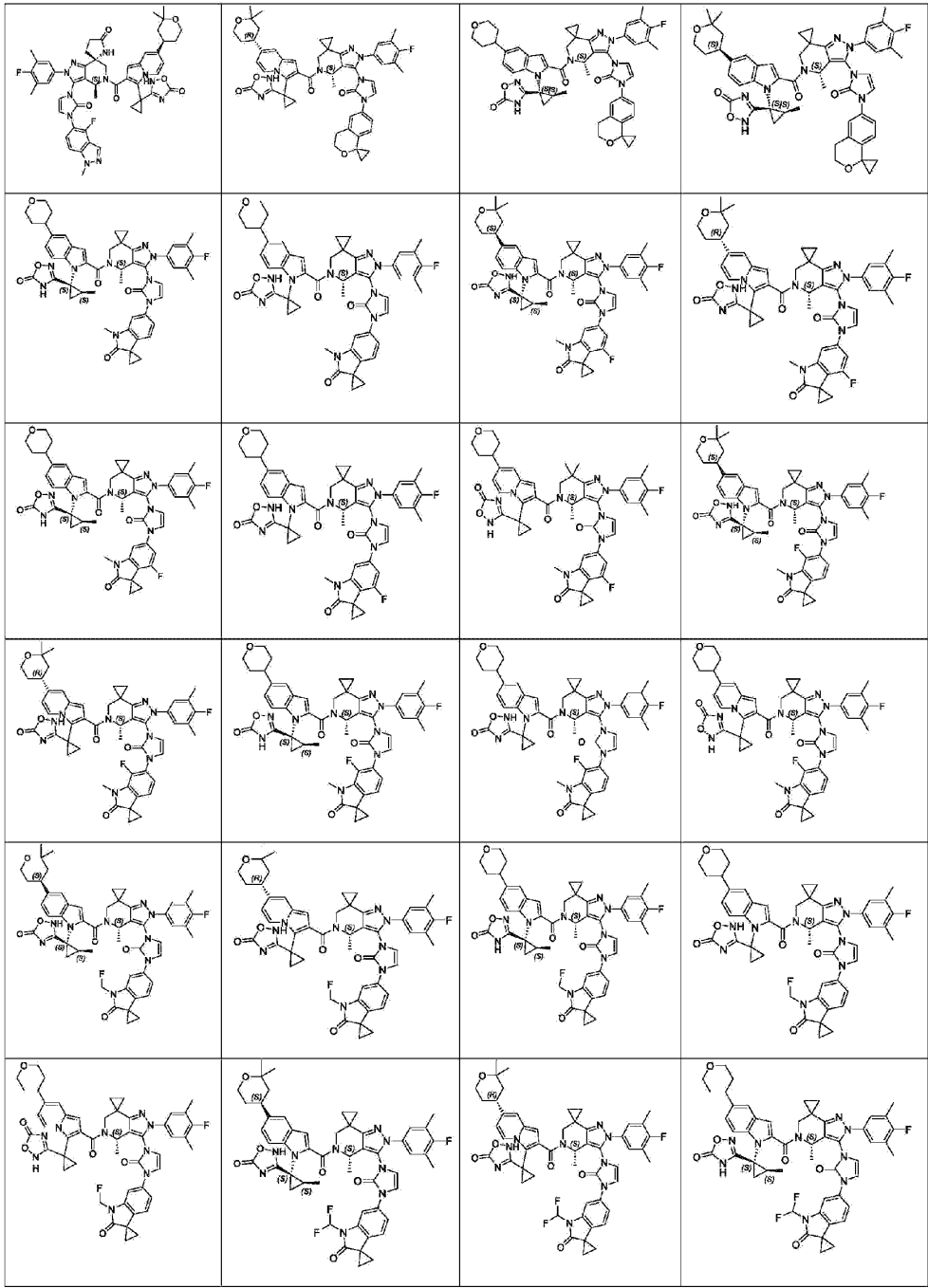
TABLE 4.2 Exemplary Compounds

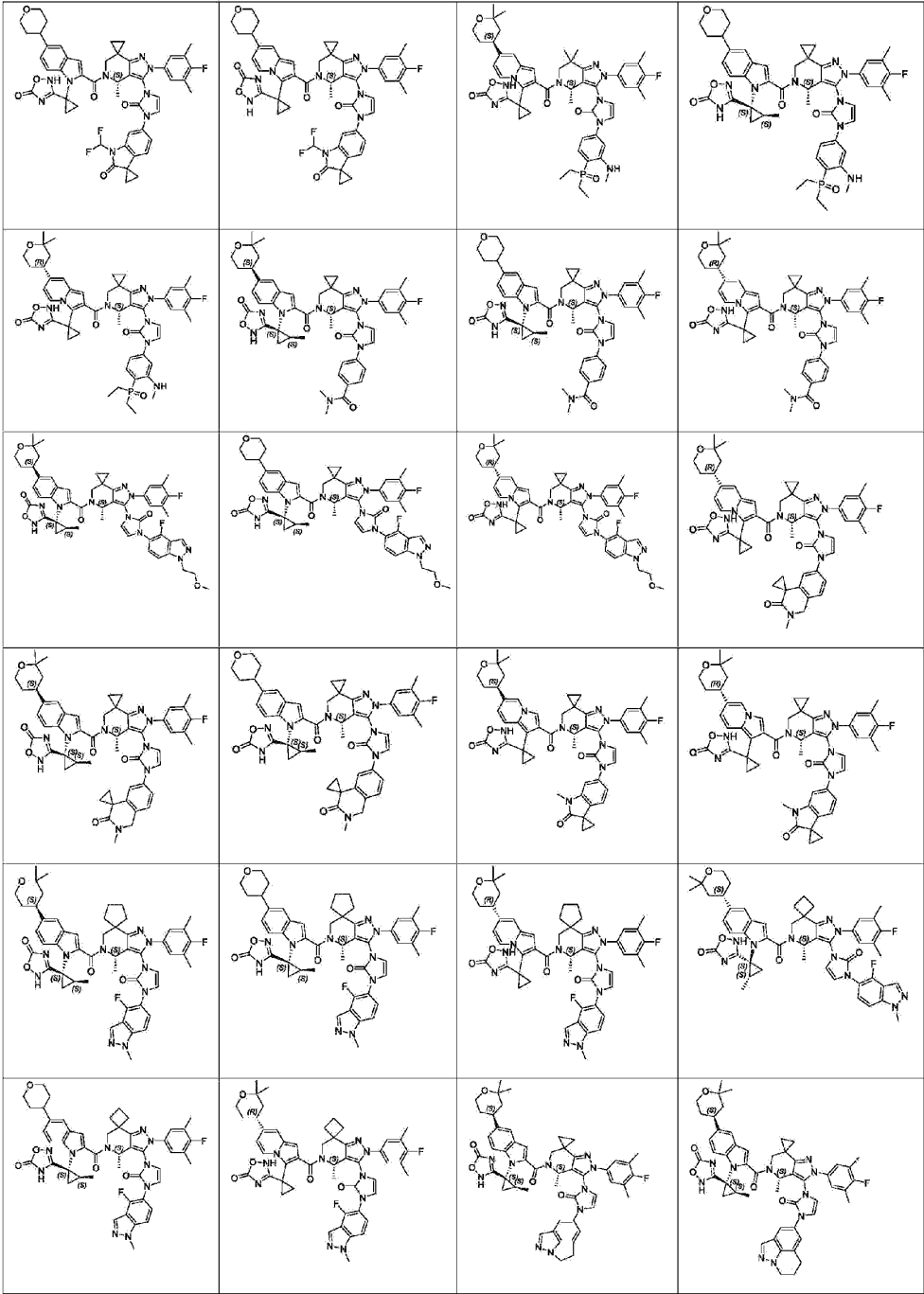
			
			
			
			
			

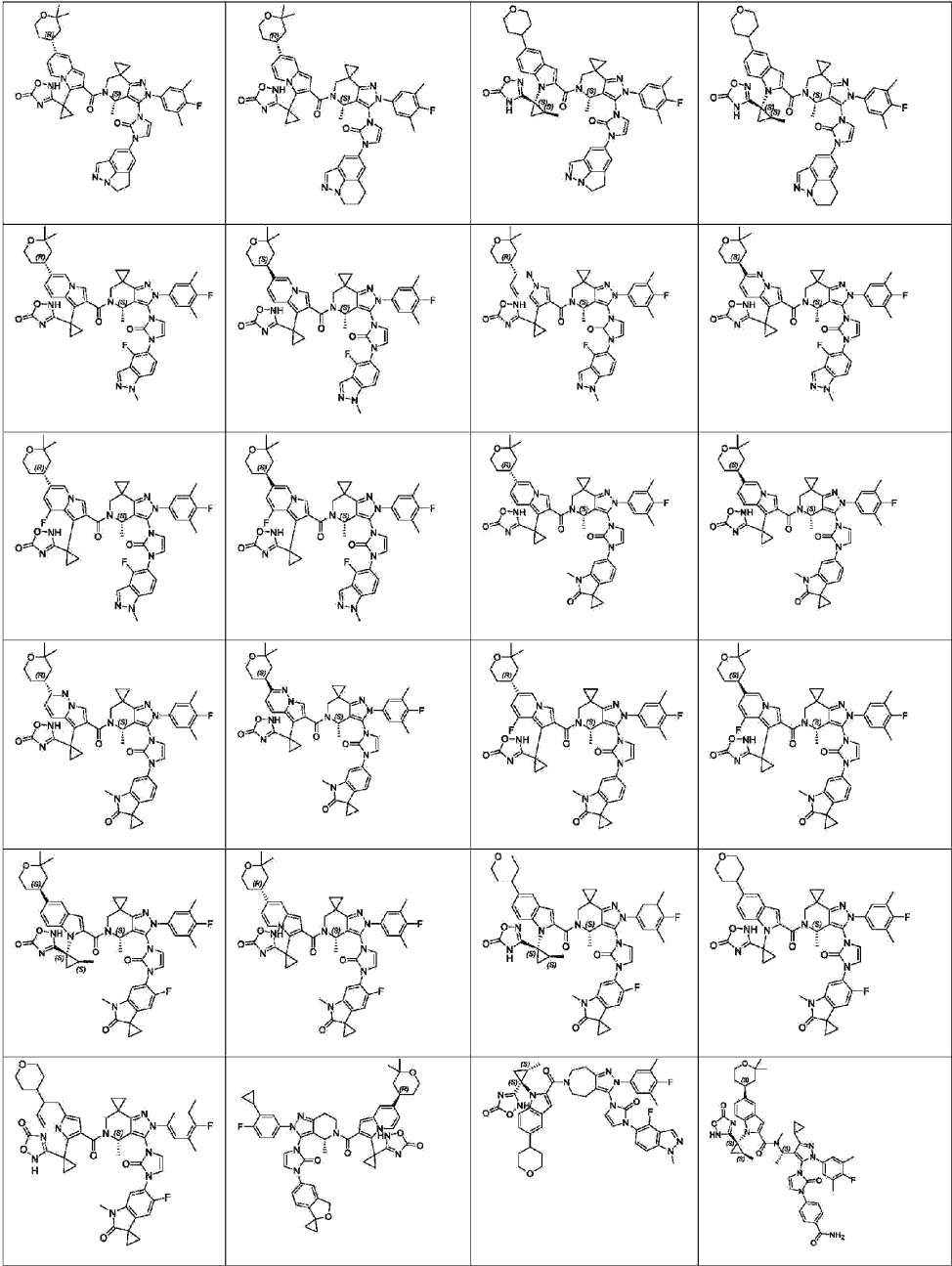


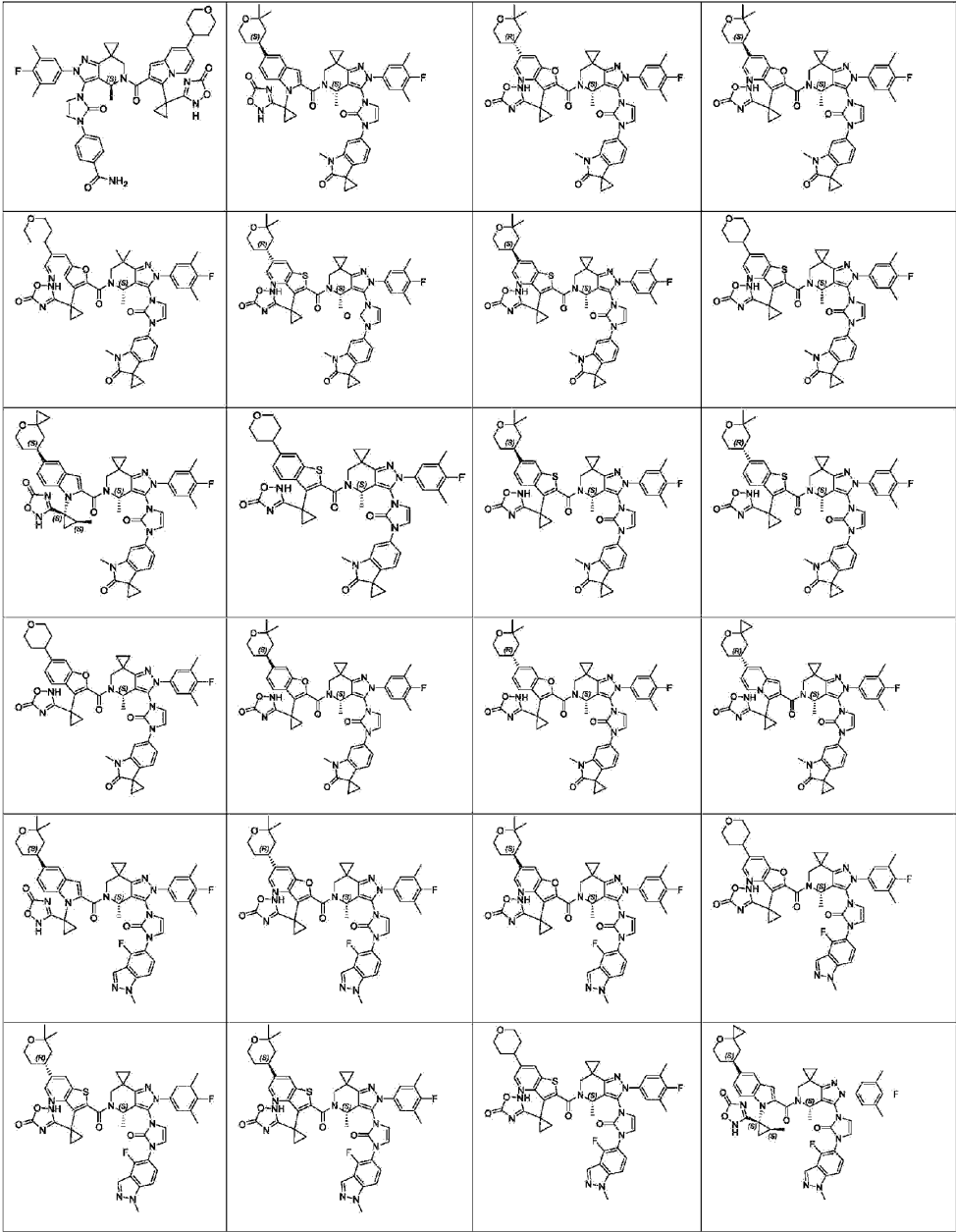


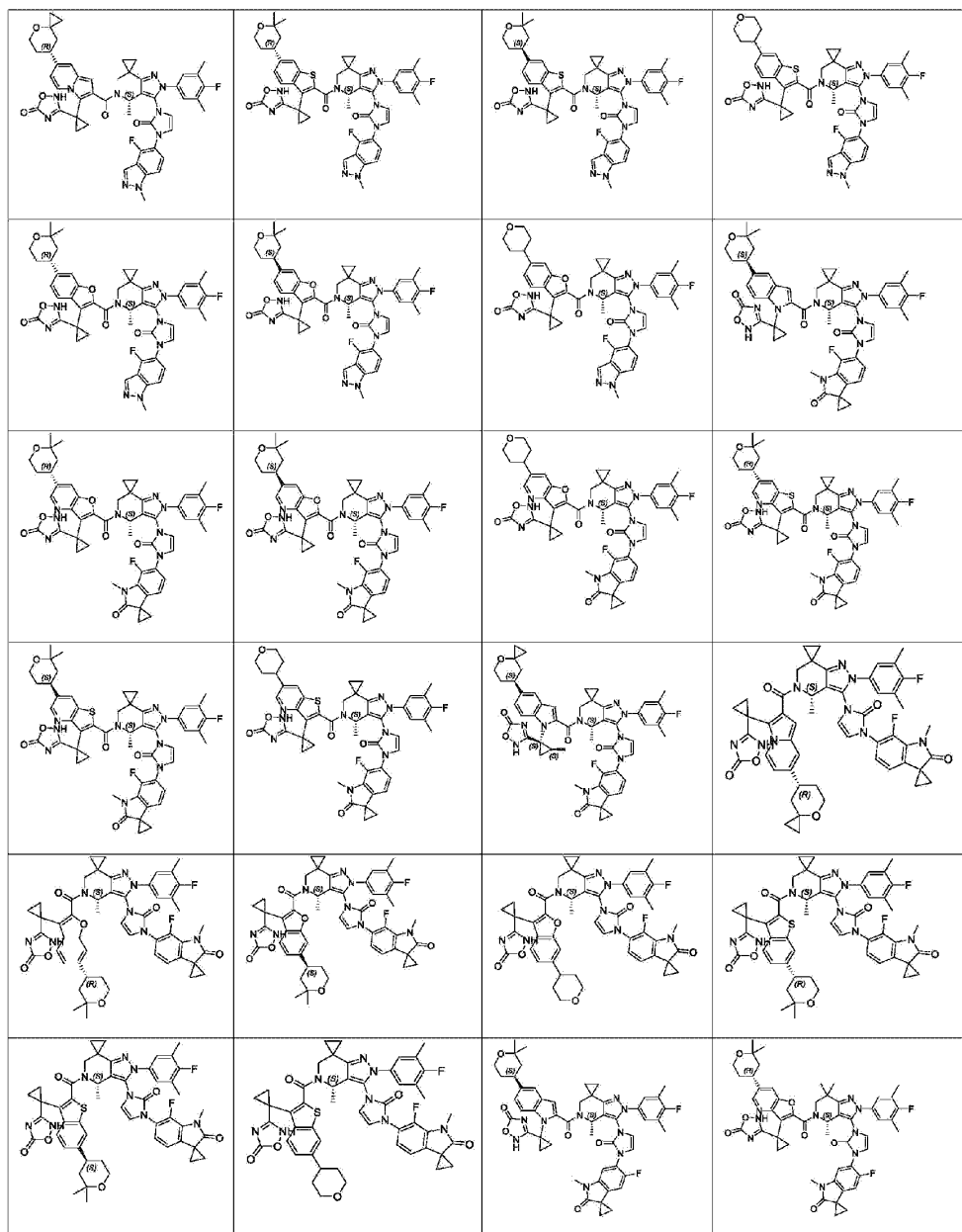


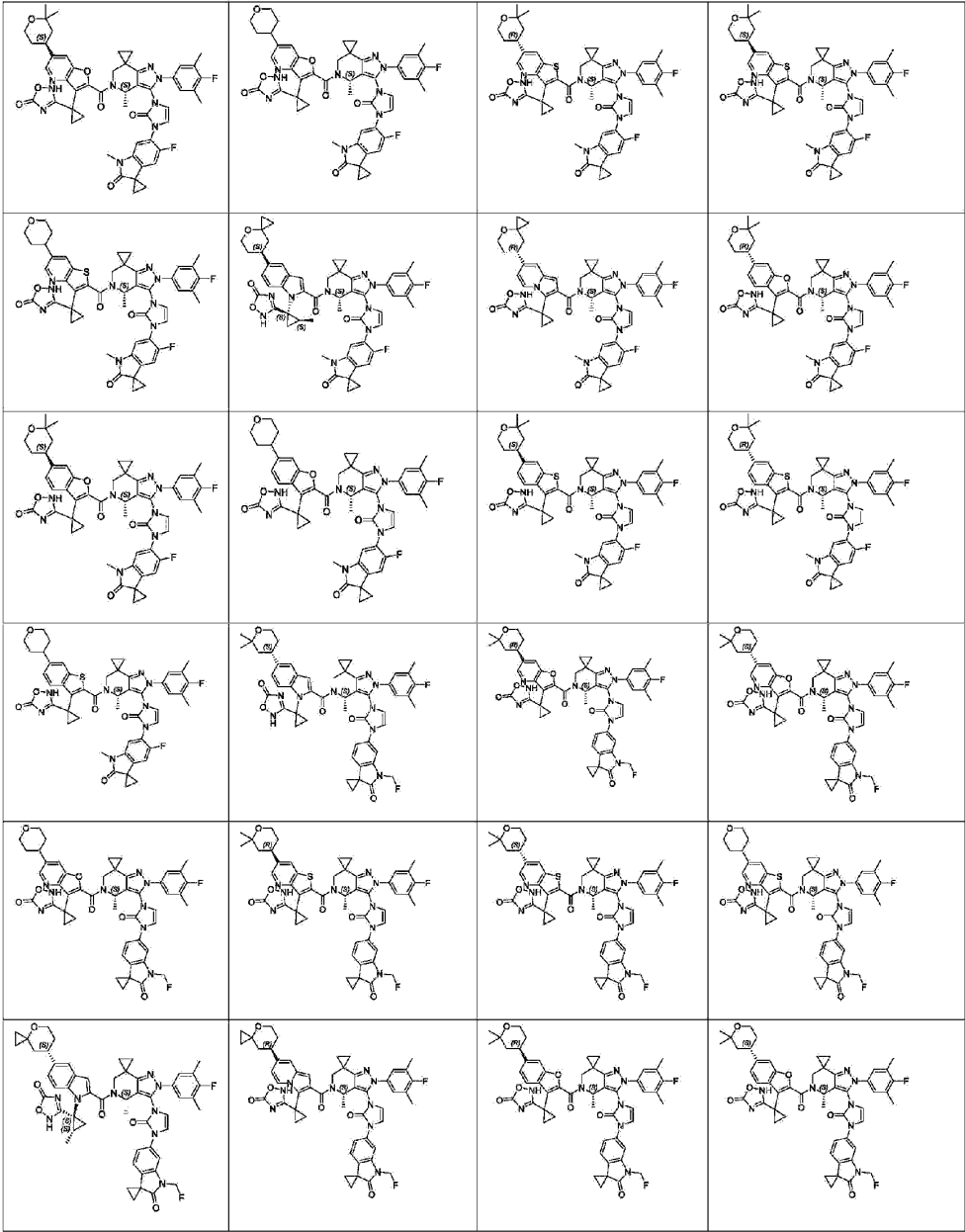


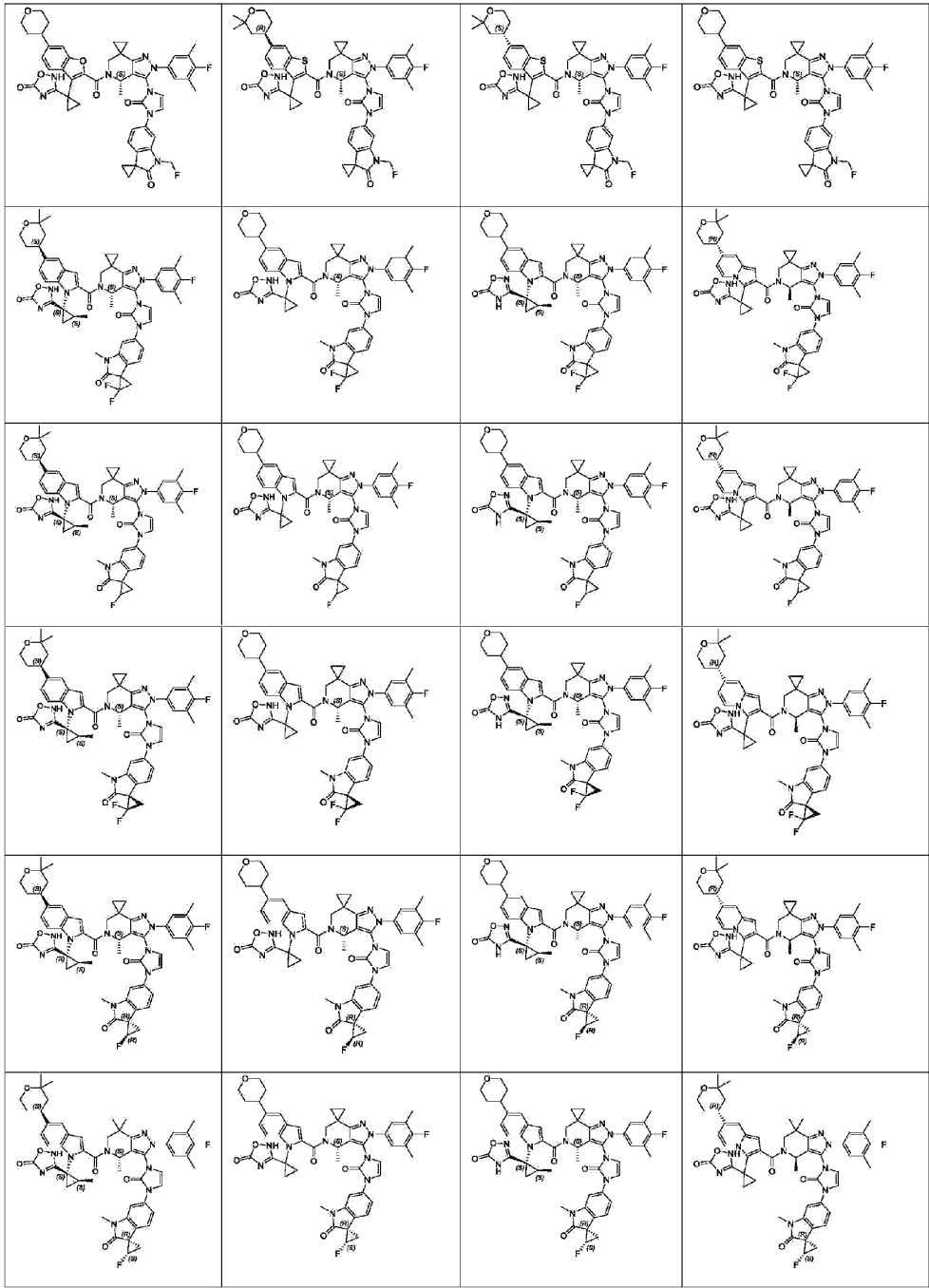


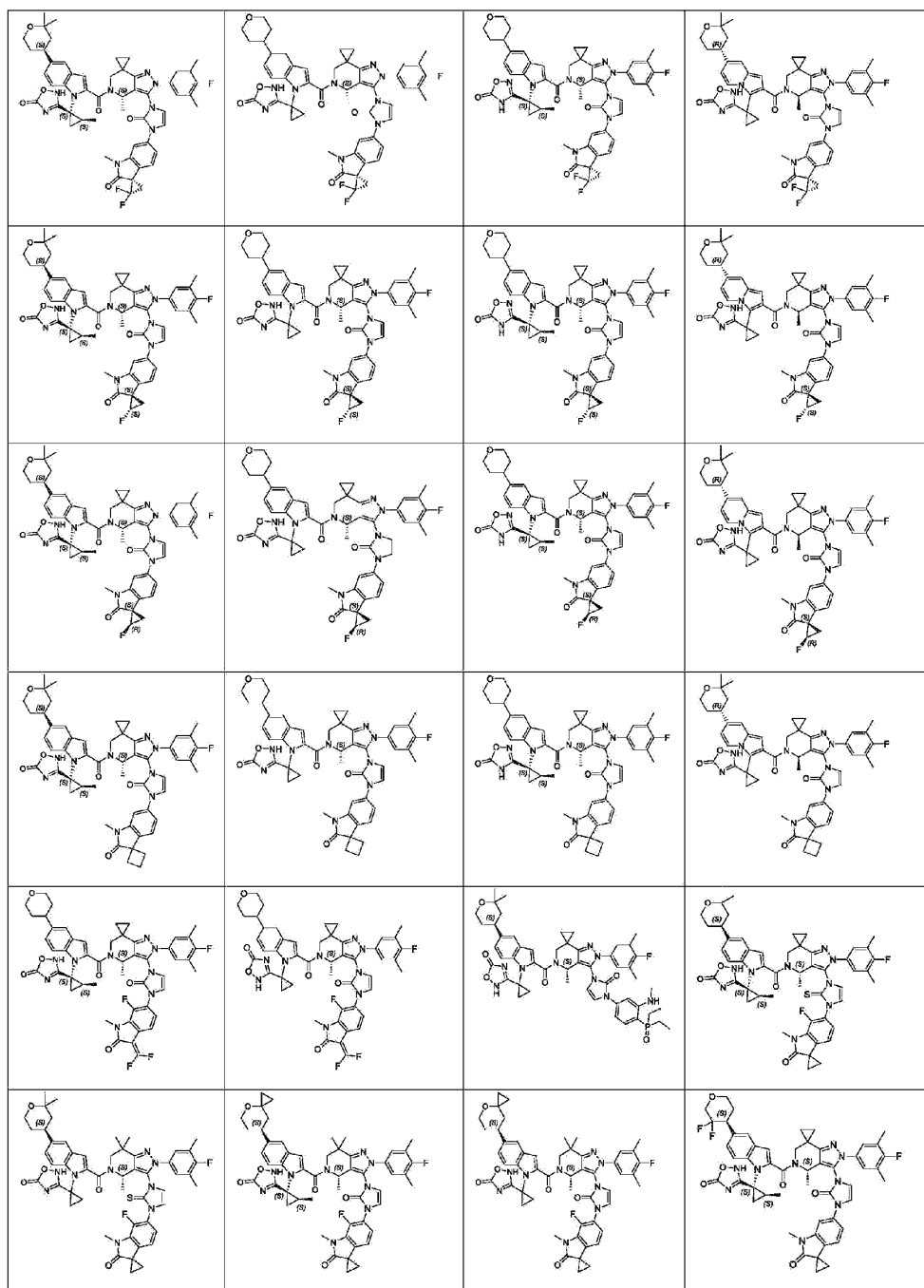


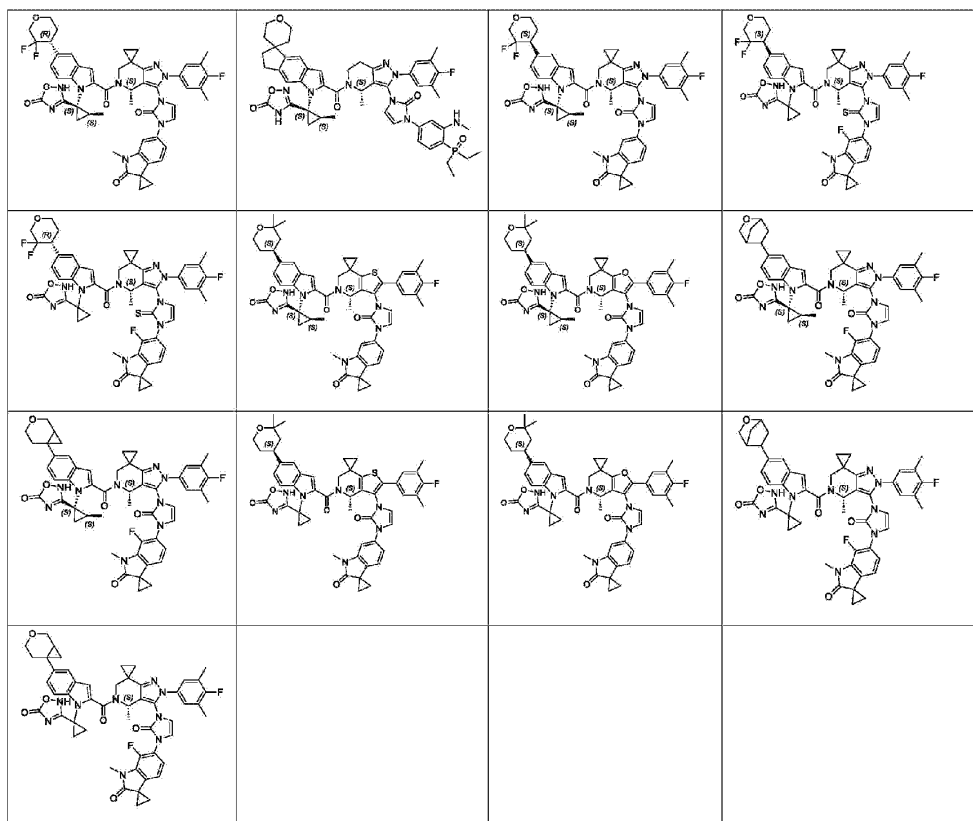










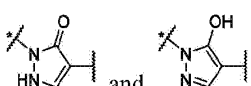


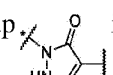
Further Forms of Compounds Disclosed Herein Isomers/Stereoisomers

[0098] 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

[0099] 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.

[0100] For example,  and  are tautomers, and can be used interchangeably

herein. A compound disclosed herein with group  include the corresponding

compound with group  Isotopic form

[0101] 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.

[0102] 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.

- [0103] 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.
- [0104] 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.
- [0105] 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
- [0106] 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.
- [0107] 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.
- [0108] 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, ben-

zenesulfonate, 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.

[0109] 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.

[0110] 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} alkyl)₄, and the like.

[0111] 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

[0112] Disclosed herein are methods of modulating glucagon-like peptide-1 receptor (GLP-1R) 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.

[0113] Disclosed herein are methods of activating GLP-1R 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 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 GLP-1 associated disease or disorder.

[0115] In some embodiments, the GLP-1 associated disease or disorder is non-insulin-dependent diabetes mellitus (Type 2 diabetes), hyperglycemia, impaired glucose tolerance, insulin dependent diabetes mellitus (Type 1 diabetes), diabetic complication, obesity, hypertension, hyperlipidemia, arteriosclerosis, coronary heart disease, brain infarction, non-alcoholic steatohepatitis, Parkinson's disease or dementia. In some embodiments, the GLP-1 associated disease or disorder is non-insulin-dependent diabetes mellitus (Type 2 diabetes) or obesity.

[0116] 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 GLP-1R, in a subject in need thereof.

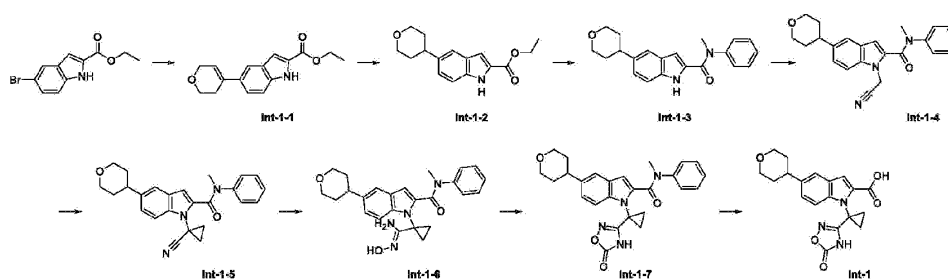
[0117] Also disclosed herein is use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for activating GLP-1R, in a subject in need thereof.

[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 treating a disease or disorder, in a subject in need thereof. In some embodiments, the disease or disorder is a GLP-1 associated disease or disorder.

- [0119] In some embodiments, the GLP-1 associated disease or disorder is non-insulin-dependent diabetes mellitus (Type 2 diabetes) , hyperglycemia, impaired glucose tolerance, insulin dependent diabetes mellitus (Type 1 diabetes) , diabetic complication, obesity, hypertension, hyperlipidemia, arteriosclerosis, coronary heart disease, brain infarction, non-alcoholic steatohepatitis, Parkinson's disease or dementia. In some embodiments, the GLP-1 associated disease or disorder is non-insulin-dependent diabetes mellitus (Type 2 diabetes) or obesity. Dosing
- [0120] 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.
- [0121] 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
- [0122] 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
- [0123] 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.
- [0124] 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 admin-

istration 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 Decker, 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

[0125] 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 a: Synthesis of int-1



Step 1: int-1-1

[0126] A mixture of ethyl 5-bromo-1H-indole-2-carboxylate (25.0 g, 93.0 mmol) , 2- (3, 6-dihydro-2H-pyran-4-yl) -4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolane (29.4 g, 140.0 mmol) , K₂CO₃ (25.8 g, 186.0 mmol) and PdCl₂ (dppf) (3.41 g, 4.66 mmol) in 1, 4-

dioxane (200 mL) and water (67 mL) was degassed and purged with N₂ for 3 times, the resulting mixture was stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to r. t., the reaction was concentrated. After being diluted with water (200 mL), the residue was extracted with EtOAc (200 mL × 3), washed with brine (50 mL × 3), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-1-1 (22.2 g, 81.67 mmol, 87.8 %yield). LCMS: 272.2 [M+ H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 11.77 (s, 1H), 7.48 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 4.33 (q, J = 8.0 Hz, 2H), 4.03 -3.88 (m, 2H), 3.48 -3.41 (m, 2H), 2.86 -2.74 (m, 1H), 1.78 -1.63 (m, 4H), 1.34 (t, J = 8.0 Hz, 3H). Step 2: int-1-2

[0127] To a solution of int-1-1 (11.0 g, 40.5 mmol) in MeOH (330 mL) was added Pd (OH)₂/C (1.1 g, 10%). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 12 hrs under H₂ (15 Psi). The mixture was filtered and the cake was washed with MeOH and DCM (10: 1, 330 mL × 3). The filtrate was concentrated and triturated with PE: EA (1: 1, 100 mL) to afford int-1-2 (7.65 g, 28.0 mmol, 69.0%yield). LCMS: 274.2 [M+ H]⁺. Step 3: int-1-3

[0128] To a solution of int-1-2 (12.60 g, 46.10 mmol) in Toluene (100 mL) was added N-methylaniline (12.5 mL, 115.0 mmol) and Trimethylaluminium (69.0 mL, 138.0 mmol, 2 M in Toluene) at 0 °C. The mixture was degassed and purged with N₂ for 3 times and stirred at 90 °C for 2 hrs. After pouring into cold water (200 mL), the mixture was stirred for 10 mins, filtered, the cake was washed with EtOAc (150 mL × 3). The filtrate was washed with brine (500 mL), dried over Na₂SO₄, filtered, concentrated, triturated with MeOH (50 mL) to afford int-1-3 (9.00 g, 26.90 mmol, 58.4%yield). LCMS: 335.2 [M+ H]⁺. Step 4: int-1-4

[0129] To a solution of int-1-3 (8.00 g, 23.92 mmol) in DMF (80 mL) was added NaH (2.39 g, 59.80 mmol, 60%) at 0 °C under N₂ atmosphere portionwise and the mixture was stirred at 20 °C for 1 hr, 2-bromoacetonitrile (3.30 mL, 47.8 mmol) was added afterward and the mixture was stirred for another hr. The reaction was poured into water (200 mL), extracted with EtOAc (200 mL × 3). Combined organic layers were washed with water (200 mL × 3) and brine (200 mL), dried over Na₂SO₄, filtered, concentrated and triturated with PE: EtOAc (1: 1, 30 mL) to afford int-1-4 (7.00 g, 18.74 mmol, 78.4%yield). LCMS: 374.2 [M+ H]⁺. Step 5: int-1-5

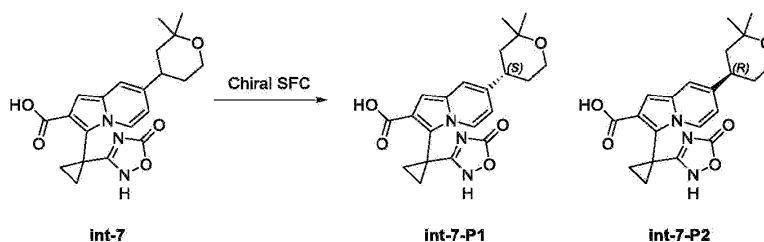
[0130] To a solution of int-1-4 (4.40 g, 11.78 mmol) and 1, 3, 2-dioxathiolane 2, 2-dioxide (3.66 g, 29.5 mmol) in THF (45 mL) was added LiHMDS (47.0 mL, 47.0 mmol, 1 M in THF) at 5 °C. Resulting mixture was stirred at 5 °C for 1 hr, was poured into water (100 mL), extracted with EtOAc (100 mL × 4). Combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified

by column chromatography to afford int-1-5 (2.60 g, 6.51 mmol, 55.2%yield) . LCMS: 400.2 [M+ H]⁺ . ¹HNMR (400 MHz, DMSO-d₆) δ 7.55 (d, J = 8.0 Hz, 1H) , 7.40 -7.31 (m, 4H) , 7.30 -7.23 (m, 3H) , 5.97 (s, 1H) , 3.98 -3.86 (m, 2H) , 3.44 (s, 3H) , 3.43 -3.37 (m, 2H) , 2.78 (p, J = 8.0 Hz, 1H) , 2.08 -1.92 (m, 2H) , 1.77 -1.69 (m, 2H) , 1.69 -1.61 (m, 4H) .Step 6: int-1-6

[0131] To a solution of int-1-5 (2.10 g, 5.26 mmol) and hydroxylamine hydrochloride (1.83 g, 26.3 mmol) in EtOH (33.6 mL) was added K₂CO₃ (3.63 g, 26.3 mmol) . Resulting mixture was stirred at 90 °C for 2 hrs. After cooling to r. t., the reaction was poured into water (30 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with brine (30 mL × 2) , dried over Na₂SO₄, filtered, concentrated and triturated with Pe and EA (5: 1, 20 mL) to afford int-1-6 (1.84 g, 4.25 mmol, 81%yield) . LCMS: 433.3 [M+ H]⁺ . ¹HNMR (400 MHz, DMSO-d₆) δ 9.27 (s, 1H) , 7.64 (d, J = 8.0 Hz, 1H) , 7.42 (t, J = 8.0 Hz, 2H) , 7.37 -7.27 (m, 4H) , 7.21 (dd, J = 8.0, 4.0 Hz, 1H) , 6.13 (brs, 2H) , 4.01 -3.95 (m, 2H) , 3.52 (s, 3H) , 3.49 -3.45 (m, 2H) , 2.84 -2.73 (m, 1H) , 1.99 -1.88 (m, 1H) , 1.74 -1.67 (m, 4H) , 1.59 -1.44 (m, 1H) , 1.36 -1.29 (m, 1H) , 1.07 -0.93 (m, 1H) .Step 7: int-1-7

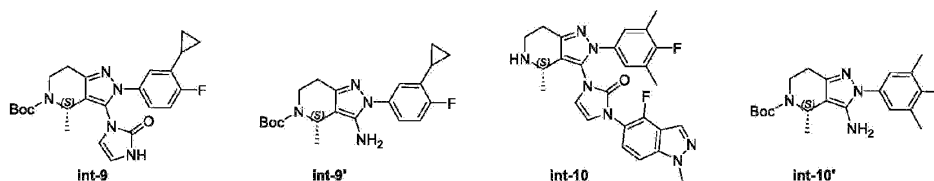
[0132] To a solution of int-1-6 (2.00 g, 4.62 mmol) in DMSO (20 mL) were added CDI (1.50 g, 9.25 mmol) and DBU (1.8 mL, 11.56 mmol) . Resulting mixture was degassed and purged with N₂ for 3 times and stirred at 80 °C for 2 hrs under N₂ atmosphere. After cooling to r. t., the mixture was poured into water (30 mL) , extracted with EtOAc (50 mL × 3) . The aqueous phase was adjusted pH to 5~6 with HCl (1 N) and extracted with EtOAc (40 mL × 2) . Combined organic layers were washed with brine (30 mL × 2) , dried over Na₂SO₄, filtered, concentrated to afford int-1-7 (2.30 g, 4.51 mmol, 98%yield) . LCMS: 459.2 [M+ H]⁺ . ¹HNMR (400 MHz, DMSO-d₆) δ 12.07 (brs, 1H) , 7.43 (d, J = 8.0 Hz, 1H) , 7.39 -7.34 (m, 2H) , 7.33 -7.25 (m, 3H) , 7.25 -7.21 (m, 1H) , 7.17 (dd, J = 8.0, 4.0 Hz, 1H) , 5.93 (s, 1H) , 3.95 -3.86 (m, 2H) , 3.45 -3.39 (m, 2H) , 3.39 (s, 3H) , 2.80 -2.69 (m, 1H) , 1.91 -1.85 (m, 2H) , 1.70 -1.61 (m, 6H) .Step 8: int-1

[0133] To a solution of int-1-7 (2.00 g, 4.36 mmol) in THF (120 mL) was added potassium tert-butoxide (4.89 g, 43.6 mmol) and water (0.3 mL) . The mixture was stirred at 25 °C for 1 hr and was poured into water (60 mL) , extracted with EtOAc (100 mL × 3) . The aqueous phase was adjusted pH to 4~5 with HCl (1 N) and extracted with EtOAc (80 mL × 4) . Combined organic layers were washed with brine (50 mL × 2) , dried over Na₂SO₄, filtered, concentrated to afford int-1 (1.43 g, 3.87 mmol, 89 %yield) . LCMS: 370.1 [M+ H]⁺ .Example g: Int-7, Int-7-P1 and Int-7-P2



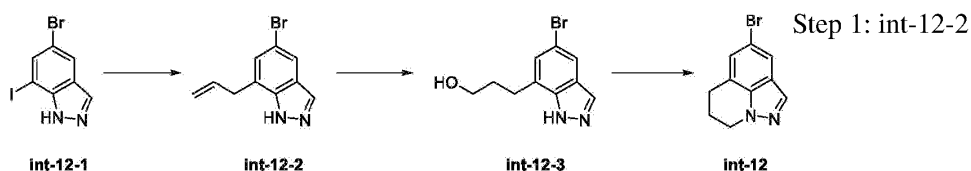
The synthesis of int-7 was referred to intermediate 31 of WO-2022017338.

[0134] Int-7 (100 mg) was separated by chiral SFC to afford int-7-P1 (9 mg) and int-7-P2 (9 mg). Preparative separation method: Instrument: WATERS 150 preparative SFC (SFC-26). Column: ChiralCel OJ, 250×30mm I. D., 10μm. mobile phase: A for CO₂ and B for Methanol (0.1% NH₃H₂O), Gradient: B 35%, flow rate: 120 mL/min, back pressure: 100 bar. Retention time: int-7-P1 1.090min, int-7-P2 1.277min. LCMS: 398.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 12.20 (brs, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 6.71 (dd, J = 8.0, 4.0 Hz, 1H), 6.67 (s, 1H), 3.74-3.66 (m, 2H), 2.96-2.83 (m, 1H), 1.83-1.76 (m, 2H), 1.72-1.65 (m, 2H), 1.57-1.41 (m, 3H), 1.34-1.12 (m, 8H). Example i: Synthesis of int-9, int-9', int-10 and int-10'



[0135] The syntheses of int-9 and int-9' was referred to intermediates 46d and 46b of WO-2018056453.

[0136] The synthesis of int-10 and int-10' was referred to intermediates 3 and 3-C in WO-2022017338. Example k: Synthesis of int-12

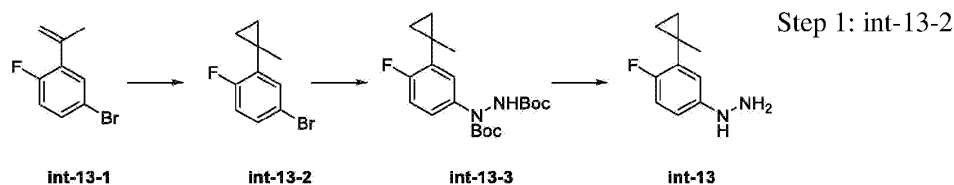


[0137] To a solution of int-12-1 (10.0 g, 31.10 mmol) and 2-allyl-4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolane (6.26 g, 37.30 mmol) in dioxane (200 mL) and water (40 mL) were added K₂CO₃ (5.15 g, 37.30 mmol) and PdCl₂ (dppf) *DCM (1.90 g, 2.33 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 100 °C under N₂ atmosphere for 12 hrs. After cooling to room temperature, the reaction mixture was poured into water (2 L) and extracted with EtOAc (1 L × 2). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-12-2 (5.60 g, 23.62

mmol, 76.0%yield) . LCMS: 237.0 [M+H]⁺. ¹HNMR (400 MHz, CDCl₃) δ 10.12 (brs, 1H) , 8.17 (s, 1H) , 7.88 (d, J =4.0 Hz, 1H) , 7.86 (d, J = 4.0 Hz, 1H) , 6.13 -5.97 (m, 1H) , 5.37 -5.31 (m, 1H) , 5.30 -5.25 (m, 1H) , 3.66 (d, J = 8.0 Hz, 2H) .Step 2: int-12-3

[0138] To a solution of int-12-2 (5.60 g, 23.62 mmol) in THF (10 mL) was added BH₃ (56 mL, 560 mmol, 10 M in Me₂S) at 0 °C under N₂ atmosphere and the mixture was stirred at the 60 °C for 2 hrs. After being cooled to 0 °C, a solution of NaOH (2.83 g, 70.9 mmol) in water (50 ml) was added dropwise, followed by H₂O₂ (48.3 ml, 472 mmol, 30%purity) . The resulting mixture was stirred at 30 °C for 4 hrs. The reaction mixture was quenched by water (1 L) and extracted with EtOAc (300 mL × 3) . The combined organic layers were washed with water (200 mL) , followed by brine (200 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-12-3 (650 mg, 2.55 mmol, 10.8 %yield) . LCMS: 255.1 [M+H]⁺.Step 3: int-12

[0139] To a solution of int-12-3 (200 mg, 0.78 mmol) in THF (12 mL) was added TEA (0.2 ml, 1.5 mmol) , followed by MsCl (0.1 mL, 0.9 mmol) dropwise at 0 °C. The mixture was stirred at 25 °Cfor 0.5 hrs and cooled to 0 °C, NaH (69 mg, 1.73 mmol, 60%purity) was added in portions. The resulting mixture was stirred at 60 °C for 2 hrs. After cooling to room temperature, the reaction mixture was quenched by water (50 mL) and extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with water (100 mL) , followed by brine (100 mL) . The combined organic layers dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-12 (20 mg, 0.084 mmol, 10.8%yield) . LCMS: 237.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 7.94 (s, 1H) , 7.77 (s, 1H) , 7.24 (s, 1H) , 4.35 (t, J = 8.0 Hz, 2H) , 2.99 (t, J = 8.0 Hz, 2H) , 2.25 -2.16 (m, 2H) .Example I: Synthesis of int-13

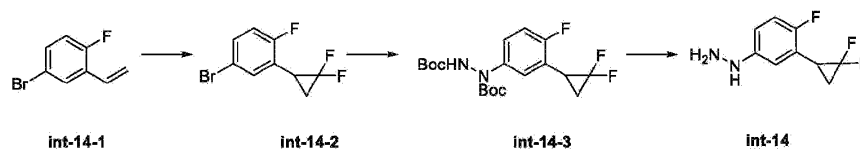


[0140] To a solution of diethylzinc (23 mL, 23.4 mmol, 1 M in toluene) in DCM (25 mL) was added TFA (1.8 mL, 23.3 mmol) dropwise at 0 °C and the mixture was stirred at 0 °C for 0.5 hr, then diiodomethane (6.23 g, 23.25 mmol) was added dropwise. After being stirred for 0.5 hr at 0 °C, int-13-1 (500 mg, 2.33 mmol) was added dropwise. The resulting mixture was stirred at 20 °C for 8 hrs and quenched by water (100 mL) , extracted with DCM (100 mL × 2) . The organic layers were washed with water (100 mL) , followed by brine (100 mL × 2) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-13-2 (350 mg, 1.53 mmol,

66%yield) . ¹HNMR (400 MHz, DMSO-d₆) δ 7.45 -7.32 (m, 2H) , 7.07 (dd, J = 12.0, 8.0 Hz, 1H) , 1.23 (s, 3H) , 0.74 -0.69 (m, 2H) , 0.66 -0.61 (m, 2H) .Step 2: int-13-3

[0141] To a solution of int-13-2 (2.00 g, 8.73 mmol) in THF (20 mL) was added n-BuLi (3.5 mL, 2.5 M in hexane) dropwised at -78 °C and the mixture was stirred at -78 °C for 0.5 hr, then a solution of di-tert-butyl diazene-1, 2-dicarboxylate (2.01 g, 8.73 mmol) in THF (20 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 hrs under N₂ and quenched by water (100 mL) . After extraction with EtOAc (50 mL × 2) , the combined organic layers were washed with water (50 mL) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-13-3 (2.20 g, 1.96 mmol, 22%yield) . LCMS: 225.2 [M-156+H]⁺.Step 3: int-13

[0142] A mixture of int-13-3 (2.20 g, 5.78 mmol) in HCl solution (22 mL, 4 M in dioxane) was stirred at 20 °C for 8 hrs. The reaction was concentrated to afford int-13 (1.0 g, crude) . LCMS: 181.3 [M+H]⁺.Example m: Synthesis of int-14



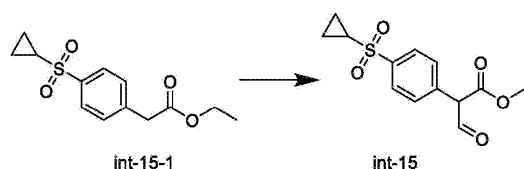
Step 1: int-14-2

[0143] To a solution of int-14-1 (1.80 g, 8.95 mmol) and trimethyl (trifluoromethyl) silane (26.5 mL, 179.0 mmol) in THF (30 mL) was added sodium iodide (2.01 g, 13.43 mmol) , followed by TBAF (2.3 mL, 2.24 mmol) dropwise. The mixture was stirred at 70 °C under N₂ for 6 hrs in a sealed tube. After cooling to room temperature, the reaction mixture was poured into water (100 mL) , extracted with EtOAc (100 mL × 2) . The combined organic layers were washed with brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-14-2 (1.30 g, 5.18 mmol, 57.8%yield) . ¹HNMR (400 MHz, DMSO-d₆) δ 7.56 -7.47 (m, 2H) , 7.22 (t, J = 8.0 Hz, 1H) , 3.07 -2.95 (m, 1H) , 2.17 -2.08 (m, 1H) , 2.07 -1.97 (m, 1H) .Step 2: int-14-3

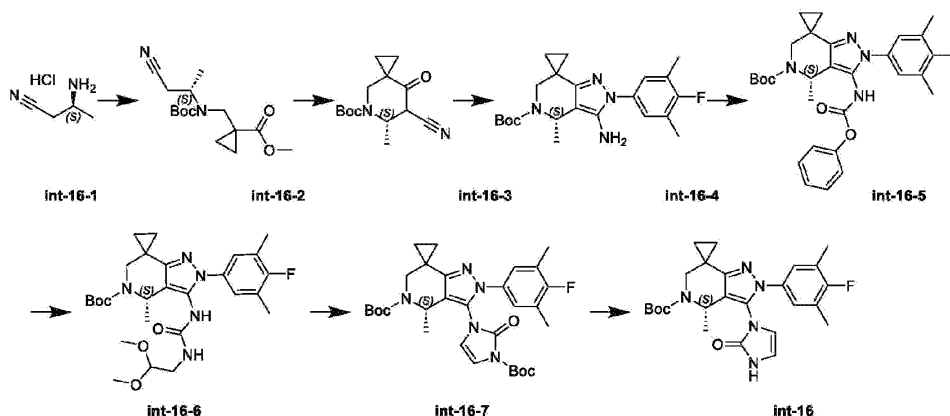
[0144] To a solution of int-14-2 (1.50 g, 5.97 mmol) in DMF (30 mL) were added di-tert-butyl hydrazine-1, 2-dicarboxylate (2.78 g, 11.95 mmol) , 1, 10-phenanthroline (2.15 g, 11.95 mmol) , Cs₂CO₃ (3.89 g, 11.95 mmol) and CuI (2.28 g, 11.95 mmol) . The resulting mixture was degassed and purged with N₂ for 3 times, stirred at 100 °C for 4 hrs. After cooling to room temperature, the reaction was poured into 20 mL of water and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with brine (20 mL × 2) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-14-3 (1.30 g, 3.23 mmol, 54.0%yield) . LCMS:

425.2 [M+Na]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 9.64 (s, 1 H) , 7.33 -7.11 (m, 3H) , 3.09 -2.98 (m, 1H) , 2.06 -2.02 (m, 1H) , 1.79 -1.66 (m, 1H) , 1.47 -1.40 (m, 18H) .Step 3: int-14

[0145] A mixture of int-14-3 (1.30 g, 3.23 mmol) in HCl solution (13 mL, 4 M in dioxane) was stirred at 25 °C for 12 hrs. The reaction mixture was concentrated to afford int-14 (700 mg, crude) . LCMS: 203.2 [M+H]⁺.Example n: Synthesis of int-15



[0146] To a solution of int-15-1 (200 mg, 0.75 mmol) in THF (2 ml) was added NaH (54 mg, 2.24 mmol, 60%purity) in portions at 0 °C and the mixture was stirred at 25 °C for 0.5 hr. Methyl formate (2 mL, 32.4 mmol) was then added dropwise. The resulting mixture was stirred at 25 °C for 1 hr. The reaction mixture was quenched by water (20 mL) and extracted with EtOAc (30 mL ×3) .The combined organic layers were washed with (20 mL) , followed by brine (20 mL × 2) , dried over Na₂SO₄, filtered and concentrated to afford int-15 (200 mg, crude) . LCMS: 283.1 [M+H]⁺.Example o: Synthesis of int-16



Step 1: int-16-2

[0147] To a mixture of int-16-1 (7.00 g, 49.9 mmol) in DCM (100 ml) was added methyl 1-formylcyclopropane-1-carboxylate (8.32 g, 64.9 mmol) and the mixture was stirred at 25 °C for 0.5 hr, then added NaBH₃CN (4.71 g, 74.9 mmol) . The mixture was stirred at for 25 °C for 12 hrs, (Boc)₂O (16.3 g, 74.9 mmol) was added and the mixture was stirred at 25 °C for another 12 hrs. The reaction was diluted with water (10 mL) and extracted with EtOAc (30 mL × 3) . The organic layers were combined, dried over Na₂SO₄, concentrated and purified by column chromatography to afford int-16-2 (3.00 g, 20%yield) . ¹HNMR (400 MHz, CDCl₃) : δ 4.21 -4.05 (m, 1H) , 3.69 -3.63 (m, 5H) ,

3.18 -2.75 (m, 1H) , 2.65 -2.55 (m, 1H) , 1.50 -1.43 (m, 9H) , 1.38 -1.26 (m, 5H) , 1.08 (s, 2H) .Step 2: int-16-3

[0148] To a mixture of int-16-2 (5.00 g, 16.8 mmol) in THF was added KOtBu (1.89 g, 16.8 mmol) . The mixture was stirred at 25 °C for 12 hrs. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (50 mL × 3) . The organic layers were combined, dried over Na₂SO₄, concentrated and purified by column chromatography to afford int-16-3 (4.0 g, 90%yield) . LCMS: 265.2 [M+H]⁺.Step 3: int-16-4

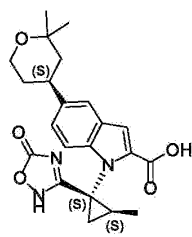
[0149] To a mixture of int-16-3 (2.00 g, 7.57 mmol) in EtOH (30 ml) was added (4-fluoro-3, 5-dimethylphenyl) hydrazine (1.51 g, 9.84 mmol) and H₂O (0.954 ml, 53.0 mmol) . The mixture was stirred at 80 °C for 12 hrs, diluted with H₂O (20 mL) and extracted with EtOAc (100 mL × 3) . The organic layers were combined, dried over Na₂SO₄, concentrated and purified by column chromatography to afford int-16-4 (2.00 g, 66%yield) . LC-MS: 401.3 [M+H]⁺.Step 4: int-16-5

[0150] To a mixture of int-16-4 (2.00 g, 4.99 mmol) in THF (20 ml) was added DIEA (2.62 ml, 14.9 mmol) and phenyl chloroformate (1.56 g, 9.99 mmol) . The mixture was stirred at 0 °C for 2 hrs. The reaction was concentrated to give int-16-5 (2.60 g, 100 %yield) . LCMS: 543.0 [M+Na]⁺.Step 5: int-16-6

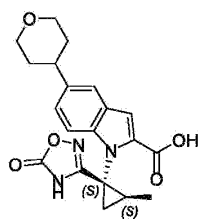
[0151] To a mixture of int-16-5 (2.00 g, 3.84 mmol) in pyridine (5 ml) and THF (20 ml) was added 2, 2-dimethoxyethan-1-amine (0.808 g, 7.68 mmol) . The mixture was stirred at 25 °C for 2 hrs. The mixture was diluted with H₂O (20 mL) and extracted with EtOAc (100 mL × 3) . The organic layers were combined, dried over Na₂SO₄, concentrated and purified by column chromatography to afford int-16-6 (0.8 g, 27%yield) . LCMS: 532.4 [M+H]⁺.Step 6: int-16-7

[0152] To a mixture int-16-6 (1.40 g, 1.84 mmol) in THF (25 ml) was added methane sulfonic acid (1.41 g, 14.7 mmol) , the mixture was stirred at 60 °C for 2 hrs. Then (Boc)₂O (1.71 ml, 7.37 mmol) and K₃PO₄ (3.91 g, 18.43 mmol) were added to the mixture at 25 °C. The mixture was stirred for 2 hrs at 25 °C. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (50 mL × 3) . The organic layers were combined, dried over Na₂SO₄, concentrated and purified by column chromatography to afford int-16-7 (430 mg, 34%yield) . LCMS: 568.3 [M+H]⁺.Step 7: int-16

[0153] To a mixture of int-16-7 (430 mg, 0.757 mmol) in ACN (5 mL) was added K₂CO₃ (126 mg, 0.909 mmol) . The mixture was stirred at 25 °C for 2 hrs. The reaction was filtered, concentrated and purified by column chromatography to afford int-16 (241 mg, 68%yield) . LCMS: 468.4 [M+H]⁺. ¹HNMR (400 MHz, METHANOL-d₄) : δ 7.04 (d, J = 6.4 Hz, 2H) , 6.51 (d, J = 3.2 Hz, 1H) , 6.44 (s, 1H) , 5.33 (s, 1H) , 4.17 -4.03 (m, 1H) , 3.57 (s, 2H) , 2.21 (d, J = 2.4 Hz, 6H) , 1.47 (s, 9H) , 1.29 (d, J = 9.8 Hz, 3H) , 1.05 -1.02 (m, 1H) , 0.95 -0.92 (m, 3H) .Example p: Synthesis of int-17, int-18



int-17

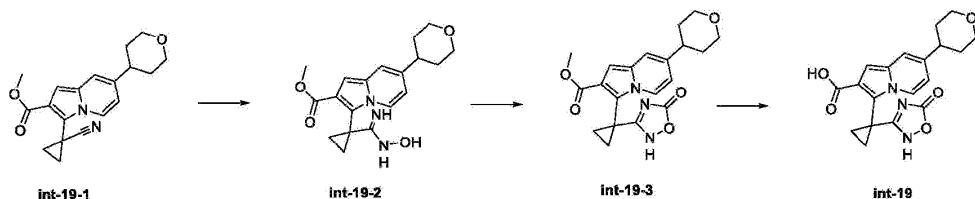


int-18

[0154] The synthesis of int-17 was referred to intermediates 31k of WO-2018056453.

[0155] The synthesis of int-18 was referred to intermediates 8b of

WO-2018056453. Example q: Synthesis of int-19



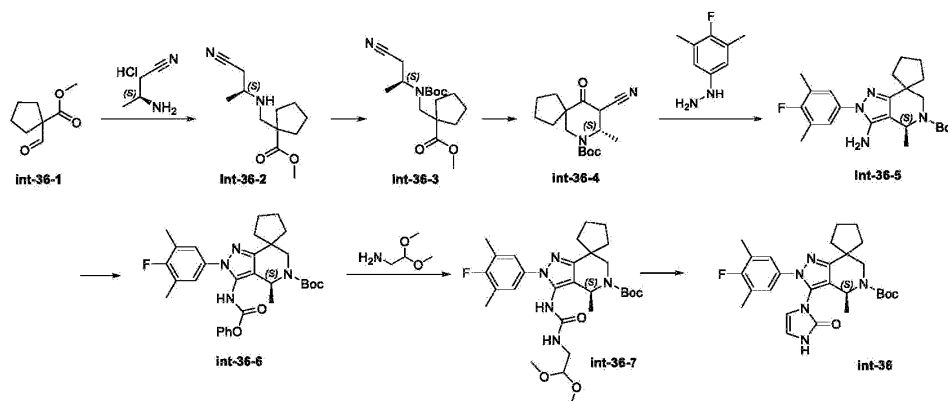
Step 1: int-19-2

[0156] To a solution of int-19-1 (4.25 g, 13.10 mmol, WO2023169456) in EtOH (50 mL) was added hydroxylamine hydrochloride (2.73 g, 39.3 mmol) and triethylamine (7.95 g, 79.00 mmol). The resulting mixture was stirred at 90 °C for 1 hr. After cooling to room temperature, the reaction mixture was poured into water (150 mL), and extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography to afford int-19-2 (4.68 g, 11.78 mmol, 90.0% yield). LC-MS (ESI⁺): m/z 358.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.09 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 5.34 (s, 2H), 4.04–3.92 (m, 2H), 3.85 (s, 3H), 3.52–3.39 (m, 2H), 2.80–2.64 (m, 1H), 1.80–1.39 (m, 6H), 0.92 (s, 2H). Step 2: int-19-3

[0157] To a solution of int-19-2 (4.38 g, 12.25 mmol) and CDI (3.97 g, 24.51 mmol) in 1, 4-Dioxane (50 mL) was added DBU (5.60 mL, 36.90 mmol). The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction mixture was poured into water (150 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-19-3 (4.30 g, 10.65 mmol, 87.0% yield). LC-MS (ESI⁺): m/z 384.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 12.06 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 4.03–3.93 (m, 2H), 3.80 (s, 3H), 3.46 (t, J = 8.0 Hz, 2H), 2.80–2.70 (m, 1H), 1.89–1.82 (m, 2H), 1.80–1.76 (m, 1H), 1.75

−1.73 (m, 1H) , 1.72 –1.62 (m, 2H) , 1.59 –1.43 (m, 1H) , 1.42 –1.29 (m, 1H) .Step 3:
int-19

[0158] To a solution of int-19-3 (4.20 g, 10.95 mmol) in THF (10 mL) were added a solution of lithium hydroxide (2.62 g, 110 mmol) in water (0.75 mL) dropwise. The resulting mixture was stirred at 50 °C for 2 hrs. The reaction mixture was poured into 50 mL of water and extracted with MTBE (100 mL) . After being separated, the aqueous phase was acidified with diluted HCl (aq., 1 M) to pH~3 and extracted with ethyl acetate (100 mL × 3) . The combined organic layers were washed with brine (100 mL) , dried Na₂SO₄, filtered and concentrated to afford int-19 (3.90 g, 9.50 mmol, 87 %yield) .
LC-MS (ESI+) : m/z 370.1 (M+H)⁺ . ¹H NMR (400 MHz, DMSO-d₆) δ 12.32 (brs, 1H) , 12.06 (brs, 1H) , 8.21 (d, J = 8.0 Hz, 1H) , 7.32 (s, 1H) , 6.74 (dd, J = 8.0, 4.0 Hz, 1H) , 6.71 (s, 1H) , 4.03 –3.92 (m, 2H) , 3.45 (t, J = 8.0 Hz, 2H) , 2.81 –2.67 (m, 1H) , 1.89 –1.79 (m, 2H) , 1.78 –1.61 (m, 4H) , 1.59 –1.47 (m, 1H) , 1.39 –1.26 (m, 1H) .Example af: Synthesis of int-36



Step1: int-36-2

[0159] To a solution of (S) -3-aminobutanenitrile hydrochloride (10.4 g, 87.0 mmol) in DCM (60 mL) was added DIEA (15.2 mL, 87.0 mmol) stirred at 25°C for 1 h. HOAc (4.99 mL, 87.0 mmol) and int-36-1 (6.20 g, 43.6 mmol) were then added to the reaction mixture. The reaction was stirred at 25°C for 12 h. LCMS showed the reaction was complete. The reaction mixture was added H₂O (60 mL) and extracted with EA (60 mL × 3) . The combined organic layers were washed with brine (60 mL × 3) , dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography to give int-36-2 (6.50 g, 67%yield) . LC-MS: [ESI] [M+H]⁺ = 225.3.Step 2: int-36-3

[0160] To a solution of int-36-2 (6.00 g, 26.7 mmol) in (Boc)₂O (60 mL) was added K₂CO₃ (7.39 g, 53.5 mmol) , The reaction was stirred at 25°C for 12 h. The reaction mixture was added H₂O (100 mL) and extracted with EA (200 mL × 3) . The combined organic layers were washed with brine (100 mL × 3) , dried over anhydrous Na₂SO₄, filtered

and concentrated under vacuum. The residue was purified by column chromatography to give int-36-2 (2.36 g, 26%yield) . LC-MS: [ESI] [M-100] + =225.2.Step 3: int-36-4

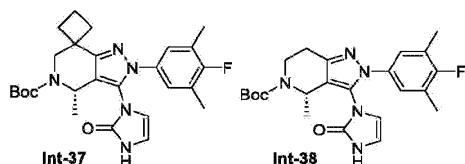
[0161] To a solution of int-36-3 (3.30 g, 10.8 mmol) in THF (30 mL) was added t-BuOK (1.37 g, 12.2 mmol) at 25°C under N₂ atmosphere. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under vacuum. The residue was purified by column chromatography to give int-36-4 (2.60 g, 83%yield) .Step 4: int-36-5

[0162] To a solution of int-36-4 (700 mg, 2.39 mmol) in EtOH (10 mL) was added H₂O (1 mL) , (4-fluoro-3, 5-dimethylphenyl) hydrazine (554 mg, 3.59 mmol) and pyridin-1-ium chloride (221 mg, 1.91 mmol) . The reaction was stirred at 80 °C for 12 hr. The mixture was concentrated and purified by column chromatography to afford int-36-5 (550 mg, 54%yield) . LC-MS: [ESI] [M+1] + = 429.5.Step 5: int-36-6

[0163] To a solution of N-ethyl-N-isopropylpropan-2-amine (151 mg, 1.17 mmol) in THF (10 mL) was added int-36-5 (500 mg, 1.17 mmol) and phenyl chloroformate (183 mg, 1.17 mmol) at 25°C. The reaction was stirred at 0°C for 2 hr. The mixture was concentrated to give a residue (650 mg) , which was used for the next step without purification. LC-MS: [ESI] [M+1] + = 549.3.Step 6: int-36-7

[0164] To a solution of int-36-6 (650 mg, 1.18 mmol) in pyridine (10 mL) was added 2, 2-dimethoxyethan-1-amine (249 mg, 2.36 mmol) at 25°C. The reaction was stirred at 60°C for 2 hr. The mixture was diluted with H₂O (10 mL) and extracted with EA (30 mL × 3) . The combined organic layers were washed with brine (10 mL × 3) , dried, filtered, concentrated and purified by column chromatography to give int-36-7 (420 mg, 63%yield) . LC-MS: [ESI] [M+1] + = 560.3.Step 7: int-36

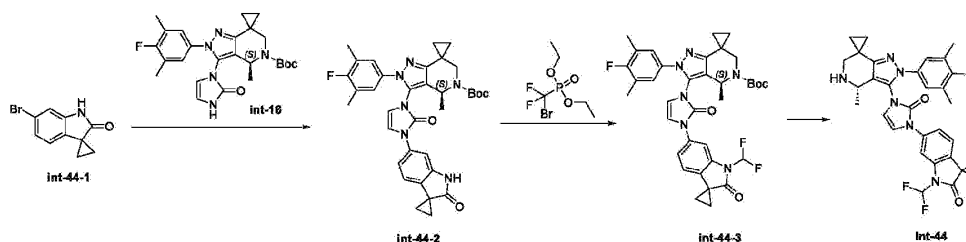
[0165] To a solution of int-36-7 (400 mg, 0.715 mmol) in THF (5 mL) was added 4-methyl-benzenesulfonic acid (73.8 mg, 0.429 mmol) at 25°C. The reaction was stirred at 60°C for 2 hr. LCMS showed the reaction was complete. The mixture was concentrated and purified by column chromatography to give int-36 (192 mg, 54%yield) . LC-MS: [ESI] [M+1] + = 496.4. ¹H NMR (400 MHz, MeOD) : δ 7.07 (d, J = 6.3 Hz, 2H) , 6.52 –6.44 (m, 2H) , 5.25 –5.15 (m, 1H) , 4.20 –4.00 (m, 1H) , 3.00 –2.95 (s, 1H) , 2.40 –2.33 (m, 1H) , 2.24 (d, J = 2.4 Hz, 6H) , 1.92 –1.79 (m, 5H) , 1.65-1.60 (m, 2H) , 1.49 (s, 9H) , 1.22 (d, J = 6.4 Hz, 3H) .Example ag: Synthesis of int-37, int-38



[0166] Int-37 was synthesized following the procedure for int-36 using cyclobutanecarboxylic acid, 1-formyl-, ethyl ester instead of int-36-1. Int-37 was obtained in

62% yield (326 mg) . LC-MS: [ESI] $[M+H]^+ = 482.3$. ^1H NMR (400 MHz, DMSO) : δ 10.32 (s, 1H) , 7.09 (d, $J = 6.3$ Hz, 2H) , 6.58 (s, 2H) , 5.00 –4.95 (m, 1H) , 4.36 –4.27 (m, 1H) , 2.98 –2.93 (m, 1H) , 2.76 –2.67 (m, 1H) , 2.21 –2.20 (m, 6H) , 2.10 –1.77 (m, 5H) , 1.10-1.08 (m, 3H) .

[0167] The synthesis of int-38 was referred to intermediates 11k of WO-2018056453. Example ai: Synthesis of int-44, int-67



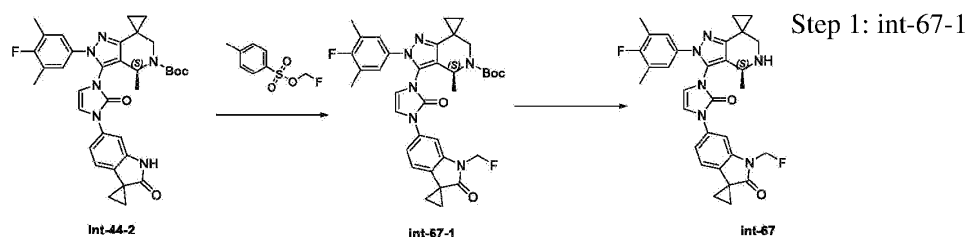
Step 1: int-44-2

[0168] To a solution of int-44-1 (2.04 g, 8.56 mmol) and int-16 (2.00 g, 4.28 mmol) and copper (I) iodide (0.82 g, 4.28 mmol) and K_2CO_3 (1.77 g, 12.83 mmol) in NMP (20 mL) was added (1R, 2R) - N^1 , N^2 -dimethylcyclohexane-1, 2-diamine (0.31 g, 2.14 mmol) . The resulting mixture was degassed and purged with N_2 for three times and stirred at 130 °C for 3 hrs under N_2 . After cooling to room temperature, the mixture was poured into water (100 mL) and extracted with EtOAc (100 mL $\times$ 3) . The combined organic layers were washed with water (100 mL $\times$ 2) , followed by brine (100 mL) , dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-44-2 (1.90 g, 2.89 mmol, 67.5% yield) . LC-MS (ESI+) : m/z 625.2 ($M+H$) $^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.66 (s, 1H) , 7.30 (s, 1H) , 7.24 (d, $J = 4.0$ Hz, 1H) , 7.10 –7.03 (m, 4H) , 7.00 –6.93 (m, 1H) , 5.36 –5.14 (m, 1H) , 3.64 –3.45 (m, 2H) , 2.17 (s, 6H) , 1.61 –1.55 (m, 2H) , 1.50 –1.46 (m, 2H) , 1.43 (s, 9H) , 1.38 –1.32 (m, 1H) , 1.23 (d, $J = 8.0$ Hz, 3H) , 1.00 –0.94 (m, 2H) , 0.88 –0.80 (m, 1H) .Step 2: int-44-3

[0169] To a solution of int-44-2 (500.0 mg, 0.80 mmol) in MeCN (50.0 mL) and water (3.0 mL) was added diethyl (bromodifluoromethyl) phosphonate (855.0 mg, 3.20 mmol) and NaOH (640.0 mg, 16.01 mmol) . The resulting mixture was stirred at 70 °C for 2 hrs. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (100 mL $\times$ 3) . The combined organic layers were washed with water (200 mL $\times$ 2) , followed by brine (200 mL) , dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-44-3 (150.0 mg, 0.21 mmol, 26.4% yield) . LC-MS (ESI+) : m/z 675.2 ($M+H$) $^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 –7.51 (m, 2H) , 7.35 (d, $J = 8.0$ Hz, 1H) , 7.31 (d, $J = 4.0$ Hz, 1H) , 7.26 (d, $J = 8.0$ Hz, 1H) , 7.06 (d, $J = 6.0$ Hz, 2H) , 7.03 –6.96 (m, 1H) , 5.35 –5.15 (m,

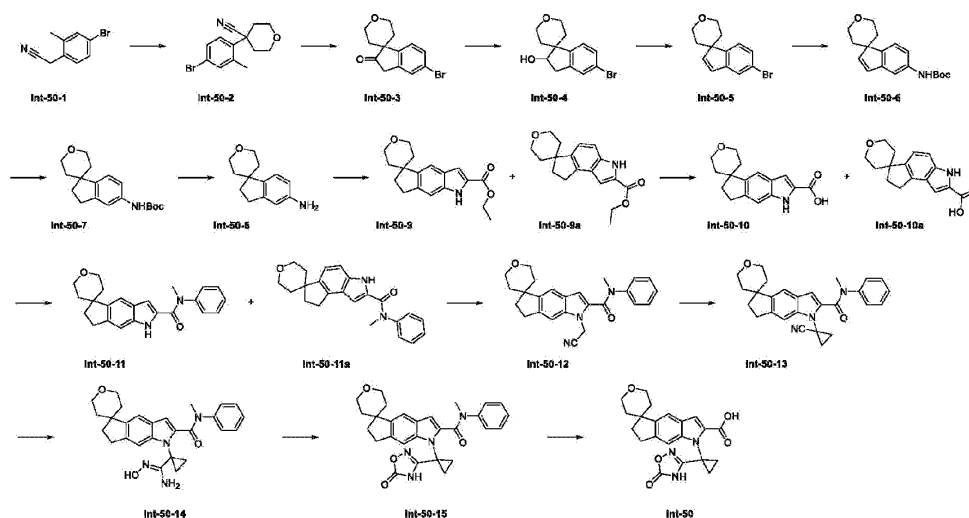
1H) , 3.69 –3.42 (m, 2H) , 2.17 (s, 6H) , 1.85 –1.78 (m, 2H) , 1.75 –1.67 (m, 2H) , 1.43 (s, 9H) , 1.38 –1.33 (m, 1H) , 1.28 –1.21 (m, 4H) , 0.99 –0.97 (m, 1H) , 0.88 –0.79 (m, 1H) .Step 3: int-44

[0170] A mixture of int-44-3 (140.0 mg, 0.21 mmol) in HCl solution (4M in dioxane, 2 mL) was stirred at 25 °C for 2 hrs. After completion, the reaction mixture was concentrated to give a residue, which was diluted with DCM (10 mL) and washed with saturated NaHCO₃ (aq., 20 mL) . The organic layer was washed with brine (20 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-44 (80.0 mg, 0.13 mmol, 63.7%yield) . LC-MS (ESI+) : m/z 575.2 (M+H)⁺.



[0171] To a solution of int-44-2 (500.0 mg, 0.80 mmol) in DMF (5 mL) was added Cs₂CO₃ (522.0 mg, 1.60 mmol) and fluoromethyl 4-methylbenzenesulfonate (327.0 mg, 1.60 mmol) . The mixture was stirred at 50 °C under N₂ for 2 hrs. After cooling to room temperature, the reaction mixture was quenched into cold water (50 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with water (50 mL × 2) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-67-1 (420.0 mg, 0.64 mmol, 80.0%yield) . LC-MS (ESI+) : m/z 657.4 (M+H)⁺.Step 2: int-67

[0172] To a solution of int-67-1 (200.0 mg, 0.31 mmol) in DCM (3 mL) were added 2, 6-lutidine (0.12 mL, 0.92 mmol) and TMS-OTf (203.0 mg, 0.92 mmol) . The resulting mixture was stirred at 25 °C for 1 hr. After completion, the reaction mixture was quenched by cold water (10 mL) and extracted with DCM (10 mL × 3) . The combined organic layers were washed with brine (10 mL × 3) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-67 (230.0 mg, 0.41 mmol, 77.0%yield) . LC-MS (ESI+) : m/z 557.4 [M+H]⁺Example aj: Synthesis of int-50



Step 1: int-50-2

[0173] To a mixture of NaH (38.1 g, 952 mmol) in DMF (1 L) was added a solution of int-50-1 (100g, 476 mmol) in DMF (500 mL) at 0 °C and the mixture was stirred at 25 °C for 30 min. The mixture reaction was added a solution of 1-bromo-2- (2-bromoethoxy) ethane (221 g, 952 mmol) in DMF (500 mL) and the mixture was stirred at 25 °C for 16 hrs. The reaction was quenched with saturated NH_4Cl (2 L) and extracted with EA (500 mL $\times$ 3) . The combined organic layers were wash with H_2O (500 mL $\times$ 2) , dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography to give int-50-2 (80.0 g, 60%yield) . ^1H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 2.1 Hz, 1H) , 7.47 –7.40 (m, 1H) , 7.30 (d, J = 8.6 Hz, 1H) , 4.01 –3.90 (m, 2H) , 3.72 –3.65 (m, 2H) , 2.57 (s, 3H) , 2.26 –2.20 (m, 2H) , 1.99 –1.90 (m, 2H) .Step 2: int-50-3

[0174] To a mixture of int-50-2 (60.0 g, 214 mmol) in THF (1.2 L) was added LDA (214 mL, 428 mmol, 2M THF) at -78 °C under nitrogen, the mixture was stirred at -78 °C for 3 hrs. The reaction was quenched with saturated hydrochloric acid aqueous solution (2N, 500 mL) and extracted with EA (500 mL $\times$ 3) . The combined organic layers wash with H_2O (500 mL $\times$ 2) , the organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography to give int-50-3 (30.0 g, 50%yield) . LCMS: 283.0 $[\text{M} + \text{H}]^+$.Step 3: int-50-4

[0175] To a mixture of int-50-3 (45.0 g, 160 mmol) in MeOH (450 ml) was added NaBH_4 (18.2 g, 480 mmol) at 0 °C under nitrogen, the mixture was stirred at 25 °C for 18 hrs. The solvent was concentrated. The residue was partitioned between DCM (500 mL) and water (500 mL) . The aqueous layer was extracted with DCM (250 mL $\times$ 2) , wash with brine (300 mL) , dried over sodium sulfate, filtered and concentrated to afford int-50-4 (35.0 g, 77%yield) . LCMS: 283.4 $[\text{M} + \text{H}]^+$.Step 4: int-50-5

- [0176] To a mixture of int-50-4 (52.0 g, 184 mmol) in THF (1 L) was added pyridine (21.8 g, 275 mmol), TsCl (43.8 g, 230 mmol) and t-BuOK (72.1 g, 643 mmol) at 25 °C, the mixture was stirred at 25 °C for 18 hrs. The reaction was quenched with H₂O (1 L) and extracted with EA (500 mL × 3). The combined organic layers were wash with H₂O (500 mL × 2), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography to give int-50-5 (48.0 g, 99%yield). LCMS: 265.0 [M+ H]⁺. Step 5: int-50-6
- [0177] To a mixture of int-50-5 (38.0 g, 143 mmol) in toluene (380 ml) was added tert-butyl carbamate (33.6 g, 287 mmol), K₂CO₃ (39.6 g, 287 mmol), XPhos (13.7 g, 28.7 mmol) and Pd (OAc)₂ (1.6 g, 7.17 mmol) under nitrogen, the mixture was stirred at 100 °C for 18 hrs. The mixture was filtered and concentrated and purified by column chromatography to give int-50-6 (30.0 g, 70%yield). LCMS: 324.2 [M+ H]⁺. Step 6: int-50-7
- [0178] To a mixture of int-50-6 (30.0 g, 100 mmol) in MeOH (300 mL) was added Pd/C (3.0 g, 10%wt, 55%H₂O) at 25 °C under hydrogen, the mixture was stirred at 25°C for 18 hrs. The mixture was filtered and concentrate to give int-50-7 (28.0 g, 93%yield). LCMS: 326.2 [M+ Na]⁺. Step 7: int-50-8
- [0179] To a mixture of int-50-7 (28.0 g, 92.0 mmol) in DCM (280 mL) was added HCl/dioxane (115 mL, 461 mmol, 4 M) at 25 °C under nitrogen, the mixture was stirred at 25 °C for 18 hrs. The reaction was quenched with saturated sodium bicarbonate aqueous solution (500 mL) and extracted with DCM (300 mL × 3). The combined organic layers wash with H₂O (200 mL × 2), the organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to give int-50-9 (11.0 g, 59%yield). LCMS: 204.0 [M+ H]⁺. Step 8: int-50-9 & int-50-9a
- [0180] To a mixture of int-50-8 (11.0 g, 54.1 mmol) in DMSO (110 mL) was added HOAc (6.50 g, 108 mmol), ethyl 2-oxopropanoate (25.1 g, 216 mmol), 4A molecular sieve (5.0 g) and Pd (OAc)₂ (1.20 g, 5.41 mmol) under oxygen, the mixture was stirred at 70 °C for 18 hrs. The reaction was partitioned between EA (200 mL) and water (200 mL). The aqueous layer was extracted with EA (200 mL × 2), The combined organic extracts were wash with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-50-9 and int-50-9a (7.00g, 43%yield). LCMS: 300.2 [M+ H]⁺. Step 9: int-50-10 & int-50-10a
- [0181] To a mixture of int-50-9 and int-50-9a (10.0 g, 33.4 mmol) in MeOH (100 mL) was added a solution of LiOH (4.0 g, 167 mmol) in H₂O (50 ml) at 25 °C, the mixture was stirred at 40 °C for 18 hrs. The mixture reaction was adjusted pH to 3 ~ 4 with 2N HCl. The aqueous layer was extracted with EA (200 mL × 2), The combined organic extracts were wash with brine (100 mL) and dried over sodium sulfate, dried over

anhydrous Na_2SO_4 , filtered and concentrated to give int-50-10 and int-50-10a (6.00 g, 66%yield) . LCMS: 272.2 $[\text{M} + \text{H}]^+$. Step 10: int-50-11 & int-50-11a To a mixture of int-50-10 and int-50-10a (6.00 g, 22.1 mmol) and HATU (12.6 g, 33.2 mmol) in DMF (60 ml) was added DIEA (8.6 g, 66.3 mmol) and N-methylaniline (2.40 g, 22.1 mmol) , the mixture was stirred at 40 °C for 18 hrs. The reaction was partitioned between EA (200 mL) and water (100 mL) . The aqueous layer was extracted with EA (100 mL $\times$ 2) , the combined organic extracts were washed with brine (50 mL) , dried over sodium sulfate, filtered, concentrated and purified by column chromatography to afford int-50-11 and int-50-11a (5.60 g, 70%yield) . LCMS: 361.2 $[\text{M} + \text{H}]^+$. Step 11: int-50-12 & int-50-12a

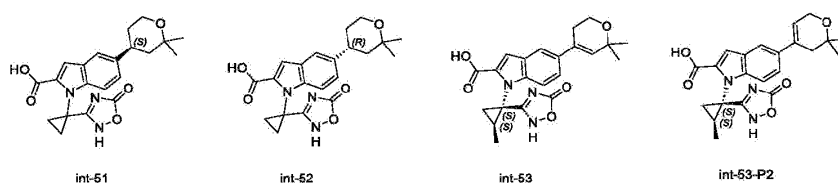
[0182] To a mixture of NaH (1.3 g, 53.3 mmol) in DMF (80 mL) was added a solution of int-50-11 and int-50-11a (6.40 g, 17.76 mmol) in DMF (10 mL) at 0 °C, the mixture was stirred at 25 °C for 30 min, then added a solution of 2-bromoacetonitrile (4.30 g, 35.5 mmol) in DMF (20 mL) and the mixture was stirred at 25 °C for 18 hrs. The reaction was quenched with saturated ammonium chloride aqueous solution (100 mL) and extracted with EA (100 mL $\times$ 3) . The combined organic layers were wash with H_2O (50 mL $\times$ 2) , dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by SFC to give int-50-12. (2.80 g, 39%yield) . LCMS: 400.2 $[\text{M} + \text{H}]^+$, $t_{\text{R}} = 1.81$ min. ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 –7.42 (m, 1H) , 7.38 –7.30 (m, 4H) , 7.29 –7.23 (m, 1H) , 7.19 (s, 1H) , 5.95 (s, 1H) , 5.59 (s, 2H) , 3.79 –3.70 (m, 2H) , 3.49 –3.40 (m, 2H) , 3.42 (s, 3H) , 2.95 (t, $J = 7.1$ Hz, 2H) , 2.11 –2.02 (m, 2H) , 1.79 –1.70 (m, 2H) , 1.43 –1.30 (m, 2H) . Step 12: int-50-13

[0183] To a solution of int-50-12 (1.90 g, 4.76 mmol) and 1, 3, 2-dioxathiolane 2, 2-dioxide (1.48 g, 11.89 mmol) in THF (5 ml) was added KHMDS (38 mL, 38.0 mmol, 1M THF) slowly at 0 °C. The mixture was further stirred at 25 °C under N_2 for 2 hrs. The mixture reaction was quenched with NH_4Cl (100 mL) and extracted with EA (200 mL $\times$ 3) . The combined organic layers were washed with brine (50 mL $\times$ 2) , dried over Na_2SO_4 , filtered, concentrated to give int-50-13 (1.90 g, 80%yield) . LCMS: 425.7 $[\text{M} + \text{H}]^+$. Step 13: int-50-14

[0184] To a solution of int-50-13 (2.00 g, 4.70 mmol) in DMSO (20 ml) was added sodium bicarbonate (1.97 g, 23.50 mmol) and hydroxylamine hydrochloride (1.63 g, 23.5 mmol) . The mixture was stirred at 50 °C for 12 hrs. The suspension was quenched with NH_4Cl (100 mL) and extracted with EA (200 mL $\times$ 3) . The combined organic layers were washed with brine (50 mL $\times$ 2) , dried over Na_2SO_4 , filtered and concentrated to give int-50-14 (2.00 g, 93%yield) . LCMS: 458.7 $[\text{M} + \text{H}]^+$. Step 14: int-50-15

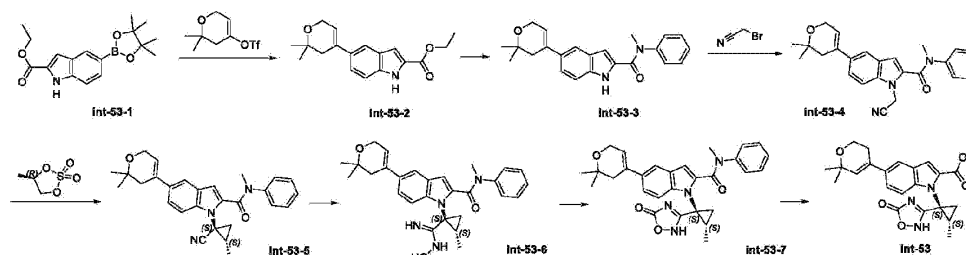
[0185] To a solution of int-50-14 (1.50 g, 3.27 mmol) in DMSO (15 ml) was added CDI (1.59 g, 9.81 mmol) and DBU (1.48 ml, 9.81 mmol). The mixture was stirred at 25 °C for 12 hrs. The mixture reaction was quenched with H₂O (100 mL) and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (25 mL × 2), dried over Na₂SO₄, filtered and concentrated to give int-50-15 (1.00 g, 63% yield). LCMS: 485.2 [M+H]⁺. Step 15: int-50

[0186] To a solution of int-50-15 (500 mg, 1.03 mmol) in n-PrOH was added KOH (579 mg, 10.32 mmol). The mixture was stirred at 90 °C for 5 hrs. The reaction was adjusted pH = 2 with 2 N HCl aq. The mixture extracted with EA (50 mL × 3). The combined organic layers were washed with brine (25 mL × 2), dried over Na₂SO₄, filtered and concentrated to afford int-50 (186.9 mg, 42% yield). LCMS: 394.1 [M+H]⁺. Example ak: Synthesis of int-51, int-52, int-53 and int-53-P2



[0187] The synthesis of int-51 was referred to intermediate 46-P1 of WO2022017338.

[0188] The synthesis of int-52 was referred to intermediate 46-P2 of WO2022017338.



Step 1: int-53-2

[0189] To a solution of int-53-1 (20.00 g, 63.50 mmol) in 1,4-dioxane (300 mL) and water (30 mL) was added 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (19.82 g, 76.00 mmol), Pd(dppf)Cl₂ (2.32 g, 3.17 mmol) and potassium carbonate (17.54 g, 127.00 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 100 °C for 2 hrs under N₂. After cooling to room temperature, the mixture was poured into 500 mL of water and extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-53-2 (11.45 g, 38.20 mmol, 60.3% yield). LC-MS (ESI⁺): m/z 300.1 (M+H)⁺. ¹H NMR (400 MHz, Chloroform-d) δ 9.05 (s, 1H), 7.68 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.26–7.15 (m, 1H), 6.12 (s, 1H), 4.44 (q, J = 8.0 Hz,

2H) , 4.41 –4.37 (m, 2H) , 2.58 –2.43 (m, 2H) , 1.45 (t, J = 8.0 Hz, 3H) , 1.40 –1.35 (m, 6H) .Step 2: int-53-3

[0190] To a solution of int-53-2 (4.10 g, 13.70 mmol) and N-methylaniline (3.70 mL, 34.20 mmol) in toluene (80 mL) was added trimethylaluminium (20.54 mL, 2 M in toluene) dropwise at 0 °C. The resulting mixture was stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched by cold H₂O (100 mL) at 0 °C and extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with H₂O (100 mL × 2) , followed by brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-53-3 (3.60 g, 9.99 mmol, 72.9%yield) . LC-MS (ESI+) : m/z 361.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 11.58 (s, 1H) , 7.51 -7.44 (m, 3H) , 7.41 -7.36 (m, 2H) , 7.35 -7.26 (m, 3H) , 6.09 -6.03 (m, 1H) , 5.33 –5.16 (m, 1H) , 4.20 -4.14 (m, 2H) , 3.38 (s, 3H) , 2.31 -2.25 (m, 2H) , 1.17 (s, 6H) .Step 3: int-53-4

[0191] To a solution of int-53-3 (1.80 g, 4.99 mmol) in DMF (36 mL) was added NaH (499.0 mg, 12.48 mmol, 60%purity) in portions at 0 °C. After being stirred at 25 °C for 1 hr, 2-bromoacetonitrile (0.70 mL, 9.99 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3) . The organic phase was separated, washed with H₂O (50 mL × 2) , brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-53-4 (1.70 g, 4.26 mmol, 85%yield) . LC-MS (ESI+) : m/z 400.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.62 (d, J = 8.0 Hz, 1H) , 7.52 -7.40 (m, 3H) , 7.37 -7.35 (m, 3H) , 7.31 -7.26 (m, 1H) , 6.19 –6.06 (m, 1H) , 5.99 (s, 1H) , 5.65 (s, 2H) , 4.24 -4.15 (m, 2H) , 3.44 (s, 3H) , 2.34 -2.28 (m, 2H) , 1.19 (s, 6H) .Step 4: int-53-5

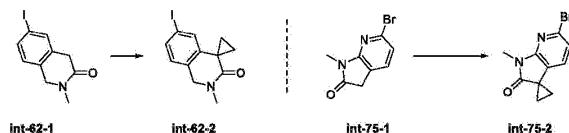
[0192] To a solution of int-53-4 (1.70 g, 4.26 mmol) and (R) -4-methyl-1, 3, 2-dioxathiolane 2, 2-dioxide (1.47 g, 10.64 mmol) in THF (34 mL) was added LiHMDS (17.02 mL, 1 M in THF) dropwise at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 1 hr. After completion, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with water (100 mL) , followed by brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-53-5 (1.45 g, 3.30 mmol, 78%yield) . LC-MS (ESI+) : m/z 440.1 (M+H)⁺.Step 5: int-53-6

[0193] To a solution of int-53-5 (1.45 g, 3.30 mmol) and hydroxylamine hydrochloride (688.0 mg, 9.90 mmol) in EtOH (29 mL) was added K₂CO₃ (912 mg, 6.60 mmol) . The resulting mixture was stirred at 90 °C for 1 hr. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with water (50 mL) , followed

by brine (50 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-53-6 (1.10 g, 2.33 mmol, 70.6%yield). LC-MS (ESI+): m/z 473.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 9.24 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.43 -7.32 (m, 4H), 7.31 -7.22 (m, 3H), 6.39 -5.88 (m, 4H), 4.34 -4.07 (m, 2H), 3.47 (s, 3H), 2.35 -2.25 (m, 2H), 1.75 -1.65 (m, 1H), 1.63 -1.58 (m, 1H), 1.21 -1.13 (m, 9H), 1.03 -0.95 (m, 1H). Step 6: int-53-7

[0194] To a solution of int-53-6 (1.070 g, 2.26 mmol) and DBU (1.03 mL, 6.79 mmol) in Dioxane (10 mL) was added CDI (1.10 g, 6.79 mmol). The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with water (50 mL $\times$ 2), followed by brine (50 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-53-7 (1.05 g, 2.11 mmol, 93.0%yield). LC-MS (ESI+): m/z 499.2 (M+H)⁺. Step 7: int-53 and int-53-P2

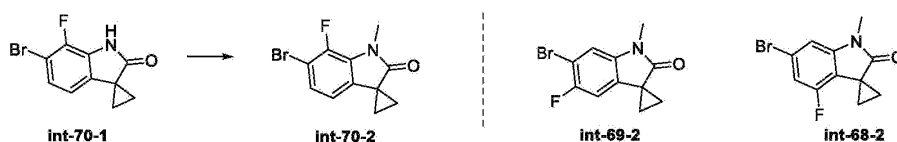
[0195] To a solution of int-53-7 (1.00 g, 2.01 mmol) in *t*-BuOK in THF (20.06 mL, 1 M in THF) was added H_2O (0.04 mL, 2.01 mmol). The resulting mixture was stirred at 25 °C for 12 hrs. After completion, the reaction mixture was poured into water (50 mL), acidified by HCl (2 N) to adjusted pH $\sim$ 1 and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 , filtered, concentrated and purified by SFC (ChiralCel OJ, 250*30 mm I.D., 10 μm ; Mobile Phase [A%: CO_2 ; B%: 25 %MeOH; Flow rate: 120 mL /min; Back pressure: 100 bar; Column temperature: 38 °C) to afford two isomers (int-53, int-53-P2). LC-MS (ESI+): m/z 410.1 (M+H)⁺. Int-53: (186.0 mg, 0.45 mmol, 22.65%yield). ¹H NMR (400 MHz, DMSO- d_6) δ 12.32 (brs, 1H), 7.72 -7.68 (m, 1H), 7.53 -7.46 (m, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.24 -7.21 (m, 1H), 6.09 (d, J = 8.0 Hz, 1H), 3.88 -3.79 (m, 2H), 2.44 -2.37 (m, 2H), 2.03 -1.89 (m, 1H), 1.84 -1.73 (m, 1H), 1.69 -1.51 (m, 1H), 1.43 -1.25 (m, 9H). Int-53-P2: (454 mg, 1.11 mmol, 55.3%yield). ¹H NMR (400 MHz, DMSO- d_6) δ 12.28 (brs, 1H), 7.71 -7.67 (m, 1H), 7.56 -7.47 (m, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 4.0 Hz, 1H), 6.25 -6.08 (m, 1H), 4.29 -4.19 (m, 2H), 2.40 -2.34 (m, 2H), 2.02 -1.88 (m, 1H), 1.83 -1.74 (m, 1H), 1.69 -1.52 (m, 1H), 1.42 -1.25 (m, 3H), 1.23 (d, J = 4.0 Hz, 6H). Example al: Synthesis of int-62-2, int-75-2



[0196] To a solution of int-62-1 (220.0 mg, 0.77 mmol) in DMF (2 mL) was added diphenyl (vinyl) sulfonium trifluoromethanesulfonate (417.0 mg, 1.15 mmol) and zinc (50.0 mg, 0.77 mmol), followed by DBU (350 mg, 2.23 mmol) was added dropwise at 0 °C.

The resulting mixture was stirred at 25 °C under nitrogen atmosphere for 12 hrs. After completion, the reaction mixture was poured into ice water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-62-2 (29.0 mg, 0.09 mmol, 12.1 %yield). LC-MS (ESI+) : m/z 314.0 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.05 (d, J = 8.0 Hz, 1H), 4.66 (s, 2H), 3.02 (s, 3H), 1.66 – 1.59 (m, 2H), 1.28 – 1.24 (m, 2H).

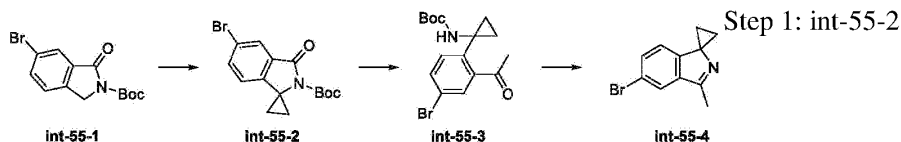
[0197] Int-75-2 was prepared following the procedure for int-62-2. LC-MS (ESI+) : m/z 253.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.38 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 3.20 (s, 3H), 1.77 – 1.71 (m, 2H), 1.63 – 1.56 (m, 2H). Example am: Synthesis of int-70-2, int-69-2, int-68-2



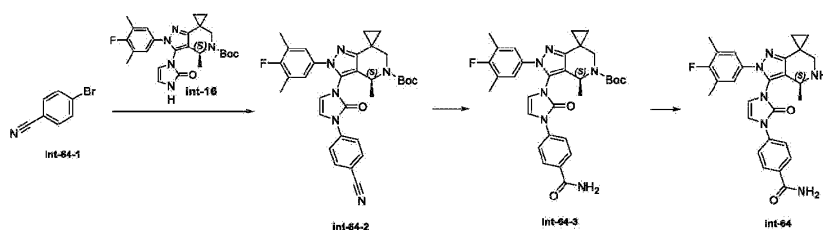
[0198] To a solution of int-70-1 (1.07 g, 4.18 mmol) in DMF (5 mL) were added Cs₂CO₃ (2.04 g, 6.27 mmol) and MeI (0.34 mL, 5.43 mmol). The resulting mixture was stirred at 50 °C for 1 hr. After cooling to room temperature, the reaction mixture was poured into 20 mL of water and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with water (20 mL × 2), followed by brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-70-2 (850.0 mg, 3.15 mmol, 75.0%yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.31 – 7.23 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 3.38 (d, J = 4.0 Hz, 3H), 1.73 – 1.66 (m, 2H), 1.60 – 1.54 (m, 2H). Int-69-2, int-68-2 was prepared following the procedure for int-70-2.

[0199] Int-69-2 was obtained in 70.6%yield (400.0 mg, 1.41 mmol). ¹H NMR (400 MHz, DMSO-d₆) δ 7.41 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 3.20 (s, 3H), 1.72 – 1.66 (m, 2H), 1.59 – 1.52 (m, 2H).

[0200] Int-68-2 was obtained in 91.0%yield (530.0 mg, 1.96 mmol). LC-MS (ESI+) : m/z 270.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.25 (s, 1H), 7.14 (d, J = 8.0 Hz, 1H), 3.20 (s, 3H), 1.86 – 1.74 (m, 2H), 1.58 – 1.48 (m, 2H). Example ao: Synthesis of int-55-4



- [0201] To a solution of int-55-1 (5.00 g, 16.02 mmol) in DMSO (75 mL) was added DBU (7.3 mL, 48.10 mmol) and diphenyl (vinyl) sulfonium trifluoromethanesulfonate (11.6 g, 32.0 mmol). The resulting mixture was stirred at 80 °C for 4 hrs. After cooling to room temperature, the reaction mixture was poured into 400 mL of water and extracted with EtOAc (200 mL × 3). The combined organic layers were washed water (300 mL × 2), followed by brine (300 mL), dried over Na₂SO₄, filtered, concentrated and purified by column to afford int-55-2 (850.0 mg, 2.51 mmol, 15.7% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.92 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 2.22–2.12 (m, 2H), 1.50 (s, 9H), 1.41–1.33 (m, 2H). Step 2: int-55-3
- [0202] To a solution of int-55-2 (600.0 mg, 1.77 mmol) in THF (6 mL) was added methyllithium (1.22 mL, 1.95 mmol) dropwised at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 16 hrs under N₂. After completion, the reaction mixture was quenched by 50 mL of water and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-55-3 (500.0 mg, 1.41 mmol, 80.0% yield). Step 3: int-55-4
- [0203] A solution of int-55-3 (400.0 mg, 1.13 mmol), TMSOTf (4.5 mL, 19.37 mmol) and 2, 6-lutidine (0.40 mL, 3.39 mmol) in DCM (10 mL) was stirred at 25 °C for 2 hrs under N₂. After completion, the reaction mixture was diluted with dichloromethane (50 mL) and washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-55-4 (250.0 mg, 0.98 mmol, 87.0% yield). LC-MS (ESI+) : m/z=236.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H), 1.95-1.92 (m, 2H), 1.81-1.77 (m, 2H). Example ap: Synthesis of int-64



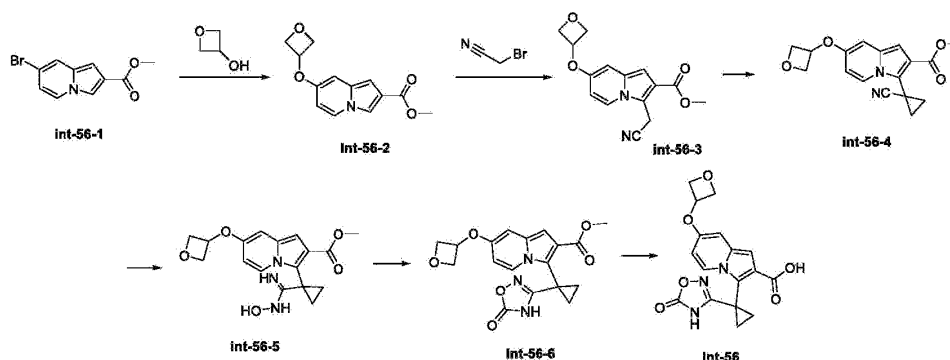
int-64-2

- [0204] To a solution of int-16 (300.0 mg, 0.64 mmol) and int-64-1 (117.0 mg, 0.64 mmol) in 1, 4-dioxane (3 mL) were added (1R, 2R) -N¹, N²-dimethylcyclohexane-1, 2-diamine (37.0 mg, 0.26 mmol), CuI (25.0 mg, 0.13 mmol) and Cesium carbonate (627.0 mg, 1.93 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 110 °C for 12 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was poured into 10 mL of water and extracted with EtOAc (10 mL × 3).

The combined organic layers were washed with water (10 mL $\times$ 2), followed by brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-64-2 (336.0 mg, 0.59 mmol, 92.0 %yield). LC-MS (ESI⁺): m/z 569.2 (M+H)⁺. Step 2: int-64-3

[0205] To a solution of int-64-2 (336.0 mg, 0.59 mmol) in MeOH (3 mL) and water (1 mL) were added NaOH (118.0 mg, 2.95 mmol), followed by H₂O₂ (3 mL, 29.38 mmol) dropwise. The resulting mixture was stirred at 25°C for 2 hrs. After completion, the reaction was poured into 30 mL of water and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 2), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-64-3 (260.0 mg, 0.44 mmol, 75.0%yield). LC-MS (ESI⁺): m/z 587.4 (M+H)⁺. Step 3: int-64

[0206] To a mixture of int-64-3 (380.0 mg, 0.65 mmol) in DCM (5 mL) was added HCl solution (5 mL, 4 M in EtOAc). The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated to give a residue that was diluted with MeOH (10 mL) and ammonia solution (2 mL, 7 M in methanol) was added. The organic layer was concentrated to afford int-64 (410 mg, crude), which was used directly for the next step. LC-MS (ESI⁺): m/z 487.2 (M+H)⁺. Example aq: Synthesis of int-56



Step 1: int-56-2

[0207] To a solution of int-56-1 (1.00 g, 3.94 mmol) in dioxane (10 ml) were added oxetan-3-ol (1.46 g, 19.68 mmol), Cs₂CO₃ (3.85 g, 11.81 mmol), CuI (0.15 g, 0.79 mmol) and (1R, 2R) -N¹, N²-dimethylcyclohexane-1, 2-diamine (0.22 g, 1.57 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 110°C for 18 hrs. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with water (100 mL $\times$ 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford

int-56-2 (200.0 mg, 6.30 mmol, 20.0%yield) . LC-MS (ESI+) : m/z 248.1 (M+H)
+.Step 2: int-56-3

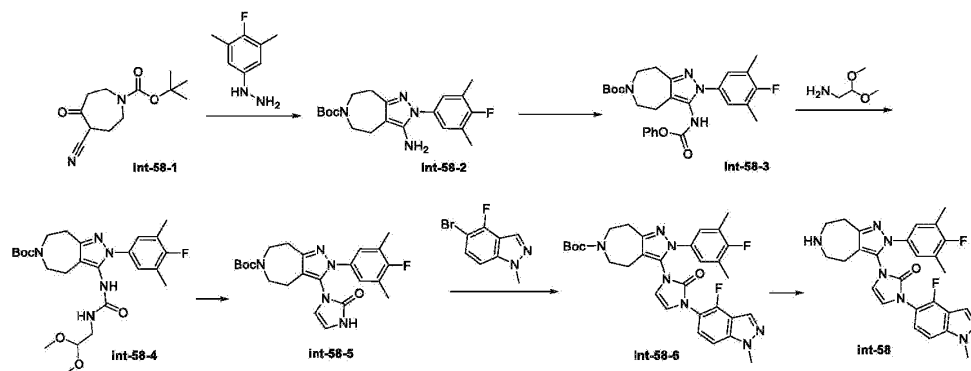
[0208] To a solution of int-56-2 (250.0 mg, 1.01 mmol) and 2-bromoacetonitrile (133.0 mg, 1.11 mmol) in DMSO (3 mL) and water (0.6 mL) were added sodium iodide (152.0 mg, 1.01 mmol) and iron (II) sulfate heptahydrate (141.0 mg, 0.51 mmol) , followed by hydrogen peroxide (0.124 ml, 1.213 mmol) dropwise below 10 °C. The resulting mixture was stirred at 5 °C for 1 hr. After completion, the reaction mixture was poured into 30 mL of cold water and stirred for 10 mins. After being filtered, the cake was rinsed with water (3 mL × 3) and dissolved in 20 mL DCM. The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-56-3 (370.0 mg, 1.29 mmol, 49.2%yield) . LC-MS (ESI+) : m/z 287.1 (M+H) .Step 3: int-56-4

[0209] To a solution of int-56-3 (370.0 mg, 1.29 mmol) in DMSO (7 mL) was added DBU (0.40 mL, 2.58 mmol) and diphenyl (vinyl) sulfonium trifluoromethanesulfonate (703.0 mg, 1.94 mmol) . The resulting mixture was stirred at 15 °C for 1 hr. After completion, the reaction mixture was poured into 50 mL of water and extracted with EtOAc (20 mL × 3) . The combined organic layers were washed with brine (20 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-56-4 (350.0 mg, 1.12 mmol, 87.0%yield) . LC-MS (ESI+) : m/z 313.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.36 (d, J = 8.0 Hz, 1H) , 6.76–6.62 (m, 2H) , 6.57 (s, 1H) , 5.39–5.24 (m, 1H) , 4.96 (t, J = 8.0 Hz, 2H) , 4.62–4.49 (m, 2H) , 3.84 (s, 3H) , 1.98–1.92 (m, 2H) , 1.50–1.37 (m, 2H) .Step 4: int-56-5To a solution of int-56-4 (350.0 mg, 1.12 mmol) in ethanol (7 mL) was added TEA (0.24 mL, 1.68 mmol) and hydroxylamine hydrochloride (93.0 mg, 1.35 mmol) . The resulting mixture was stirred at 90 °C for 4 hrs. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, diluted with 10 mL water, acidified with HCOOH to pH~4 and extracted with EtOAc (20 mL × 3) . The combined organic layers were washed with brine (20 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-56-5 (270.0 mg, 0.78 mmol, 69.8%yield) . LC-MS (ESI+) : m/z 346.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.06 (s, 1H) , 8.24 (d, J = 8.0 Hz, 1H) , 6.59 (d, J = 8.0 Hz, 1H) , 6.54 (s, 1H) , 6.46 (s, 1H) , 5.32 (s, 2H) , 5.30–5.23 (m, 1H) , 4.98–4.89 (m, 2H) , 4.58–4.49 (m, 2H) , 3.82 (s, 3H) , 1.69–1.32 (m, 2H) , 1.10–0.63 (m, 2H) .Step 5: int-56-6

[0210] To a solution of int-56-5 (250.0 mg, 0.72 mmol) in DMSO (5 mL) was added DBU (0.22 mL, 1.45 mmol) and 1, 1'-carbonyldiimidazole (235.0 mg, 1.45 mmol) . The resulting mixture was stirred at 20 °C for 1 hr. After completion, the reaction mixture was poured into 50 mL of water and acidified with diluted HCl (2 M aqueous) to pH~

4 and extracted with EtOAc (10 mL $\times$ 4). The combined organic layers were washed with water (20 mL $\times$ 2), followed by brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford int-56-6 (270.0 mg, crude), which was used directly for the next step without purification. LC-MS (ESI⁺): m/z 372.2 (M+H)⁺. Step 6: int-56

[0211] To a solution of int-56-6 (250.0 mg, 0.67 mmol) in MeOH (3 mL) and water (0.6 mL) was added LiOH (81.0 mg, 3.37 mmol). The resulting mixture was stirred at 50 °C for 8 hrs. After cooling to room temperature, the reaction mixture was poured into 10 ml of water, acidified by diluted HCl (2 M aqueous) to pH $\sim$ 3 and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with water (10 mL $\times$ 2), followed by brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford int-56 (200.0 mg, crude), which was used directly for the next step without purification. LC-MS (ESI⁺): m/z 358.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 12.11 (brs, 1H), 8.23 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 6.57 – 6.51 (m, 2H), 5.29 (p, J = 4.0 Hz, 1H), 4.97 (t, J = 8.0 Hz, 2H), 4.61 – 4.52 (m, 2H), 1.86 – 1.76 (m, 2H), 1.60 – 1.43 (m, 1H), 1.39 – 1.26 (m, 1H). Example ar: Synthesis of int-58

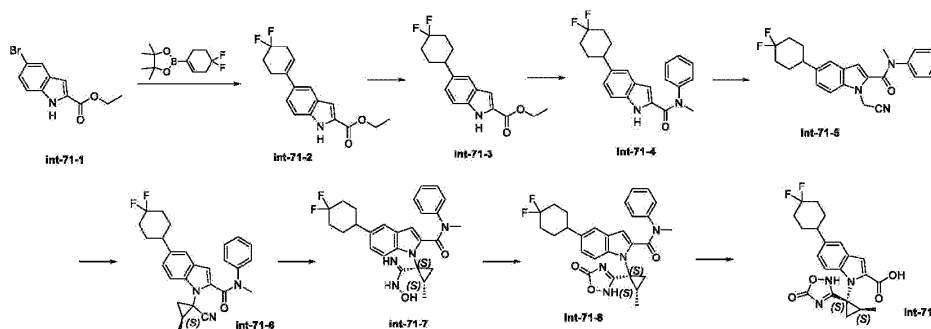


Step 1: int-58-2

[0212] To a solution of int-58-1 (110 mg, 0.462 mmol) in EtOH (2 mL) was added H_2O (41.0 mg, 2.31 mmol) and (4-fluoro-3,5-dimethylphenyl) hydrazine (85.0 mg, 0.554 mmol). The mixture was stirred at 80 °C under N_2 for 12 hr. The reaction mixture was diluted with EA (50 mL) and washed with brine (30 mL) for three times. The organic layer was concentrated and purified by flash chromatography to give int-58-2 (140 mg, 81% yield). LC-MS: [ESI] [M+1]⁺ = 375.4. Step 2: int-58-3

[0213] To a solution of int-58-2 (970 mg, 2.59 mmol) in THF (12 mL) was added phenyl chloroformate (608 mg, 3.89 mmol) and DIEA (0.905 mL, 5.18 mmol) at 25 °C. The reaction was stirred at 30 °C for 2 hr. The mixture was concentrated to give int-58-3 (1.00 g, 78% yield). LC-MS: [ESI] [M-56]⁺ = 439.2. Step 3: int-58-4

- [0214] To a solution of int-58-3 (1.00 g, 2.02 mmol) in pyridine (10 mL) was added 2, 2-dimethoxyethan-1-amine (0.425 g, 4.04 mmol) at 25°C. The reaction was stirred at 50°C for 2 hrs. The mixture was diluted with H₂O (10 mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried, filtered, concentrated and purified by column chromatography to give int-58-4 (300 mg, 29%yield). LC-MS: [ESI] [M+H]⁺ = 506.4. Step 4: int-58-5
- [0215] To a solution of int-58-4 (300 mg, 0.593 mmol) in THF (4ml) was added 4-methylbenzenesulfonic acid (82.0 mg, 0.475 mmol) at 25°C. The reaction was stirred at 60°C for 1 hr. The mixture was diluted with H₂O (10 mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried, filtered, concentrated and purified by column chromatography to give int-58-5 (222 mg, 83%yield). LC-MS: [ESI] [M+H]⁺ = 386.2. ¹H NMR (400 MHz, CD₃OD) δ 7.04 (d, J = 6.4 Hz, 2H), 6.51 (d, J = 3.0 Hz, 1H), 6.40 (d, J = 2.8 Hz, 1H), 3.60–3.55 (m, 4H), 2.98–2.84 (m, 2H), 2.59–2.43 (m, 2H), 2.22–2.20 (m, 6H), 1.51–2.45 (m, 9H). Step 5: int-58-6
- [0216] To a solution of int-58-5 (200.0 mg, 0.45 mmol) in NMP (3 mL) were added 5-bromo-4-fluoro-1-methyl-1H-indazole (208 mg, 0.91 mmol), (1R, 2R)-N¹, N²-dimethylcyclohexane-1, 2-diamine (64.0 mg, 0.45 mmol), copper (I) iodide (173.0 mg, 0.91 mmol) and K₂CO₃ (188.0 mg, 1.36 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 130 °C under N₂ for 2 hrs. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with water (50 mL x 2), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-58-6 (220.0 mg, 0.37 mmol, 82.0%yield). LC-MS (ESI⁺): m/z 590.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.45–7.39 (m, 1H), 7.08 (d, J = 4.0 Hz, 2H), 7.01 (d, J = 4.0 Hz, 1H), 6.84 (d, J = 4.0 Hz, 1H), 4.10 (s, 3H), 3.65–3.44 (m, 4H), 2.95–2.84 (m, 2H), 2.56–2.52 (m, 2H), 2.23 (s, 6H), 1.45 (s, 9H). Step 6: int-58
- [0217] A mixture of int-58-6 (220.0 mg, 0.37 mmol) in HCl solution (4 M in dioxane, 6 mL) was stirred at 20 °C for 1 hr. After completion, the reaction mixture was concentrated to give a residue that was diluted with DCM (50 mL) and washed with saturated NaHCO₃ (aq, 50 mL). The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford int-58 (150.0 mg, 0.31 mmol, 82.0%yield). LC-MS (ESI⁺): m/z 490.3 (M+H)⁺. Example as: Synthesis of int-71



Step 1: int-71-2

[0218] To a solution of int-71-1 (3.00 g, 11.19 mmol) in 1, 4-dioxane (60 mL) and water (6 mL) were added 2- (4, 4-difluorocyclohex-1-en-1-yl) -4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolane (4.10 g, 16.78 mmol) , PdCl₂ (dppf) (819.0 mg, 1.12 mmol) and K₂CO₃ (4.64 g, 33.60 mmol) . The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with H₂O (100 mL × 2) , followed by brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-71-2 (2.40 g, 7.86 mmol, 70.2%yield) . LC-MS (ESI+) : m/z 306.1 (M+H)⁺ . ¹H NMR (400 MHz, DMSO-d₆) δ 11.87 (s, 1H) , 7.68 (s, 1H) , 7.44 -7.38 (m, 2H) , 7.13 (s, 1H) , 6.07 -5.78 (m, 1H) , 4.33 (q, J = 8.0 Hz, 2H) , 2.79 -2.66 (m, 4H) , 2.27 -2.13 (m, 2H) , 1.34 (t, J = 8.0 Hz, 3H) .Step 2: int-71-3

[0219] To a solution of int-71-2 (2.40 g, 7.86 mmol) in MeOH (72 mL) was added Pd/C (240 mg, 10%w/w.) . The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 2 hrs under H₂ atmosphere (15 psi) . After completion, the reaction mixture was filtered through a celite and resined with MeOH (10 mL × 3) . the filtrate was concentrated under reduced pressure to afford int-71-3 (2.5 g, crude) , which was used directly for the next step without purification. LC-MS (ESI+) : m/z 306.0 (M-H)⁻ .Step 3: int-71-4

[0220] To a solution of int-71-3 (2.50 g, 8.13 mmol) in toluene (50 mL) was added N-methylaniline (2.20 mL, 20.34 mmol) and trimethylaluminium (12.20 mL, 24.40 mmol) dropwisely at 0 °C under N₂ atmosphere and stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into ice-water (50 mL) , The mixture was filtered through a Celite pad and rinsed with EtOAc (10 mL × 2) . The filtrate was extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with water (100 mL × 2) , followed by brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chro-

matography to afford int-71-4 (2.70 g, 7.3 mmol, 90%yield) . LC-MS (ESI+) : m/z 369.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 11.47 (s, 1H) , 7.52 -7.41 (m, 3H) , 7.40 -7.34 (m, 2H) , 7.33 -7.28 (m, 1H) , 7.14 -7.09 (m, 1H) , 7.03 (dd, J = 8.0, 4.0 Hz, 1H) , 5.22 (s, 1H) , 3.38 (s, 3H) , 2.71 -2.57 (m, 1H) , 2.14 -2.00 (m, 2H) , 1.98 -1.75 (m, 4H) , 1.70 -1.53 (m, 2H) .Step 4: int-71-5

[0221] To a solution of int-71-4 (2.70 g, 7.33 mmol) in DMF (68 mL) were added NaH (733.0 mg, 18.32 mmol) in portions at 0°C under N₂ atmosphere. The mixture was stirred at 25 °C for 1 hr and then 2-bromoacetonitrile (1.02 mL, 14.66 mmol) was added dropwise at 0°C. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was poured into ice-water (50 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with H₂O (50 mL × 2) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-71-5 (2.82 g, 6.92 mmol, 94.0%yield) . LC-MS (ESI+) : m/z 408.2 (M+H)⁺.Step 5: int-71-6

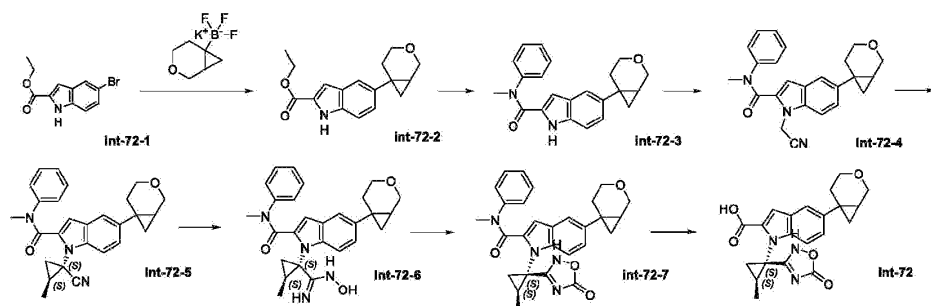
[0222] To a solution of int-71-5 (2.72 g, 6.68 mmol) and (R) -4-methyl-1, 3, 2-dioxathiolane 2, 2-dioxide (2.31 g, 16.69 mmol) in THF (54.0 mL) was added LiHMDS (27.0 mL, 1 M in THF) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hr under N₂ atmosphere. After completion, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with water (50 mL × 2) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-71-6 (1.73 g, 3.87 mmol, 57.9%yield) . LC-MS (ESI+) : m/z 448.2 (M+H)⁺.Step 6: int-71-7

[0223] To a solution of int-71-6 (1.7.0 g, 3.80 mmol) and hydroxylamine hydrochloride (792.0 mg, 11.40 mmol) in EtOH (34 mL) were added K₂CO₃ (1.05 g, 7.60 mmol) . The resulting mixture was stirred at 90 °C for 3 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3) . The combined organic layers were washed with water (50 mL × 2) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-71-7 (960.0 mg, 2.00 mmol, 52.6%yield) . LC-MS (ESI+) : m/z 481.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.22 (s, 1H) , 7.56 (d, J = 8.0 Hz, 1H) , 7.41 -7.32 (m, 2H) , 7.30 -7.17 (m, 4H) , 7.10 (d, J = 8.0 Hz, 1H) , 6.63 -5.63 (m, 3H) , 3.46 (s, 3H) , 2.73 -2.61 (m, 1H) , 2.12 -2.00 (m, 2H) , 1.97 -1.76 (m, 4H) , 1.72 -1.55 (m, 4H) , 1.17 -1.14 (m, 3H) , 1.01 -0.96 (m, 1H) .Step 7: int-71-8

[0224] To a solution of int-71-7 (930.0 mg, 1.94 mmol) and DBU (0.88 mL, 5.81 mmol) in dioxane (9.3 mL) were added CDI (941.0 mg, 5.81 mmol) . The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction mixture was

poured into water (50 mL), acidified by diluted HCl solution (2 M aqueous) to pH ~ 3 and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (50 mL × 2), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-71-8 (760.0 mg, 1.50 mmol, 78% yield). LC-MS (ESI⁺): m/z 507.2 (M+H)⁺. Step 8: int-71

[0225] To a solution in int-71-8 (730mg, 1.44 mmol) in tBuOK in THF (14.44 mL, 1 M in THF) was added water (26.0 mg, 1.44 mmol). The resulting mixture was stirred at 25 °C for 12 hrs. After completion, the reaction mixture was poured into cold water (40 mL) and extracted with EtOAc (20 mL × 2). The aqueous layer was acidified by diluted HCl (3 M aqueous) to pH=2 and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford int-71 (560.0 mg, 1.34 mmol, 93.0% yield). LC-MS (ESI⁺): m/z 416.0 (M-H)⁻. ¹H NMR (400 MHz, DMSO-d₆) δ 12.38 (brs, 1H), 7.57-7.51 (m, 1H), 7.38-7.32 (m, 1H), 7.31-7.23 (m, 1H), 7.20-7.14 (m, 1H), 2.85-2.72 (m, 1H), 2.17-2.00 (m, 3H), 1.98-1.84 (m, 4H), 1.82-1.52 (m, 4H), 1.41-1.38 (m, 1H), 1.29-1.22 (m, 2H). Example at: Synthesis of int-72



Step 1: int-72-2

[0226] To a solution of potassium trifluoro ({3-oxabicyclo [4.1.0] heptan-6-yl}) boranuide (1.98 g, 9.70 mmol, WO2022238335) and int-72-1 (2.60 g, 9.70 mmol) in toluene (26 mL) were added 1, 1'-bis(diphenylphosphino) ferrocene-palladium (II) dichloride dichloromethane complex (1.19 g, 1.46 mmol), Cs₂CO₃ (9.48 g, 29.1 mmol) and water (2.60 mL). The resulting mixture was degassed and purged with N₂ for three times and stirred at 90 °C for 16 hrs. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-2 (1.38 g, 4.35 mmol, 44.9% yield). LC-MS (ESI⁺): m/z 284.0 (M-H)⁻. ¹H NMR (400 MHz, DMSO-d₆) δ 11.76 (s, 1H), 7.51 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 4.33 (q, J = 8.0 Hz, 2H), 4.02 (dd, J =

12.0, 4.0 Hz, 1H), 3.82 (d, J = 12.0 Hz, 1H), 3.53–3.42 (m, 1H), 3.42–3.38 (m, 1H), 2.12–2.02 (m, 1H), 1.98–1.90 (m, 1H), 1.38–1.30 (m, 4H), 1.04–0.97 (m, 1H), 0.86–0.81 (m, 1H). Step 2: int-72-3

[0227] To a solution int-72-2 (1.28 g, 4.49 mmol) and N-methylaniline (1.2 mL 11.21 mmol) in toluene (26 mL) was added trimethylaluminium (6.73 mL, 2 M in toluene) dropwise at 0 °C under N₂ atmosphere and stirred at 90 °C for 2 hrs. After cooling to room temperature, the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (50 mL), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-3 (1.38 g, 3.78 mmol, 84.0% yield). LC-MS (ESI+) : m/z 347.1 (M+H)⁺. Step 3: int-72-4

[0228] To a solution of int-72-3 (1.30 g, 3.75 mmol) in DMF (25 mL) was added NaH (375.0 mg, 9.38 mmol, 60% purity) in portions at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 1 hr and then 2-bromoacetonitrile (900.0 mg, 7.51 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was poured into cold water (100 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-4 (890.0 mg, 2.19 mmol, 58.5% yield). LC-MS (ESI+) : m/z 386.1 (M+H)⁺. Step 4: int-72-5

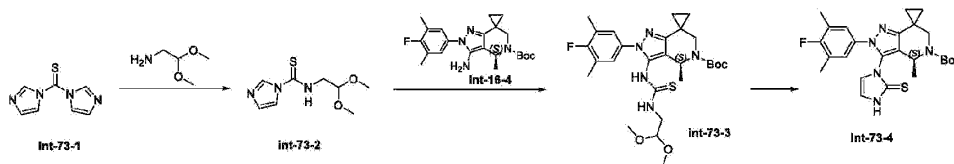
[0229] To a solution of int-72-4 (350.0 mg, 0.91 mmol) and (R)-4-methyl-1,3,2-dioxathiolane 2,2-dioxide (314.0 mg, 2.27 mmol) in THF (10 mL) was added LiHMDS (3.63 mL, 1 M in THF) dropwise at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 1 hr under N₂ atmosphere. After completion, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-5 (250.0 mg, 0.56 mmol, 61.5% yield). LC-MS (ESI+) : m/z 426.2 (M+H)⁺. Step 5: int-72-6

[0230] To a solution of int-72-5 (240.0 mg, 0.56 mmol) in MeOH (3 mL) was added hydroxylamine hydrochloride (118.0 mg, 1.69 mmol) and triethylamine (342.0 mg, 3.38 mmol). The resulting mixture was stirred at 90 °C for 4 hrs. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-6 (200.0 mg, 0.41 mmol, 73.5% yield). LC-MS (ESI+) : m/z 459.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.22 (s, 1H),

7.56 (d, $J = 8.0$ Hz, 1H) , 7.43 –7.08 (m, 8H) , 6.35 –5.88 (m, 2H) , 4.00 –3.90 (m, 1H) , 3.82 –3.74 (m, 1H) , 3.46 (s, 3H) , 3.44 –3.39 (m, 1H) , 2.08 –1.94 (m, 1H) , 1.90 –1.80 (m, 1H) , 1.73 –1.64 (m, 1H) , 1.63 –1.55 (m, 1H) , 1.29 –1.21 (m, 2H) , 1.17 (d, $J = 8.0$ Hz, 3H) , 1.03 –0.89 (m, 2H) , 0.80 –0.73 (q, $J = 4.5$ Hz, 1H) .Step 6: int-72-7

[0231] To a solution of int-72-6 (180.0 mg, 0.39 mmol) in 1, 4-dioxane (1.8 mL) was added CDI (191.0 mg, 1.18 mmol) and DBU (0.18 ml, 1.18 mmol) . The resulting mixture was stirred at 80 °C for 4 hrs. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (30 mL $\times$ 3) . The combined organic layers were washed with water (100 mL $\times$ 2) , followed by brine (100 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-72-7 (160.0 mg, 0.31 mmol, 80.0%yield) . LC-MS (ESI+) : m/z 485.2 (M +H)⁺.Step 7: int-72

[0232] To a solution of int-72-7 (150 mg, 0.310 mmol) t-BuOK in THF (3.1 mL, 1 M in THF) was added water (6.0 mg, 0.33 mmol) . The resulting mixture was stirred at 25 °C for 12 hrs. After completion, the reaction mixture was poured into cold-water (50 mL) and extracted with EtOAc (30 mL $\times$ 2) . The aqueous phase was acidified by diluted HCl solution (1 M aqueous) to pH=4, extracted with EtOAc (30 mL $\times$ 3) . The combined organic layers were washed with water (50 mL $\times$ 2) , followed by brine (50 mL) , dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford int-72 (120.0 mg, 0.30 mmol, 98.0%yield) . LC-MS (ESI+) : m/z 394.0 (M-H)⁻ . ¹H NMR (400 MHz, DMSO-d₆) δ 12.51 (brs, 1H) , 7.56 (s, 1H) , 7.39 –7.27 (m, 2H) , 7.19 –7.08 (m, 1H) , 4.06 –3.98 (m, 1H) , 3.88 –3.78 (m, 1H) , 3.50 –3.44 (m, 2H) , 2.13 –2 . 03 (m, 1H) , 1.98 –1.86 (m, 2H) , 1.82 –1.71 (m, 1H) , 1.65 –1.49 (m, 1H) , 1.41 –1.37 (m, 1H) , 1.35 –1.29 (m, 1H) , 1.25 –1.22 (m, 2H) , 1.03 –0.97 (m, 1H) , 0.87 –0.82 (m, 1H) .Example au: Synthesis of int-73-4



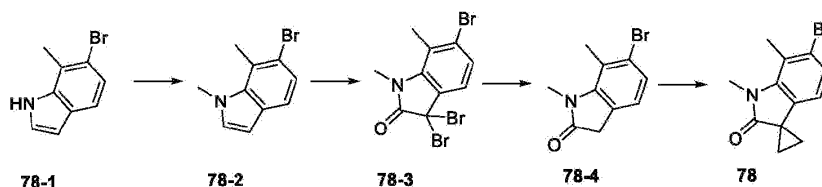
Step 1: int-73-2

[0233] To a solution of int-73-1 (8.48 g, 47.6 mmol) in EtOAc (50 mL) was added a solution of 2, 2-dimethoxyethan-1-amine (5 g, 47.6 mmol) in EtOAc (10 ml) dropwise at 0°C. The resulting mixture was stirred at 25 °C for 4 hrs under N₂. After completion, the reaction mixture was concentrated under reduced pressure and diluted with iPrOAc (60 mL) . The organic layer was washed with brine (60 mL $\times$ 3) , dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford int-73-2 (8.66 g, crude) ,

which was used directly for the next step without purification. LC-MS (ESI+) : m/z 214.0 (M-H)⁻. Step 2: int-73-3

[0234] To a solution of int-16-4 (2.00 g, 4.06 mmol) and int-73-2 (1.748 g, 8.12 mmol) in DMAc (20 mL) was added potassium tert-butoxide (1.82 g, 16.24 mmol). The resulting mixture was stirred at 85 °C for 3 hrs. After cooling to room temperature, the reaction mixture was poured into water (200 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (200 mL × 2), followed by brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-73-3 (1.10 g, 1.63 mmol, 40.2% yield). LC-MS (ESI+) : m/z 548.3 (M+H)⁺. Step 3: int-73-4

[0235] A mixture of int-73-3 (1.10 g, 2.01 mmol) in HCl solution (10 mL, 4 M in 1,4-dioxane) was stirred at 25 °C for 4 hrs. After completion, the mixture was concentrated under reduced pressure to give a residue that was dissolved in THF (10.00 mL). After adding di-tert-butyl dicarbonate (1.865 mL, 8.03 mmol) and potassium hydrogen phosphate (3.50 g, 20.08 mmol), the mixture was stirred at 25 °C for 2 hrs. Then the reaction was poured into water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water (50 mL × 2), followed by brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue that was dissolved in MeOH (10.00 mL) and then K₂CO₃ (2.78 g, 20.08 mmol) was added. The resulting mixture was stirred at 25 °C for 4 hrs and concentrated and purified by column chromatography to afford int-73-4 (630.0 mg, 1.24 mmol, 61.6% yield). LC-MS (ESI+) : m/z 484.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 12.68–12.45 (m, 1H), 7.41–6.95 (m, 4H), 5.40–4.99 (m, 1H), 3.66–3.42 (m, 2H), 2.15 (s, 6H), 1.40 (s, 9H), 1.35–1.30 (m, 1H), 1.26–1.03 (m, 3H), 0.96 (d, J = 2.1 Hz, 2H), 0.89–0.79 (m, 1H). Example aw: Synthesis of int-78



Step 1. Int-78-2

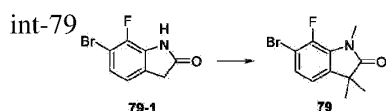
[0236] To a solution of 6-bromo-7-methyl-1H-indole (1.00 g, 4.76 mmol) in DMF (10 mL) was added NaH (286.0 mg, 7.14 mmol, 60% purity) at 0 °C in portions. The mixture was stirred at 25 °C for 0.5 hr. Then MeI (0.36 mL, 5.71 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was quenched by cold water (150 mL) and extracted with ethyl acetate (60 mL × 3). The combined organic layers were washed with water (60 mL × 2), followed by brine

(60 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-78-2 (0.91 g, 4.05 mmol, 85%yield). LC-MS (ESI+): m/z 224.2 (M+H)⁺. ^1H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 4.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 4.05 (s, 3H), 2.81 (s, 3H). Step 2. Int-78-3

[0237] To a solution of int-78-2 (900.0 mg, 4.02 mmol) in t -BuOH (45 mL) was added PyHBr_3 (5.98 g, 12.05 mmol) in portions. The resulting mixture was stirred at 25 °C for 1.5 hrs. After completion, the reaction was poured into H_2O (300 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were washed with water (100 mL $\times$ 3), followed by brine (200 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-78-3 (1.26 g, 3.16 mmol, 79%yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 3.50 (s, 3H), 2.63 (s, 3H). Step 3. Int-78-4

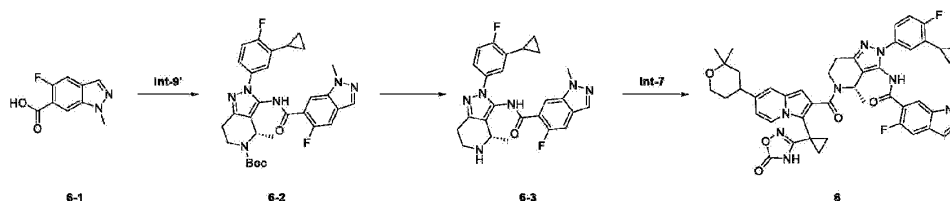
[0238] To a solution of int-78-3 (1.10 g, 2.76 mmol) in MeOH (11 mL) were added zinc (1.81 g, 27.6 mmol), followed by AcOH (0.16 mL, 2.76 mmol). The resulting mixture was stirred at 25 °C for 1 hr. After completion, the reaction mixture was filtered and the filtrate was basified by saturated NaHCO_3 solution (aq., 50 mL) to pH = 8, extracted with ethyl acetate (40 mL $\times$ 3). The combined organic layers were washed with brine (40 mL $\times$ 2), dried over Na_2SO_4 , filtered, concentrated, triturated to afford int-78-4 (582.0 mg, 2.42 mmol, 87%yield). LC-MS (ESI+): m/z 240.2 (M+H)⁺. ^1H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 3.50 (s, 2H), 3.41 (s, 3H), 2.61 (s, 3H). Step 4. Int-78

[0239] To a solution of int-78-4 (580.0 mg, 2.42 mmol) and diphenyl (vinyl) sulfonium trifluoromethanesulfonate (963.0 mg, 2.66 mmol) in DMF (6 mL) were added zinc (158.0 mg, 2.42 mmol) and 1, 8-Diazabicyclo [5, 4, 0] undec-7-ene (1.82 g, 7.25 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the reaction mixture was filtered, poured into H_2O (100 mL), extracted with EtOAc (40 mL $\times$ 3). The combined organic layers were washed with H_2O (40 mL $\times$ 3), followed by brine (40 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford int-78 (533.0 mg, 2.01 mmol, 82.8%yield). LC-MS (ESI+): m/z 266.2 (M+H)⁺. ^1H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 3.51 (s, 3H), 2.66 (s, 3H). Example ax: Synthesis of



[0240] To a solution of potassium tert-butoxide (1.22 g, 10.87 mmol) in THF (15 mL) were added int-79-1 (500.0 mg, 2.17 mmol) and copper (I) bromide-dimethyl

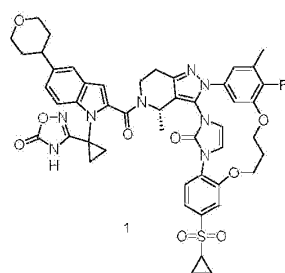
sulfide complex (89.0 mg, 0.44 mmol), followed by iodomethane (1234 mg, 8.69 mmol) dropwised at 5 °C. The resulting mixture was stirred at 25 °C for 12 hrs. After completion, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (60 mL × 2), followed by brine (60 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-79 (260.0 mg, 0.96 mmol, 44.0%yield). LC-MS (ESI+) : m/z 272.1 (M+H)⁺. Example 1.3: Synthesis of Compound 6



Step 1: 6-2

[0241] 6-1 and int-9' were combined to give 6-2 following the procedure for the synthesis of Compound 1. LCMS: 563.2 (M+H)⁺. Synthesis of Compound 1

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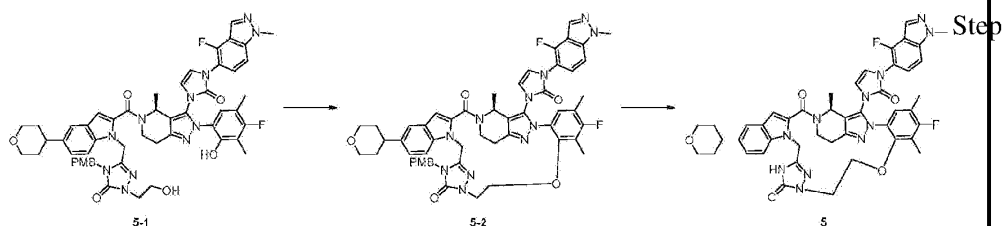
To a suspension of int-1 (11 mg, 0.03 mmol) and int-2 (22 mg,

crude) in THF (5 ml) was added T₃P (13 mg, 0.04 mmol, 50%) and TEA (12 mg, 0.12 mmol). The mixture was stirred at r.t. for 1 hr. The mixture was diluted with water (2 ml), extracted with EtOAc (10 mL × 3). Combined organic layers were dried over Na₂SO₄, filtered, concentrated, and purified by prep-HPLC to afford Compound 1 (6 mg, 6.4 μmol, 21.5% yield). LCMS: 931.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆, 80 °C) δ 11.92 (brs, 1H), 7.81 - 7.62 (m, 2H), 7.56 (td, J = 8.0, 4.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.38 - 7.36 (m, 1H), 7.33 - 7.01 (m, 4H), 7.00 - 6.89 (m, 1H), 6.89 - 6.65 (m, 1H), 5.89 (s, 1H), 5.20 (brs, 1H), 4.39 - 4.01 (m, 5H), 3.92 - 3.88 (m, 2H), 3.42 - 3.38 (m, 2H), 3.15 (brs, 1H), 3.03 - 2.97 (m, 1H), 2.80 - 2.60 (m, 3H), 2.28 - 2.25 (m, 3H), 2.21 - 1.97 (m, 2H), 1.92 - 1.83 (m, 2H), 1.74 - 1.60 (m, 6H), 1.31 - 1.16 (m, 5H), 1.11 - 1.04 (m, 2H). Step 2: 6-3

[0242] To a solution of 6-2 (100 mg, 0.18 mmol) in DCM (1 mL) was added HCl (1 mL, 4.00 mmol, 4.0 M in ethyl acetate). The reaction mixture was then stirred at 25 °C for

1 hr and concentrated to afford crude 6-3 (85 mg, crude) . LCMS: 463.2 (M+H)⁺. Step 3: compound 6

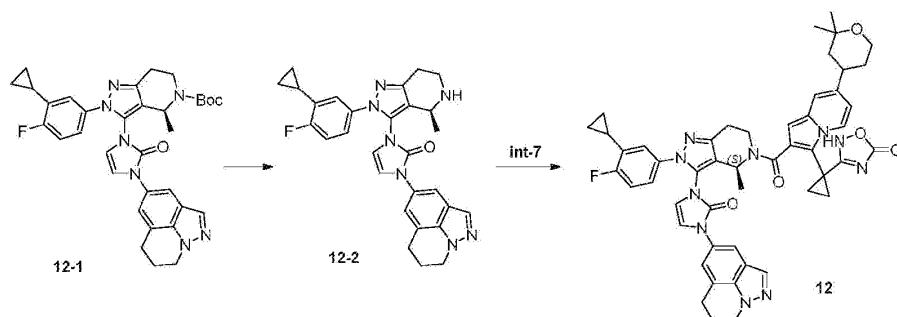
[0243] 6-3 and int-7 were combined following the procedure for the synthesis of 5-1 to give Compound 6. LCMS: 842.3 (M+H)⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 11.86 (s, 1H) , 8.11 (s, 2H) , 7.68 (s, 2H) , 7.57–7.04 (m, 4H) , 6.70 (d, J = 7.1 Hz, 1H) , 6.42 (s, 1H) , 5.73 (d, J = 19.2 Hz, 1H) , 4.10 (s, 4H) , 3.71 (d, J = 8.8 Hz, 2H) , 2.92 (s, 1H) , 1.84–1.08 (m, 20H) , 0.95 (d, J = 8.6 Hz, 2H) , 0.67 (s, 2H) .Synthesis of Compound 5



1: 5-1 To a solution of int-11 (70 mg, 0.14 mmol) and int-8 (63 mg, 0.13 mmol) in DMF (1.4 mL) was added HATU (53 mg, 0.14 mmol) and DIEA (0.08 mL, 0.42 mmol) . The resulting mixture was stirred at 25 °C for 1 hr. The reaction was poured into water (5 mL) and extracted with EtOAc (5 mL × 3) . The combined organic layers were washed with brine (5 mL) , dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford 5-1 (50 mg, 0.50 mmol, 36.2% yield) . LCMS: 994.5 [M+H]⁺. Step 2: 5-2 To a solution of 5-1 (40 mg, 40.2 μmol) in THF (1 mL) was added triphenylphosphine (21 mg, 0.08 mmol) and DIAD (16 mg, 0.08 mmol) at 0 °C. The resulting mixture was stirred at 15 °C for 2 hrs. The reaction was poured into 2 mL water and extracted with EtOAc (5 mL × 3) . The combined organic layers were washed with brine (5 mL) , dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford 5-2 (25 mg, 0.03 mmol, 63.6% yield) . LCMS: 976.5 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 8.26 (s, 1H) , 7.57 (d, J = 8.0 Hz, 1H) , 7.51–7.40 (m, 3H) , 7.38 (s, 1H) , 7.15 (d, J = 8.0 Hz, 1H) , 7.02 (d, J = 8.0 Hz, 2H) , 6.95 (d, J = 4.0 Hz, 1H) , 6.82 (d, J = 4.0 Hz, 1H) , 6.74 (d, J = 8.0 Hz, 2H) , 6.66 (s, 1H) , 5.73 (d, J = 16.0 Hz, 1H) , 5.51–5.38 (m, 2H) , 4.98–4.80 (m, 2H) , 4.41–4.32 (m, 1H) , 4.12–4.02 (m, 4H) , 3.99–3.91 (m, 2H) , 3.90–3.84 (m, 1H) , 3.65 (s, 3H) , 3.48–3.43 (m, 2H) , 3.28–3.24 (m, 2H) , 2.85–2.76 (m, 1H) , 2.68–2.59 (m, 2H) , 2.25 (s, 3H) , 2.18 (s, 1H) , 2.16 (s, 3H) , 1.74–1.67 (m, 4H) , 1.52 (d, J = 4.0 Hz, 3H) . Step 3: Compound 5 To a solution of 5-2 (5 mg, 5.12 μmol) in DCM (0.05 mL) and TFA (0.05 mL) was added trifluoromethanesulfonic acid (1.59 μL, 0.02 mmol) . After addition, the resulting mixture was stirred at 20 °C for 6 hrs. The mixture was diluted with DCM (5 mL) and washed with saturated NaHCO₃ (5 mL × 2) . The organic layer was washed

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with brine (2 mL), dried over Na_2SO_4 , filtered and concentrated to afford Compound 5. LCMS: 856.3 $[\text{M}+\text{H}]^+$. Example 1.4: Synthesis of Compound 12

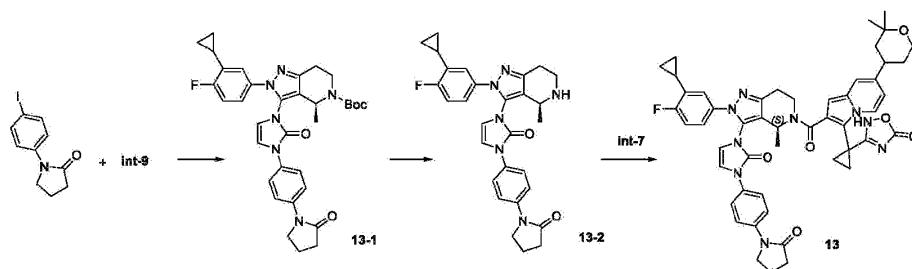


Step 1: 12-1

[0244] To a mixture of int-9 (40 mg, 0.09 mmol, WO-2018056453) and int-12 (42 mg, 0.18 mmol) in NMP (0.2 mL) was added potassium carbonate (37 mg, 0.27 mmol), (1S, 2S)-N1, N2-dimethylcyclohexane-1, 2-diamine (6 mg, 0.044 mmol) and copper (I) iodide (16.8 mg, 0.088 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 135°C for 2 hrs. After cooling to room temperature, the reaction was poured into water (50 mL) and extracted with EtOAc ($100\text{ mL} \times 3$). The combined organic layers were washed with water ($100\text{ mL} \times 3$), followed by brine (100 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford 12-1 (42 mg, 0.07 mmol, 78% yield). LCMS: 610.4 $[\text{M}+\text{H}]^+$. Step 2: 12-2

[0245] A mixture 12-1 (42 mg, 0.069 mmol) in HCl (4 M in dioxane, 1 mL) was stirred at 10°C for 1 hr. The reaction was concentrated to afford 12-2 (25 mg, crude). LCMS: 510.4 $[\text{M}+\text{H}]^+$ Step 3: Compound 12

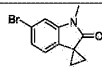
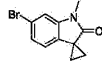
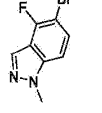
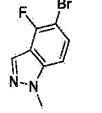
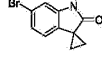
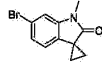
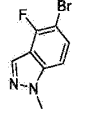
[0246] Int-7 and 12-2 were combined following the procedure for the synthesis of 5-1 to afford Compound 12. LCMS: 889.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.85 (brs, 1H), 8.12 (d, $J=8.0\text{ Hz}$, 1H), 8.00 (s, 1H), 7.70 (brs, 1H), 7.39-7.10 (m, 4H), 7.07-6.81 (m, 2H), 6.70 (d, $J=8.0\text{ Hz}$, 1H), 6.41 (s, 1H), 5.87-5.56 (m, 1H), 5.17-4.72 (m, 1H), 4.48-4.27 (m, 2H), 4.23-3.95 (m, 1H), 3.83-3.63 (m, 2H), 3.44-3.24 (m, 2H), 3.07-2.98 (m, 2H), 2.91 (t, $J=12.0\text{ Hz}$, 1H), 2.81-2.68 (m, 2H), 2.32-2.19 (m, 2H), 2.011-2.00 (m, 1H), 1.81-1.38 (m, 7H), 1.38-1.29 (m, 3H), 1.28-1.11 (m, 6H), 0.96 (d, $J=8.0\text{ Hz}$, 2H), 0.71-0.53 (m, 2H). Example 1.5: Synthesis of Compound 13

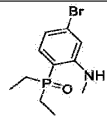
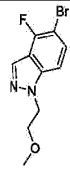
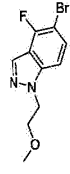
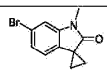


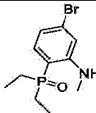
[0247] Compound 13 was prepared according to the synthetic procedure for compound 12, using 1- (4-iodophenyl) pyrrolidin-2-one in place of int-12 in the first step. LCMS: 892.4 [M+H]⁺. ¹HNMR (500 MHz, DMSO-d₆) δ 11.86 (brs, 1H) , 8.14 (d, J = 8.0 Hz, 1H) , 7.88 -7.41 (m, 4H) , 7.36 -7.04 (m, 4H) , 7.04 -6.51 (m, 3H) , 6.43 (s, 1H) , 5.88 -4.68 (m, 1H) , 4.35 -3.90 (m, 1H) , 3.89 -3.76 (m, 2H) , 3.77 -3.66 (m, 2H) , 3.47 -3.28 (m, 1H) , 3.00 -2.89 (m, 1H) , 2.87 -2.67 (m, 2H) , 2.56 -2.52 (m, 2H) , 2.14 -2.00 (m, 3H) , 1.78 -1.59 (m, 4H) , 1.58 -1.39 (m, 3H) , 1.37 -1.25 (m, 7H) , 1.20 (s, 3H) , 0.95 (d, J = 8.0 Hz, 2H) , 0.65 -0.52 (m, 2H) .

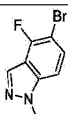
[0248] The compounds in Table b were prepared according to the synthetic procedure for-Compound 13 using the corresponding starting materials. Table b

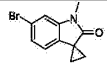
Compound No.	SM1	SM2	MW (M+H) ⁺ & ¹ H NMR
7		int-7 & int-9	LCMS: 904.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.13 (d, <i>J</i> = 7.2 Hz, 1H), 8.01 (s, 1H), 7.88 (s, 1H), 7.42 (s, 2H), 7.26 (t, <i>J</i> = 11.4 Hz, 4H), 6.94 (d, <i>J</i> = 16.4 Hz, 2H), 6.71 (d, <i>J</i> = 7.3 Hz, 1H), 6.42 (s, 1H), 5.72 (s, 1H), 3.93 (d, <i>J</i> = 5.3 Hz, 4H), 3.72 (d, <i>J</i> = 8.3 Hz, 2H), 2.82 (s, 3H), 2.71 (s, 1H), 2.68 (s, 1H), 2.03 (d, <i>J</i> = 7.3 Hz, 2H), 1.72 (s, 4H), 1.43 (s, 2H), 1.32 (s, 2H), 1.26 (s, 6H), 1.20 (s, 3H), 0.94 (d, <i>J</i> = 8.6 Hz, 2H), 0.87 (d, <i>J</i> = 6.8 Hz, 2H), 0.58 (s, 2H).
8		int-7 & int-9	LCMS: 904.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 12.02 (s, 1H), 8.14 (d, <i>J</i> = 6.8 Hz, 1H), 7.93 – 7.80 (m, 1H), 7.60 (s, 1H), 7.52 – 7.40 (m, 1H), 7.36 – 6.97 (m, 4H), 6.93 – 6.64 (m, 2H), 6.39 (d, <i>J</i> = 17.5 Hz, 1H), 5.70 – 4.76 (m, 1H), 4.19 – 3.34 (m, 4H), 2.99 – 2.64 (m, 6H), 2.10 – 1.95 (m, 1H), 1.82 – 1.10 (m, 22H), 1.01 – 0.89 (m, 2H), 0.66 – 0.47 (m, 2H).
9		int-7 & int-9	LCMS: 904.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.83 (s, 1H), 8.12 (d, <i>J</i> = 7.3 Hz, 1H), 7.51 (s, 1H), 7.30 – 7.10 (m, 6H), 6.89 (s, 2H), 6.70 (d, <i>J</i> = 7.3 Hz, 1H), 6.41 (s, 1H), 3.71 (d, <i>J</i> = 8.5 Hz, 2H), 3.23 (s, 4H), 2.90 (d, <i>J</i> = 11.1 Hz, 1H), 2.75 (d, <i>J</i> = 14.7 Hz, 2H), 1.66 (d, <i>J</i> = 18.4 Hz, 6H), 1.56 (s, 6H), 1.28 (d, <i>J</i> = 17.1 Hz, 7H), 1.19 (s, 3H), 0.94 (d, <i>J</i> = 8.7 Hz, 2H), 0.58 (s, 2H).
10		int-7 & int-9	LCMS: 904.4 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.95 (s, 1H), 8.06 (d, <i>J</i> = 7.3 Hz, 1H), 7.26 (s, 5H), 7.08 (s, 1H), 6.93 (s, 2H), 6.67 (d, <i>J</i> = 7.2 Hz, 1H), 6.36 (s, 1H), 4.20 – 3.30 (m, 3H), 3.28 – 3.19 (m, 3H), 2.98 – 2.86 (m, 1H), 2.10 – 1.98 (m, 1H), 1.76 – 1.66 (m, 2H), 1.65 – 1.40 (m, 8H), 1.38 – 0.74 (m, 15H), 0.70 – 0.54 (m, 2H).
11		int-7 & int-9	LCMS: 904.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.83 (s, 1H), 8.12 (d, <i>J</i> = 7.3 Hz, 1H), 7.68 – 6.78 (m, 9H), 6.74 – 6.67 (m, 1H), 6.41 (s, 1H), 5.42 (s, 3H), 4.15 – 3.27 (m, 3H), 3.00 – 2.64 (m, 3H), 2.10 – 1.88 (m, 3H), 1.78 – 1.14 (m, 20H), 0.94 (d, <i>J</i> = 8.7 Hz, 2H), 0.67 – 0.44 (m, 2H).
66		int-7-P2 & int-16	LCMS: 877.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.81 (bs, 1H), 8.14 – 8.01 (m, 2H), 7.99 – 7.39 (m, 3H), 7.34 – 7.25 (m, 1H), 7.23 – 7.00 (m, 3H), 7.00 – 6.80 (m, 1H), 6.70 (d, <i>J</i> = 8.0 Hz, 1H), 6.36 (bs, 1H), 5.94 – 4.98 (s, 1H), 4.06 (s, 3H), 3.93 – 3.56 (m, 3H), 3.54 – 3.18 (m, 1H), 2.95 – 2.85 (m, 1H), 2.19 (s, 6H), 1.75 – 1.59 (m, 4H), 1.50 – 1.43 (m, 2H), 1.41 – 1.34 (m, 3H), 1.29 – 1.22 (m, 5H), 1.18 (s, 3H), 1.13 – 0.97 (m, 1H), 0.91 – 0.80 (m, 2H), 0.79 – 0.68 (m, 1H).
68		int-17 & int-16	LCMS: 932.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.70 (bs, 1H), 7.48 (bs, 1H), 7.42 – 7.36 (m, 1H), 7.34 – 7.28 (m, 1H), 7.27 – 7.16 (m, 3H), 7.15 – 7.03 (m, 3H), 6.92 (bs, 1H), 6.81 – 6.62 (m, 1H), 6.00 – 5.20 (m, 1H), 4.17 – 3.80 (m, 1H), 3.71 (d, <i>J</i> = 8.0 Hz, 2H), 3.22 – 3.19 (m, 3H), 3.06 – 2.97 (m, 2H), 2.20 (s, 6H), 1.76 – 1.65 (m, 4H), 1.62 – 1.60 (m, 2H), 1.58 – 1.50 (m, 5H), 1.47 – 1.36 (m, 4H), 1.31 – 1.22 (m, 6H), 1.18 (s, 3H), 1.15 – 1.04 (m, 2H), 0.98 – 0.89 (m, 1H).

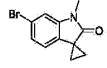
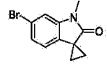
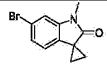
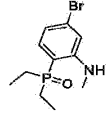
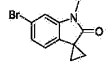
69		int-7-P2 & int-16	LCMS: 918.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.81 (brs, 1H), 8.12 (d, <i>J</i> = 8.0 Hz, 1H), 7.43 – 7.22 (m, 3H), 7.21 – 7.01 (m, 4H), 7.00 – 6.80 (m, 1H), 6.71 (d, <i>J</i> = 8.0 Hz, 1H), 6.38 (s, 1H), 5.97 – 5.05 (m, 1H), 3.93 – 3.57 (m, 3H), 3.53 – 3.30 (m, 1H), 3.27 – 3.23 (m, 3H), 2.97 – 2.88 (m, 1H), 2.20 (s, 6H), 1.77 – 1.59 (m, 6H), 1.58 – 1.54 (m, 2H), 1.53 – 1.51 (m, 1H), 1.50 – 1.44 (m, 2H), 1.43 – 1.33 (m, 4H), 1.32 – 1.23 (m, 5H), 1.20 (s, 3H), 1.15 – 0.97 (m, 1H), 0.84 – 0.67 (m, 1H).
70		int-19 & int-16	LCMS: 890.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.80 (brs, 1H), 8.11 (d, <i>J</i> = 7.1 Hz, 1H), 7.39 – 6.85 (m, 8H), 6.73 – 6.68 (m, 1H), 6.36 (s, 1H), 5.93 – 5.73 (m, 1H), 4.00 – 3.89 (m, 2H), 3.87–3.54 (m, 1H), 3.44 (t, <i>J</i> = 11.4 Hz, 2H), 3.22 (s, 4H), 2.79 – 2.68 (m, 1H), 2.18 (s, 6H), 1.81 – 1.65 (m, 4H), 1.65 – 1.59 (m, 4H), 1.56 – 1.51 (m, 2H), 1.48 – 1.42 (m, 1H), 1.41 – 1.30 (m, 4H), 1.30 – 1.25 (m, 2H), 0.84 – 0.65 (m, 2H).
71		int-7-P2 & int-36	LCMS: 923.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.28 – 8.08 (m, 2H), 7.65 – 7.22 (m, 3H), 7.12 (s, 2H), 7.04 – 6.56 (m, 3H), 6.38 (s, 1H), 5.84 – 5.64 (m, 1H), 5.16 – 4.63 (m, 1H), 4.09 (s, 3H), 4.02 – 3.00 (m, 1H), 3.75 – 3.67 (m, 2H), 2.97 – 2.87 (m, 1H), 2.54 (s, 1H), 2.27 – 2.21 (m, 6H), 1.95 – 1.62 (m, 8H), 1.62 – 1.43 (m, 5H), 1.39 – 1.27 (m, 5H), 1.27 – 1.24 (m, 3H), 1.19 (s, 3H).
72		int-7-P2 & int-37	LCMS: 909.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.87 (brs, 1H), 8.24 (s, 1H), 8.15 (d, <i>J</i> = 7.1 Hz, 1H), 7.68 – 7.49 (m, 1H), 7.46 – 7.26 (m, 2H), 7.16 (s, 2H), 7.06 – 6.78 (m, 2H), 6.72 (d, <i>J</i> = 7.1 Hz, 1H), 6.42 (s, 1H), 5.83 – 5.60 (m, 1H), 5.15 – 4.89 (m, 1H), 4.47 – 4.26 (m, 1H), 4.10 (s, 3H), 3.76 – 3.69 (m, 2H), 2.96 – 2.91 (m, 1H), 2.78 – 2.64 (m, 2H), 2.26 (s, 6H), 2.18 – 1.91 (m, 4H), 1.81 – 1.69 (m, 4H), 1.68 – 1.63 (m, 1H), 1.59 – 1.53 (m, 1H), 1.53 – 1.45 (m, 2H), 1.37 – 1.30 (m, 3H), 1.29 – 1.27 (m, 3H), 1.20 (s, 3H).
80		int-1 & int-16	LCMS: 890.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.94 (brs, 1H), 7.52 – 7.43 (m, 2H), 7.33 – 7.25 (m, 1H), 7.24 – 6.99 (m, 6H), 6.97 – 6.77 (m, 1H), 6.70 (s, 1H), 5.82 – 5.23 (m, 1H), 3.96 (d, <i>J</i> = 8.0 Hz, 2H), 3.84 – 3.72 (m, 1H), 3.51 – 3.43 (m, 2H), 3.41 – 3.37 (m, 1H), 3.21 – 3.18 (m, 3H), 2.91 – 2.78 (m, 1H), 2.19 (s, 6H), 1.84 – 1.75 (m, 2H), 1.74 – 1.65 (m, 5H), 1.64 – 1.51 (m, 5H), 1.50 – 1.28 (m, 5H), 1.06 – 0.87 (m, 2H).
81		int-18 & int-16	LCMS: 904.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 7.57 – 7.48 (m, 1H), 7.45 – 7.37 (m, 1H), 7.32 – 7.20 (m, 3H), 7.16 – 7.02 (m, 3H), 6.96 – 6.86 (m, 1H), 6.83 – 6.63 (m, 2H), 5.76 – 5.66 (m, 1H), 5.29 – 5.15 (m, 1H), 4.45 – 4.38 (m, 1H), 4.01 – 3.95 (m, 2H), 3.57 – 3.54 (m, 2H), 3.50 – 3.46 (m, 3H), 2.89 – 2.79 (m, 1H), 2.20 (s, 6H), 1.80 – 1.67 (m, 6H), 1.66 – 1.59 (m, 3H), 1.58 – 1.49 (m, 3H), 1.47 – 1.31 (m, 4H), 1.29 – 1.23 (m, 1H), 1.19 – 0.99 (m, 3H), 0.98 – 0.86 (m, 1H).
82		int-1 & int-37	LCMS: 881.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.22 (s, 1H), 7.59 – 7.45 (m, 3H), 7.43 – 7.29 (m, 1H), 7.28 – 6.97 (m, 4H), 6.94 – 6.84 (m, 1H), 6.79 – 6.72 (m, 1H), 5.42 – 5.26 (m, 1H), 4.67 – 4.53 (m, 1H), 4.23 – 4.16 (m, 1H), 4.11 – 4.08 (m, 3H), 3.99 – 3.95 (m, 2H), 3.52 –

			3.49 (m, 2H), 2.89 – 2.83 (m, 1H), 2.79 – 2.73 (m, 1H), 2.26 (s, 6H), 2.16 – 1.97 (m, 5H), 1.82 – 1.70 (m, 6H), 1.56 – 1.43 (m, 2H), 1.41 – 1.33 (m, 3H).
83		int-1 & int-16	LCMS: 928.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 7.69 (brs, 1H), 7.53 – 7.44 (m, 2H), 7.33 – 7.15 (m, 3H), 7.12 – 7.06 (m, 2H), 7.01 – 6.75 (m, 3H), 6.70 (s, 1H), 5.95 – 5.32 (m, 1H), 4.02 – 3.69 (m, 4H), 3.53 – 3.43 (m, 2H), 2.90 – 2.82 (m, 1H), 2.79 – 2.67 (m, 3H), 2.19 (s, 6H), 1.96 – 1.87 (m, 4H), 1.85 – 1.58 (m, 8H), 1.56 – 1.31 (m, 5H), 1.06 – 0.88 (m, 8H).
84	Int-68-2	int-7-P2 & int-9	LCMS: 922.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.84 (s, 1H), 8.12 (d, <i>J</i> = 7.4 Hz, 1H), 7.46 – 7.16 (m, 6H), 6.95 (d, <i>J</i> = 40.1 Hz, 2H), 6.70 (d, <i>J</i> = 7.3 Hz, 1H), 6.41 (s, 1H), 5.66 (s, 1H), 4.08 (s, 1H), 3.71 (d, <i>J</i> = 8.2 Hz, 2H), 3.38 (s, 1H), 3.23 (s, 3H), 2.90 (d, <i>J</i> = 14.1 Hz, 1H), 2.73 (s, 2H), 2.10 – 1.99 (m, 1H), 1.89 – 1.78 (m, 2H), 1.66 (d, <i>J</i> = 21.1 Hz, 4H), 1.53 (q, <i>J</i> = 4.1 Hz, 3H), 1.47 (t, <i>J</i> = 13.0 Hz, 2H), 1.28 (d, <i>J</i> = 19.7 Hz, 8H), 1.19 (s, 3H), 0.95 (d, <i>J</i> = 8.6 Hz, 2H), 0.65 – 0.52 (m, 2H).
85	Int-70-2	Int-7-P2 & int-9	LCMS: 922.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.15 – 8.10 (m, 1H), 7.35 – 7.19 (m, 3H), 7.12 – 6.84 (m, 5H), 6.74 – 6.68 (m, 1H), 6.41 (s, 1H), 5.86 – 4.66 (m, 1H), 3.78 – 3.69 (m, 2H), 3.42 (s, 3H), 2.99 – 2.89 (m, 2H), 2.80 – 2.68 (m, 2H), 2.11 – 2.06 (m, 1H), 1.78 – 1.53 (m, 10H), 1.39 – 1.26 (m, 8H), 1.21 (s, 3H), 1.05 – 0.95 (m, 2H), 0.72 – 0.62 (m, 2H).
88		int-17 & int-16	LCMS: 953.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.57 (brs, 1H), 8.26 (s, 1H), 7.71 – 7.47 (m, 2H), 7.46 – 7.32 (m, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.18 – 7.08 (m, 2H), 7.02 – 6.67 (m, 3H), 5.92 – 5.25 (m, 1H), 4.74 – 4.50 (m, 2H), 4.26 – 3.81 (m, 2H), 3.80 – 3.75 (m, 2H), 3.71 (d, <i>J</i> = 8.0 Hz, 2H), 3.19 (s, 3H), 3.07 – 2.99 (m, 1H), 2.23 (s, 6H), 1.82 – 1.65 (m, 4H), 1.63 – 1.47 (m, 5H), 1.45 – 1.35 (m, 2H), 1.34 – 1.16 (m, 9H), 1.15 – 1.01 (m, 2H), 1.00 – 0.88 (m, 1H).
89		int-1 & int-16	LCMS: 911.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.92 (brs, 1H), 8.26 (s, 1H), 7.59 (brs, 1H), 7.55 – 7.43 (m, 2H), 7.37 (brs, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.18 – 7.07 (m, 2H), 7.03 – 6.78 (m, 2H), 6.71 (s, 1H), 5.95 – 5.35 (m, 1H), 4.73 – 4.51 (m, 2H), 4.10 – 3.70 (m, 6H), 3.52 – 3.44 (3, 2H), 3.28 – 3.22 (m, 3H), 2.92 – 2.79 (m, 1H), 2.24 (s, 6H), 1.93 – 1.59 (m, 8H), 1.58 – 1.33 (m, 5H), 1.04 – 0.82 (m, 2H).
90	Int-62-2	Int-7-P2 & int-16	LCMS: 946.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.59 (brs, 1H), 7.58 – 7.32 (m, 3H), 7.30 – 7.15 (m, 3H), 7.09 (s, 2H), 7.00 – 6.63 (m, 3H), 5.88 – 5.16 (m, 1H), 4.64 (s, 2H), 4.33 – 3.76 (m, 2H), 3.76 – 3.67 (m, 2H), 3.10 – 3.01 (m, 1H), 2.99 (s, 3H), 2.19 (s, 6H), 1.78 – 1.65 (m, 4H), 1.64 – 1.45 (m, 7H), 1.46 – 1.34 (m, 3H), 1.34 – 1.30 (m, 1H), 1.23 (d, <i>J</i> = 36.0 Hz, 9H), 1.15 – 1.05 (m, 2H), 1.00 – 0.90 (m, 1H).
91		Int-17 & int-37	LCMS: 946.5 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.39 (brs, 1H), 7.59 – 7.46 (m, 1H), 7.44 – 7.35 (m, 1H), 7.34 – 7.19 (m, 3H), 7.18 – 7.11 (m, 3H), 7.09 – 6.99 (m, 1H), 6.92 – 6.66 (m, 2H), 5.50 – 5.23 (m, 1H), 4.70 – 4.39 (m, 1H), 3.72 (d, <i>J</i> = 8.0 Hz, 2H), 3.56 – 3.51 (m, 1H), 3.20 – 3.17 (m, 3H), 3.08 – 2.94 (m, 2H), 2.81 – 2.69 (m, 1H), 2.28

			- 1.92 (m, 1H), 1.77 - 1.65 (m, 4H), 1.64 - 1.59 (m, 3H), 1.58 - 1.45 (m, 5H), 1.38 - 1.33 (m, 1H), 1.31 - 1.23 (m, 6H), 1.19 (s, 3H), 1.14 - 1.05 (m, 1H).
92	Int-70-2	Int-17 & int-16	LCMS: 950.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.58 (brs, 1H), 7.63 - 7.42 (m, 1H), 7.38 (d, <i>J</i> = 8.6 Hz, 1H), 7.23 (dd, <i>J</i> = 8.5, 1.7 Hz, 1H), 7.19 - 6.50 (m, 7H), 6.10 - 5.10 (m, 1H), 4.25 - 3.76 (m, 2H), 3.75 - 3.67 (m, 2H), 3.38 (s, 3H), 3.07 - 2.97 (m, 1H), 2.29 - 2.14 (m, 6H), 1.80 - 1.63 (m, 6H), 1.63 - 1.57 (m, 3H), 1.57 - 1.47 (m, 3H), 1.46 - 1.31 (m, 3H), 1.31 - 1.15 (m, 9H), 1.15 - 1.01 (m, 2H), 0.99 - 0.88 (m, 1H).
93	Int-70-2	Int-7-P2 & int-16	LCMS: 936.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.39 (brs, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (brs, 1H), 7.19 - 7.01 (m, 3H), 7.00 - 6.79 (d, <i>J</i> = 21.1 Hz, 3H), 6.70 (d, <i>J</i> = 8.0 Hz, 1H), 6.36 (brs, 1H), 5.96 - 5.05 (m, 1H), 4.01 - 3.51 (m, 3H), 3.50 - 3.33 (m, 4H), 2.96 - 2.89 (m, 1H), 2.22 (s, 6H), 1.77 - 1.68 (m, 4H), 1.67 - 1.59 (m, 4H), 1.57 - 1.52 (m, 1H), 1.51 - 1.42 (m, 3H), 1.41 - 1.35 (m, 3H), 1.29 - 1.24 (m, 5H), 1.20 (s, 3H), 0.89 - 0.85 (m, 1H), 0.83 - 0.70 (m, 1H).
94	Int-70-2	Int-1 & int-16	LCMS: 908.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.65 (brs, 1H), 7.54 - 7.45 (m, 2H), 7.22 (dd, <i>J</i> = 8.5, 1.6 Hz, 1H), 7.15 - 7.08 (m, 2H), 7.08 - 6.75 (m, 4H), 6.70 (s, 1H), 5.73 - 5.28 (m, 1H), 4.25 - 4.03 (m, 1H), 4.01 - 3.94 (m, 2H), 3.81 - 3.67 (m, 1H), 3.51 - 3.49 (m, 2H), 3.41 - 3.38 (m, 3H), 2.92 - 2.80 (m, 1H), 2.23 (s, 6H), 1.88 - 1.65 (m, 9H), 1.64 - 1.60 (m, 2H), 1.55 - 1.35 (m, 5H), 1.32 - 1.26 (m, 2H), 1.01 - 0.90 (m, 1H).
95		Int-1 & int-37	LCMS: 904.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 7.55 - 7.43 (m, 2H), 7.34 - 7.09 (m, 6H), 7.08 - 6.97 (m, 1H), 6.92 - 6.63 (m, 2H), 5.81 - 5.19 (m, 1H), 5.06 - 4.40 (m, 1H), 4.00 - 3.92 (m, 2H), 3.50 - 3.42 (m, 2H), 3.38 - 3.31 (m, 1H), 3.13 - 3.04 (m, 3H), 2.88 - 2.80 (m, 1H), 2.78 - 2.68 (m, 1H), 2.29 - 1.93 (m, 11H), 1.89 - 1.62 (m, 8H), 1.62 - 1.55 (m, 2H), 1.56 - 1.48 (m, 2H), 1.41 - 1.27 (m, 3H).
97		Int-17 & int-16	LCMS: 970.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.77 (brs, 1H), 7.69 (s, 1H), 7.53 (s, 1H), 7.39 (d, <i>J</i> = 8.6 Hz, 1H), 7.33 - 7.02 (m, 5H), 7.00 - 6.60 (m, 4H), 5.53 (d, <i>J</i> = 146.1 Hz, 1H), 3.86 (d, <i>J</i> = 46.6 Hz, 2H), 3.77 - 3.67 (m, 2H), 3.03 (t, <i>J</i> = 12.6 Hz, 1H), 2.87 - 2.59 (m, 3H), 2.27 - 2.12 (m, 6H), 2.00 - 1.83 (m, 4H), 1.82 - 1.66 (m, 4H), 1.65 - 1.45 (m, 5H), 1.40 (s, 3H), 1.24 (d, <i>J</i> = 35.7 Hz, 8H), 1.12 (s, 1H), 1.07 - 0.81 (m, 8H).
98	Int-55-4	Int-7-P2 & int-16	LCMS: 916.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.94 - 11.16 (m, 1H), 7.74 - 7.54 (m, 1H), 7.49 - 7.21 (m, 2H), 7.19 - 7.07 (m, 2H), 7.03 - 6.93 (m, 2H), 6.88 - 6.81 (m, 2H), 6.73 - 6.64 (m, 1H), 6.55 - 6.42 (m, 1H), 5.79 - 5.34 (m, 1H), 3.85 - 3.75 (m, 1H), 3.51 - 3.41 (m, 3H), 2.83 - 2.69 (m, 4H), 1.96 (s, 6H), 1.78 - 1.68 (m, 2H), 1.60 - 1.50 (m, 2H), 1.49 - 1.39 (m, 4H), 1.30 - 1.13 (m, 7H), 1.07 - 0.99 (m, 6H), 0.94 (s, 3H), 0.88 - 0.78 (m, 2H), 0.73 - 0.66 (m, 1H).
100	Int-68-2	Int-1 & int-16	LCMS: 908.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.89 (s, 1H), 7.47 (d, <i>J</i> = 8.5 Hz, 2H), 7.40 - 7.11 (m,

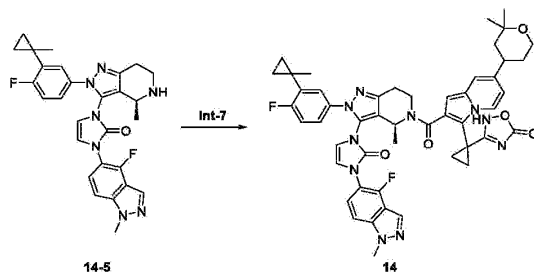
			4H), 7.08 (d, $J = 6.3$ Hz, 2H), 6.91 (s, 1H), 6.69 (s, 1H), 5.70 (s, 1H), 3.96 (d, $J = 11.3$ Hz, 4H), 3.53 – 3.38 (m, 2H), 3.21 (s, 3H), 2.83 (s, 1H), 2.18 (d, $J = 2.2$ Hz, 6H), 1.80 (q, $J = 3.8$ Hz, 4H), 1.74 – 1.63 (m, 5H), 1.53 (q, $J = 3.8$ Hz, 3H), 1.46 – 1.34 (m, 4H), 1.14 – 0.71 (m, 3H).
101	Int-69-2	Int-17 & int-16	LCMS: 950.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.58 (s, 1H), 7.53 (s, 1H), 7.38 (d, $J = 8.6$ Hz, 1H), 7.30 – 7.00 (m, 5H), 6.99 – 6.59 (, 3H), 5.51 (d, $J = 149.8$ Hz, 1H), 4.07 – 3.61 (m, 4H), 3.20 (s, 3H), 3.02 (t, $J = 12.5$ Hz, 1H), 2.21 (s, 6H), 1.76 – 1.62 (m, 6H), 1.61 – 1.56 (m, 3H), 1.52 (t, $J = 12.8$ Hz, 3H), 1.39 (s, 2H), 1.35 – 1.30 (m, 1H), 1.23 (d, $J = 35.4$ Hz, 9H), 1.15 – 1.02 (m, 2H), 1.00 – 0.88 (m, 1H).
102		Int-17 & int-38	LCMS: 906.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (s, 1H), 7.50 (s, 1H), 7.39 (d, $J = 8.5$ Hz, 1H), 7.34 – 7.22 (m, 3H), 7.21 – 6.96 (m, 4H), 6.89 (s, 2H), 5.60 (s, 1H), 4.37 (s, 1H), 3.71 (d, $J = 8.5$ Hz, 2H), 3.58 (s, 1H), 3.21 (s, 4H), 3.04 (d, $J = 12.6$ Hz, 1H), 2.89 (s, 1H), 2.21 (d, $J = 2.3$ Hz, 6H), 1.77 – 1.61 (m, 4H), 1.60 (s, 3H), 1.56 – 1.48 (m, 4H), 1.46 – 1.37 (m, 2H), 1.23 (d, $J = 36.4$ Hz, 9H), 1.12 – 1.01 (m, 1H).
103	Int-68-2	Int-17 & int-16	LCMS: 951.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.57 (brs, 1H), 7.50 (s, 1H), 7.38 (d, $J = 8.5$ Hz, 1H), 7.37 – 7.14 (m, 4H), 7.09 (s, 3H), 6.75 (s, 1H), 5.70 (s, 1H), 4.36 – 3.46 (m, 4H), 3.21 (s, 3H), 3.03 – 2.94 (m, 1H), 2.19 (d, $J = 2.1$ Hz, 6H), 1.80 (s, 2H), 1.68 (s, 4H), 1.61 – 1.35 (m, 9H), 1.22 (d, $J = 35.8$ Hz, 9H), 1.14 – 1.03 (s, 2H), 1.00 – 0.89 (s, 1H).
104	Int-68-2	Int-18 & int-16	LCMS: 922.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.79 (d, $J = 189.0$ Hz, 1H), 7.52 (s, 1H), 7.39 (d, $J = 7.9$ Hz, 2H), 7.31 – 7.21 (m, 3H), 7.09 (s, 2H), 6.99 (s, 1H), 6.75 (s, 1H), 5.67 (s, 1H), 3.95 (d, $J = 10.3$ Hz, 3H), 3.76 (s, 1H), 3.45 (t, $J = 11.1$ Hz, 2H), 3.24 – 3.21 (m, 3H), 2.84 (s, 1H), 2.19 (s, 6H), 1.80 (s, 2H), 1.76 – 1.66 (m, 6H), 1.61 – 1.45 (m, 5H), 1.44 – 1.34 (m, 3H), 1.20 – 0.86 (m, 5H).
106	Int-70-2	Int-18 & int-16	LCMS: 922.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.78 (brs, 1H), 7.63 – 7.47 (m, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.15 – 7.07 (m, 2H), 7.06 – 6.63 (m, 5H), 5.76 – 5.32 (m, 1H), 4.16 – 3.93 (m, 3H), 3.92 – 3.63 (m, 1H), 3.51 – 3.45 (m, 2H), 3.40 (s, 3H), 2.89 – 2.83 (m, 1H), 2.24 (s, 6H), 1.80 – 1.72 (m, 4H), 1.71 – 1.67 (m, 3H), 1.66 – 1.51 (m, 5H), 1.50 – 1.36 (m, 3H), 1.35 – 1.25 (m, 2H), 1.24 – 1.05 (m, 2H), 1.03 – 0.77 (m, 2H).
108	Int-69-2	Int-7-P2 & int-16	LCMS: 936.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.19 (s, 1H), 8.09 (d, $J = 7.3$ Hz, 1H), 7.29 (s, 1H), 7.23 – 7.04 (m, 4H), 6.90 (s, 2H), 6.69 (dd, $J = 7.4, 1.9$ Hz, 1H), 6.35 (s, 1H), 5.82 (s, 1H), 3.71 (d, $J = 8.4$ Hz, 3H), 3.44 (s, 1H), 3.21 (s, 3H), 2.97 – 2.85 (d, $J = 11.4$ Hz, 1H), 2.21 (s, 6H), 1.77 – 1.67 (m, 4H), 1.66 – 1.56 (m, 4H), 1.48 (d, $J = 12.9$ Hz, 2H), 1.42 – 1.29 (m, 4H), 1.25 (d, $J = 6.1$ Hz, 5H), 1.19 (s, 3H), 1.12 – 0.66 (m, 3H).
121		Int-50 & int-38	LCMS: 867.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 8.24 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.49 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 7.36 – 7.34 (m, 1H), 7.17 (d, $J = 4.0$ Hz, 2H), 7.03 – 6.92 (m, 1H), 6.91 –

			6.81 (m, 1H), 6.78 (s, 1H), 5.76 – 5.32 (m, 1H), 4.71 – 4.30 (m, 1H), 4.10 (s, 3H), 3.91 – 3.82 (m, 2H), 3.58 (t, $J = 12.0$ Hz, 2H), 3.54 – 3.39 (m, 1H), 3.06 – 2.93 (m, 3H), 2.87 – 2.79 (m, 1H), 2.25 (s, 6H), 2.14 (t, $J = 8.0$ Hz, 2H), 2.02 – 1.59 (m, 6H), 1.52 – 1.43 (m, 3H), 1.42 – 1.38 (m, 2H).
122	Int-70-2	Int-50 & int-16	LCMS: 934.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.88 (brs, 1H), 7.43 (brs, 1H), 7.33 (s, 1H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.07 – 6.98 (m, 1H), 6.97 – 6.92 (m, 1H), 6.91 – 6.72 (m, 2H), 6.67 (s, 1H), 5.83 – 5.33 (m, 1H), 4.30 – 3.66 (m, 5H), 3.57 (t, $J = 12.0$ Hz, 2H), 3.39 (s, 3H), 2.98 (t, $J = 8.0$ Hz, 1H), 2.22 (s, 6H), 2.17 – 2.08 (m, 2H), 1.95 – 1.55 (m, 10H), 1.54 – 1.32 (m, 7H), 1.04 – 0.85 (m, 2H).
123	Int-70-2	Int-53 & int-16	LCMS: 948.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.81 (brs, 1H), 7.81 – 7.59 (m, 1H), 7.47 – 7.37 (m, 2H), 7.20 – 7.08 (m, 2H), 7.04 – 6.63 (s, 5H), 6.07 (s, 1H), 5.92 – 5.11 (m, 1H), 4.20 – 3.91 (m, 1H), 3.85 (t, $J = 4.0$ Hz, 2H), 3.83 – 3.55 (m, 1H), 3.44 – 3.34 (m, 2H), 2.45 – 2.38 (m, 2H), 2.23 (s, 6H), 1.79 – 1.65 (m, 4H), 1.64 – 1.46 (m, 5H), 1.45 – 1.33 (m, 3H), 1.31 – 1.25 (m, 7H), 1.23 – 0.84 (m, 5H).
123-P2	Int-70-2	Int-53-P2 & int-16	LCMS: 948.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.80 (brs, 1H), 7.81 – 7.56 (m, 1H), 7.52 – 7.37 (m, 2H), 7.21 – 7.08 (m, 2H), 7.07 – 6.53 (m, 5H), 6.22 – 6.10 (m, 1H), 5.94 – 5.18 (m, 1H), 4.31 – 4.21 (m, 2H), 4.19 – 3.57 (m, 2H), 3.43 – 3.33 (m, 2H), 2.42 – 2.36 (m, 2H), 2.23 (s, 6H), 1.85 – 1.65 (m, 4H), 1.64 – 1.58 (m, 3H), 1.57 – 1.47 (m, 2H), 1.46 – 1.33 (m, 3H), 1.32 – 1.19 (m, 8H), 1.18 – 0.80 (m, 4H).
124	Int-70-2	Int-50 & int-38	LCMS: 908.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.89 (brs, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 7.21 – 7.11 (m, 2H), 7.07 – 6.99 (m, 1H), 6.98 – 6.86 (m, 2H), 6.86 – 6.69 (m, 2H), 5.68 – 5.35 (m, 1H), 4.59 – 4.24 (m, 1H), 3.85 (d, $J = 8.0$ Hz, 2H), 3.62 – 3.55 (m, 2H), 3.44 – 3.36 (m, 4H), 3.02 – 2.94 (m, 3H), 2.85 – 2.78 (m, 1H), 2.23 (s, 6H), 2.13 (t, $J = 8.0$ Hz, 2H), 1.93 – 1.84 (m, 2H), 1.83 – 1.73 (m, 2H), 1.72 – 1.53 (m, 6H), 1.52 – 1.42 (m, 3H), 1.40 – 1.35 (m, 2H).
125		Int-50 & int-38	LCMS: 890.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.96 (brs, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 7.32 – 7.17 (m, 3H), 7.16 – 7.11 (m, 2H), 7.09 – 7.02 (m, 1H), 6.87 (brs, 1H), 6.75 (s, 1H), 5.75 – 5.31 (m, 1H), 4.72 – 4.26 (m, 1H), 3.85 (d, $J = 8.0$ Hz, 2H), 3.57 (m, $J = 12.0$ Hz, 2H), 3.52 – 3.37 (m, 1H), 3.21 (s, 3H), 3.03 – 2.95 (m, 3H), 2.85 – 2.78 (m, 1H), 2.20 (m, 6H), 2.13 (t, $J = 8.0$ Hz, 2H), 1.95 – 1.84 (m, 2H), 1.82 – 1.64 (m, 3H), 1.63 – 1.59 (m, 2H), 1.58 – 1.54 (m, 1H), 1.54 – 1.50 (m, 2H), 1.49 – 1.40 (m, 3H), 1.39 – 1.31 (m, 3H).
126	Int-70-2	Int-52 & int-16	LCMS: 936.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.91 (brs, 1H), 7.54 – 7.44 (m, 2H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 4.0$ Hz, 2H), 7.06 – 6.75 (m, 4H), 6.71 (s, 1H), 5.88 – 5.31 (m, 1H), 4.08 – 3.77 (m, 2H), 3.73 (d, $J = 8.0$ Hz, 2H), 3.40 (s, 3H), 3.08 – 2.98 (m, 1H), 2.23 (s, 6H), 1.87 – 1.77 (m, 2H), 1.76 – 1.68 (m, 5H), 1.67 – 1.58 (m, 4H), 1.57 – 1.49 (m, 2H), 1.48 – 1.38 (m, 4H), 1.29 (s, 3H), 1.20 (s, 3H), 1.04 – 0.87 (m, 2H).

127	Int-70-2	Int-51 & int-16	LCMS: 936.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.92 (brs, 1H), 7.63 – 7.41 (m, 2H), 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.12 (d, <i>J</i> = 4.0 Hz, 2H), 7.09 – 6.74 (m, 4H), 6.70 (s, 1H), 5.99 – 5.22 (m, 1H), 3.99 – 3.87 (m, 1H), 3.73 (d, <i>J</i> = 8.0 Hz, 3H), 3.40 (s, 3H), 3.08 – 2.98 (m, 1H), 2.23 (s, 6H), 1.87 – 1.77 (s, 2H), 1.76 – 1.68 (m, 5H), 1.67 – 1.58 (m, 4H), 1.58 – 1.50 (m, 2H), 1.49 – 1.38 (m, 4H), 1.29 (s, 3H), 1.20 (s, 3H), 1.02 – 0.86 (m, 2H).
128		Int-52 & int-16	LCMS: 918.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.92 (brs, 1H), 7.53 – 7.44 (m, 2H), 7.36 – 7.15 (m, 4H), 7.12 – 7.03 (m, 3H), 6.97 – 6.77 (m, 1H), 6.70 (s, 1H), 5.81 – 5.32 (m, 1H), 4.13 – 3.76 (m, 2H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.42 – 3.25 (m, 3H), 3.07 – 2.97 (m, 1H), 2.20 (s, 6H), 1.85 – 1.75 (m, 2H), 1.74 – 1.66 (m, 3H), 1.65 – 1.59 (m, 3H), 1.58 – 1.48 (m, 4H), 1.47 – 1.37 (m, 4H), 1.33 – 1.25 (m, 4H), 1.19 (s, 3H), 1.04 – 0.86 (m, 2H).
129		Int-51 & int-16	LCMS: 918.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.91 (brs, 1H), 7.55 – 7.42 (m, 2H), 7.34 – 7.13 (m, 4H), 7.12 – 6.99 (m, 3H), 6.96 – 6.77 (m, 1H), 6.68 (s, 1H), 5.82 – 5.33 (m, 1H), 3.98 – 3.84 (m, 1H), 3.71 (d, <i>J</i> = 8.0 Hz, 3H), 3.43 – 3.36 (m, 3H), 3.06 – 2.96 (m, 1H), 2.19 (s, 6H), 1.86 – 1.74 (m, 2H), 1.73 – 1.65 (m, 3H), 1.64 – 1.51 (m, 7H), 1.50 – 1.45 (m, 1H), 1.44 – 1.35 (m, 4H), 1.27 (s, 3H), 1.18 (s, 3H), 1.02 – 0.83 (m, 2H).
130		Int-71 & int-16	LCMS: 938.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.59 (brs, 1H), 7.69 – 7.44 (m, 1H), 7.43 – 7.37 (m, 1H), 7.36 – 6.62 (m, 9H), 5.95 – 5.20 (m, 1H), 4.33 – 3.54 (m, 2H), 3.26 – 3.20 (m, 3H), 2.87 – 2.73 (m, 1H), 2.20 (s, 6H), 2.16 – 1.85 (m, 6H), 1.80 – 1.50 (m, 10H), 1.48 – 1.29 (m, 4H), 1.23 – 0.79 (m, 5H).
131		Int-51 & int-16	LCMS: 956.3 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 7.69 (s, 1H), 7.53 – 7.43 (m, 2H), 7.28 – 7.16 (m, 3H), 7.12 – 7.07 (m, 2H), 6.95 – 6.62 (m, 4H), 6.05 – 5.00 (m, 1H), 4.20 – 3.55 (m, 4H), 3.06 – 2.99 (m, 1H), 2.82 – 2.65 (m, 3H), 2.19 (s, 6H), 1.95 – 1.88 (m, 4H), 1.83 – 1.66 (m, 5H), 1.64 – 1.50 (m, 3H), 1.45 – 1.34 (m, 4H), 1.28 (s, 3H), 1.20 (s, 3H), 1.06 – 0.83 (m, 9H).
132	Int-75-2	Int-17 & int-16	LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.60 (brs, 1H), 7.91 – 7.20 (m, 6H), 7.19 – 7.03 (m, 2H), 7.02 – 6.64 (m, 2H), 5.97 – 5.10 (m, 1H), 4.33 – 3.59 (m, <i>J</i> = 8.4 Hz, 4H), 3.25 (s, 3H), 3.06 – 2.98 (m, 1H), 2.19 (s, 6H), 1.81 – 1.65 (m, 6H), 1.64 – 1.46 (m, 7H), 1.45 – 1.29 (m, 4H), 1.28 (s, 3H), 1.19 (s, 3H), 1.18 – 1.05 (m, 3H), 1.02 – 0.89 (m, 1H).
137	Int-70-2	Int-72 & int-16	LCMS: 934.4(M+H) ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.61 (brs, 1H), 7.63 – 7.48 (m, 1H), 7.38 (d, <i>J</i> = 8.0 Hz, 1H), 7.27 (d, <i>J</i> = 8.0 Hz, 1H), 7.15 – 7.06 (m, 2H), 7.00 – 6.62 (m, 5H), 5.79 – 5.37 (m, 1H), 4.26 – 3.89 (m, 2H), 3.88 – 3.59 (m, 2H), 3.50 – 3.45 (m, 1H), 3.43 – 3.35 (m, 4H), 2.22 (s, 6H), 2.11 – 2.03 (m, 1H), 1.98 – 1.92 (m, 1H), 1.73 – 1.67 (m, 3H), 1.64 – 1.58 (m, 3H), 1.54 – 1.48 (m, 1H), 1.47 – 1.27 (m, 6H), 1.18 – 1.08 (m, 2H), 1.05 – 0.95 (m, 2H), 0.89 – 0.79 (m, 2H).
138		Int-17 & int-73-4	LCMS: 555.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 7.94 – 7.67 (m, 1H), 7.46 – 7.22 (m, 1H), 6.97 – 6.45 (m, 5H), 4.01 – 3.59 (m, 1H), 3.10 – 3.05 (m, 2H), 3.02 – 2.94

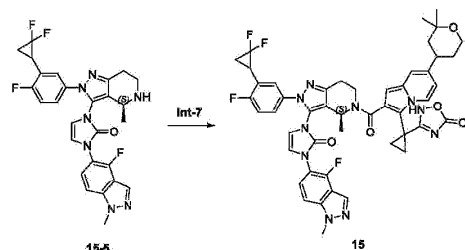
			(m, 1H), 2.70 (s, 1H), 2.64 – 2.55 (m, 1H), 1.99 (s, 3H), 1.93 – 1.88 (m, 3H), 1.63 – 1.45 (m, 4H), 1.24 – 1.19 (m, 1H), 1.12 – 1.05 (m, 1H), 0.93 – 0.88 (m, 2H), 0.87 – 0.79 (m, 2H), 0.78 – 0.74 (m, 1H).
139	Int-78	Int-17 & int-16	LCMS: 946.4(M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.60 (brs, 1H), 7.56 (brs, 1H), 7.40 (d, <i>J</i> = 8.0 Hz, 1H), 7.26 (d, <i>J</i> = 8.0 Hz, 1H), 7.19 – 7.05 (m, 2H), 7.02 – 6.58 (m, 5H), 5.98 – 5.20 (m, 1H), 4.29 – 3.78 (m, 2H), 3.77 – 3.71 (m, 2H), 3.50 (s, 3H), 3.11 – 2.98 (m, 1H), 2.50 (s, 3H), 2.24 (s, 6H), 1.82 – 1.67 (m, 4H), 1.66 – 1.49 (m, 9H), 1.48 – 1.34 (m, 3H), 1.33 – 1.25 (m, 5H), 1.20 (s, 3H), 1.17 – 1.03 (m, 2H), 1.01 – 0.89 (m, 1H).
140		Int-17 & int-16	LCMS: 962.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.61 (brs, 1H), 7.61 – 7.47 (m, 1H), 7.39 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 – 7.09 (m, 2H), 7.03 – 6.54 (m, 5H), 5.87 – 5.06 (m, 1H), 4.22 – 3.64 (m, 4H), 3.48 – 3.34 (m, 3H), 3.22 – 3.18 (m, 3H), 3.07 – 3.00 (m, 1H), 2.23 (s, 6H), 1.79 – 1.66 (m, 4H), 1.65 – 1.47 (m, 10H), 1.45 – 1.37 (m, 2H), 1.36 – 1.27 (m, 5H), 1.20 (s, 3H), 1.14 – 1.03 (m, 2H), 1.01 – 0.90 (m, 1H).
141	Int-79	Int-17 & int-16	LCMS: 952.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.80 (brs, 1H), 7.55 (brs, 1H), 7.39 (d, <i>J</i> = 8.0 Hz, 1H), 7.35 – 7.20 (m, 2H), 7.18 – 7.00 (m, 3H), 6.99 – 6.65 (m, 3H), 5.98 – 5.13 (m, 1H), 4.28 – 3.65 (m, 4H), 3.32 (s, 3H), 3.07 – 2.99 (m, 1H), 2.23 (s, 6H), 1.82 – 1.65 (m, 4H), 1.64 – 1.49 (m, 5H), 1.48 – 1.36 (m, 3H), 1.31 (s, 6H), 1.29 – 1.25 (m, 4H), 1.23 – 1.17 (m, 4H), 1.16 – 1.06 (m, 2H), 1.00 – 0.89 (m, 1H).

Example 1.6: Synthesis of Compounds 14

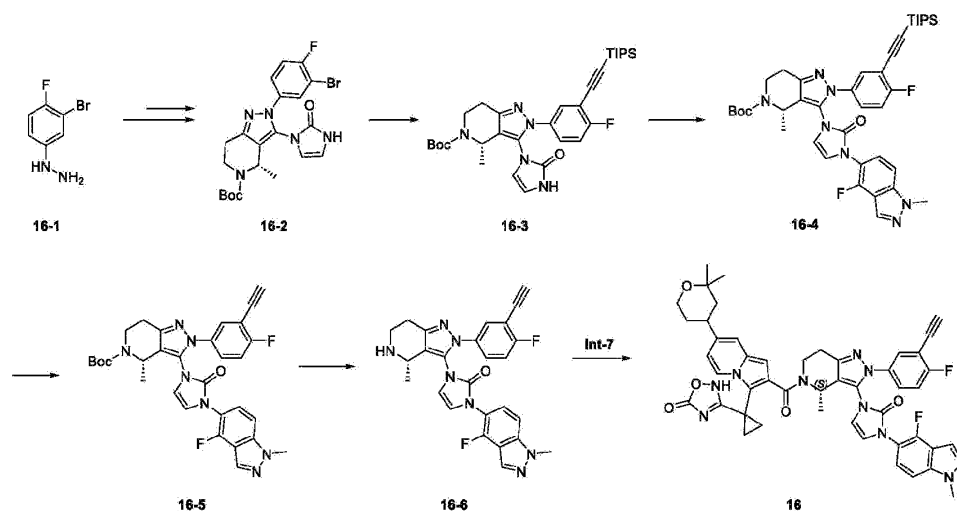


[0249] For the synthesis of 14-5 from int-13, please refer to the synthesis of intermediate 57 from intermediate 57-A in WO-202217338. The synthesis of Compounds 14 was referred to the synthesis of 5-1. LCMS: 895.3 [M+H]⁺. ¹HNMR (500 MHz, DMSO-*d*₆) δ 11.85 (brs, 1H), 8.23 (brs, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.71 - 7.48 (m, 1H), 7.47 - 7.20 (m, 5H), 7.14 - 6.77 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 1H), 6.07 - 5.25 (m, 1H), 4.27 - 3.92 (m, 4H), 3.79 - 3.64 (m, 2H), 3.48 - 3.27 (m, 1H), 2.92 (t, *J* = 12.0 Hz, 1H), 2.85 - 2.65 (m, 2H), 1.78 - 1.62 (m, 4H), 1.57 - 1.40 (m, 3H), 1.37 - 1.25 (m,

10H) , 1.19 (s, 3H) , 0.77 -0.68 (m, 4H) .Example 1.7: Synthesis of Compounds 15



[0250] Compound 15 was synthesized following the procedure of Compound 14 started from int-14. LCMS: 917.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 8.25 (brs, 1H) , 8.12 (d, J = 8.0 Hz, 1H) , 7.66 -7.52 (m, 1H) , 7.50 -7.20 (m, 5H) , 7.13 -6.82 (m, 2H) , 6.71 (d, J = 8.0 Hz, 1H) , 6.42 (s, 1H) , 5.85 -5.55 (m, 1H) , 5.17 -4.73 (m, 1H) , 4.11 (s, 3H) , 3.76 -3.68 (m, 2H) , 3.42 -3.36 (m, 1H) , 3.10 -3.00 (m, 2H) , 2.98 -2.90 (m, 1H) , 2.82 -2.70 (m, 2H) , 2.14 -1.99 (m, 1H) , 1.90 -1.79 (m, 1H) , 1.78 -1.57 (m, 4H) , 1.56 -1.43 (m, 2H) , 1.42 -1.23 (m, 8H) , 1.20 (s, 3H) .Example 1.8: Synthesis of Compound 16



[0251] For the conversion of 16-1 to 16-2, please refer to the synthesis of intermediate 57-D in WO-202217338. Step 1: 16-3

[0252] A mixture of 16-2 (500 mg, 1.02 mmol) , ethynyltriisopropylsilane (926 mg, 5.08 mmol) , Pd(PPh₃)₂Cl₂ (71 mg, 0.10 mmol) and copper (I) iodide (39 mg, 0.20 mmol) in TEA (15 mL) was degassed and purged with N₂ for 3 times and then stirred at 70 °C for 12 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was filtered, concentrated and purified by column chromatography to afford 16-3 (540 mg, 0.91 mmol, 90.0% yield) . LCMS: 594.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 10.41 (s, 1H) , 7.44 -7.38 (m, 3H) , 6.65 (s, 1H) , 6.63 -6.61 (m, 1H) , 5.08 (brs, 1H) ,

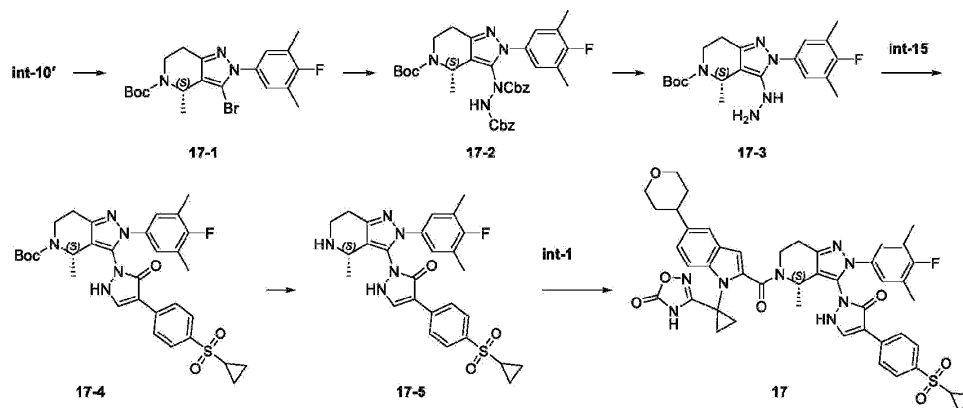
4.38 -4.13 (m, 1H) , 3.10 -3.03 (m, 1H) , 2.77 -2.70 (m, 1H) , 2.68 -2.60 (m, 1H) , 1.43 (s, 9H) , 1.27 -1.10 (m, 24H) .Step 2: 16-4

[0253] A mixture of 16-3 (550 mg, 0.93 mmol) , 5-bromo-4-fluoro-1-methyl-1H-indazole (255.0 mg, 1.11 mmol) , (1S, 2S) -N1, N2-dimethylcyclohexane-1, 2-diamine (66 mg, 0.46 mmol) , copper (I) iodide (88 mg, 0.46 mmol) and K₂CO₃ (256 mg, 1.85 mmol) in NMP (10 mL) was degassed and purged with N₂ for 3 times and then was stirred at 120 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (200 mL) and extracted with EtOAc (100 mL × 3) . The combined organic layers were washed with water (100 mL × 3) , followed by brine (200 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 16-4 (140 mg, 0.19 mmol, 20.3%yield) . LCMS: 742.5 [M +H] ⁺ . ¹HNMR (400 MHz, DMSO-d₆) δ 8.23 (s, 1H) , 7.60 (d, J = 8.0 Hz, 1H) , 7.51 -7.40 (m, 4H) , 7.11 -6.98 (m, 2H) , 5.17 (brs, 1H) , 4.25 (brs, 1H) , 4.11 (s, 3H) , 3.20 -3.09 (m, 1H) , 2.79 -2.65 (m, 2H) , 1.45 (s, 9H) , 1.23 -1.20 (m, 3H) , 1.11 -1.03 (m, 21H) .Step 3: 16-5

[0254] To a solution of 16-4 (120 mg, 0.16 mmol) in THF (2 mL) was added TBAF (0.16 mL, 1 M in THF) dropwise. The resulting mixture was stirred at 10 °C for 1 hr. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3) . The combined organic layers were washed with water (30 mL × 3) , followed by brine (30 mL) , dried over Na₂SO₄, filtered and concentrated to afford 16-5 (110 mg, 0.15 mmol, crude) . LCMS: 586.2 [M+H] ⁺ .Step 4: 16-6

[0255] A solution of 16-5 (110 mg, 0.19 mmol) in HCl (4 M in dioxane, 2 mL) was stirred at 10 °C for 1 hr. The reaction was concentrated to afford 16-6 (100 mg, crude) . LCMS: 486.2 [M+H] ⁺ .Step 5: Compound 16

[0256] Please refer to the synthesis of 5-1. LCMS: 865.2 [M+H] ⁺ . ¹HNMR (400 MHz, DMSO-d₆) δ 11.86 (brs, 1H) , 8.25 (s, 1H) , 8.14 (d, J = 8.0 Hz, 1H) , 7.65 -7.39 (m, 5H) , 7.30 (s, 1H) , 7.14 -6.83 (m, 2H) , 6.72 (d, J = 8.0 Hz, 1H) , 6.44 (s, 1H) , 5.71 (brs, 1H) , 4.52 (s, 1H) , 4.27 -3.99 (m, 4H) , 3.73 (d, J = 8.0 Hz, 2H) , 3.49 -3.34 (m, 1H) , 2.94 (t, J = 12.0 Hz, 1H) , 2.87 -2.70 (m, 2H) , 1.81 -1.61 (m, 4H) , 1.58 -1.41 (m, 3H) , 1.40 -1.33 (m, 3H) , 1.31 -1.24 (m, 4H) , 1.21 (s, 3H) .Example 1.9: Synthesis of Compound 17



Step 1: 17-1

[0257] To a solution of int-10' (400 mg, 1.07 mmol, WO2022017338) in ACN (2 mL) was added a solution of isoamyl nitrite (0.29 mL, 2.14 mmol) in ACN (2 mL) at 0 °C. The mixture was stirred at this temperature for 0.5 hrs, then CuBr (184 mg, 1.28 mmol) and CuBr₂ (286.0 mg, 1.28 mmol) were added. The resulting mixture was degassed and purged with N₂ for 3 times, stirred at 50 °C for 2 hrs. After cooling to room temperature, the reaction was poured into 20 mL of water and extracted with EtOAc (20 mL × 4). The combined organic layers were washed with water (20 mL × 2), followed by brine (30 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 17-1 (690 mg, 1.57 mmol, 15%yield). LCMS: 438.0 [M+H]⁺. Step 2: 17-2

[0258] To a solution of 17-1 (400 mg, 0.91 mmol) in THF (2 mL) was added nBuLi (0.73 mL, 1.83 mmol, 2.5 M) dropwise at -78 °C. The mixture was stirred at this temperature for 0.5 hr, then a solution of dibenzyl diazene-1, 2-dicarboxylate (408 mg, 1.37 mmol) in THF (1 mL) was added dropwise at -78 °C. After addition, the mixture was stirred at -40 °C for 0.5 hr, and then warmed up to 25 °C for 2 hrs. The reaction was poured into 20 mL of water and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with water (30 mL), followed by brine (30 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 17-2 (500 mg, 0.76 mmol, 83.0%yield). LCMS: 658.4 [M+H]⁺. Step 3: 17-3

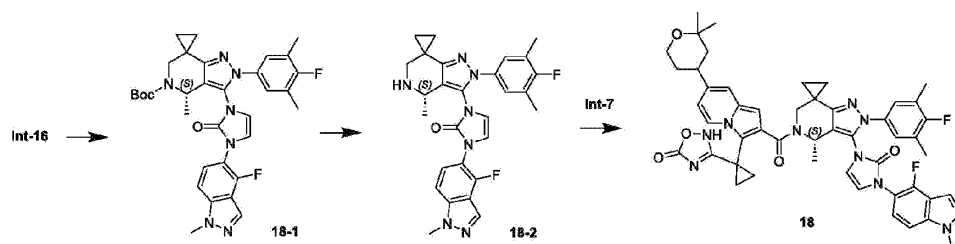
[0259] To a solution of 17-2 (400 mg, 0.61 mmol) in THF (10 mL) was added Pd/C (40 mg, 10%w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 1 hr under H₂ (15 Psi). The reaction mixture was filtered and washed with solvent (MeOH: DCM=10: 1, 33 mL × 3). The combined organic layers were concentrated to give 17-3 (250 mg, crude). LCMS: 390.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 7.50 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 5.54 -5.22 (m,

1H), 4.27 -4.00 (m, 2H), 3.19 -2.94 (m, 2H), 2.26 (d, J = 8.0 Hz, 6H), 1.46 -1.41 (m, 12H). Step 4: 17-4

[0260] To a solution of 17-3 (193 mg, 0.50 mmol) in EtOH (3 mL) was added int-15 (140 mg, 0.50 mmol) and sodium ethoxide (34 mg, 0.50 mmol). The resulting mixture was stirred at 25 °C for 1 hr. The reaction was poured into water (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water (20 mL), followed by brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 17-4 (120 mg, 0.19 mmol, 39.0% yield). LCMS: 622.2 [M+H]⁺. Step 5: 17-5

[0261] To a solution of 17-4 (120 mg, 0.19 mmol) in 1, 4-dioxane (2 mL) was added HCl solution (1.0 mL, 4 M in dioxane) dropwise. The resulting mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated to afford 17-5 (110 mg, crude). LCMS: 522.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 8.15 -7.90 (m, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.28 -6.84 (m, 3H), 5.19 -5.02 (m, 1H), 4.40 -4.07 (s, 2H), 3.20 -3.11 (m, 1H), 2.86 -2.79 (m, 1H), 2.77 -2.72 (m, 1H), 2.14 (s, 6H), 1.43 (s, 9H), 1.18 -1.05 (m, 5H), 1.04 -0.98 (m, 2H). Step 6: Compound 17

[0262] Compound 17 was synthesized following the procedure for 5-1 using int-1 instead of int-7. LCMS: 873.3 [M+H]⁺. ¹HNMR (500 MHz, DMSO-d₆) δ 11.89 (brs, 1H), 8.35 -7.55 (m, 5H), 7.52 -7.44 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.18 -6.41 (m, 4H), 5.92 -5.10 (m, 1H), 4.63 -4.21 (m, 1H), 3.97 (d, J = 8.0 Hz, 2H), 3.51 -3.44 (m, 3H), 2.91 -2.79 (m, 3H), 2.75 -2.68 (m, 1H), 2.15 (s, 6H), 1.87 -1.62 (m, 8H), 1.33 -1.25 (m, 3H), 1.09 -1.06 (m, 2H), 1.04 -0.93 (m, 2H). Example 1.10: Synthesis of Compound 18



Step 1: 18-1

[0263] To a solution of int-16 (210 mg, 0.45 mmol) in NMP (2 mL) were added 5-bromo-4-fluoro-1-methyl-1H-indazole (206 mg, 0.90 mmol), (1R, 2R)-N1, N2-dimethylcyclohexane-1, 2-diamine (32 mg, 0.23 mmol), K₂CO₃ (186 mg, 1.35 mmol) and copper (I) iodide (86 mg, 0.45 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 130 °C for 5 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (30 mL), extracted with EtOAc (20 mL × 3). The combined organic layers were washed with water (50

mL ×3) , followed by brine (50 mL) , dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 18-1 (200 mg, 0.33 mmol, 72.0%yield) . LCMS: 616.3 [M+H]⁺.Step 2: 18-2

[0264] A mixture of 18-1 (100 mg, 0.16 mmol) in HCl solution (4 M in dioxane, 1 mL) was stirred at 15 °C for 1 hr. The reaction mixture was concentrated to afford 18-2 (80 mg, 0.16 mmol, 96.0%yield) . LCMS: 516.2 [M+H]⁺.Step 3: Compound 18

[0265] Compound 18 was synthesized following the procedure for 5-1. LCMS (ESI⁺) : 895.4 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ 8.25 (brs, 1H) , 8.06 (d, J = 8.0 Hz, 1H) , 7.59 (brs, 1H) , 7.44 (brs, 1H) , 7.27 (s, 1H) , 7.10 (s, 2H) , 7.04 -6.74 (m, 2H) , 6.67 (d, J = 8.0, 1H) , 6.33 (s, 1H) , 6.08 -5.06 (m, 1H) , 4.10 (s, 3H) , 3.83 -3.63 (m, 3H) , 3.61 -3.44 (m, 1H) , 2.93 -2.88 (m, 1H) , 2.23 (s, 6H) , 1.77 -1.67 (m, 2H) , 1.65 -1.30 (m, 10H) , 1.27 (s, 3H) , 1.19 (s, 3H) , 1.17 -1.12 (m, 1H) , 0.91 -0.64 (m, 3H) .

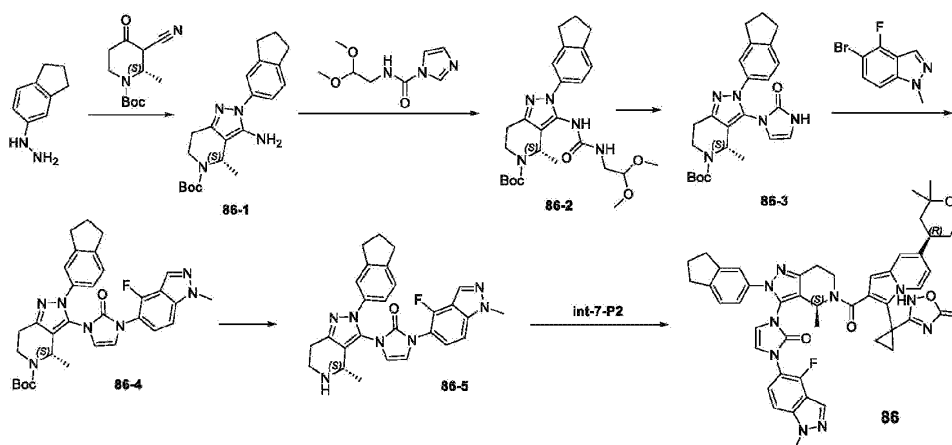
[0266] The Compounds in Table c below were prepared in accordance with the synthetic sequence in Compound 18 using the corresponding starting materials.TABLE c

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
61	int-7-P2 & 18-2	LCMS: 917.3 [M+H] ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 80 °C) δ 7.73 (d, <i>J</i> = 8.0 Hz, 1H), 7.61 (s, 2H), 7.49 (d, <i>J</i> = 8.0 Hz, 2H), 7.31 - 7.13 (m, 2H), 7.08 (dd, <i>J</i> = 4.0, 2.5 Hz, 1H), 6.83 - 6.51 (m, 3H), 5.57 (s, 1H), 4.67 - 4.14 (m, 5H), 3.98 (ddt, <i>J</i> = 12.0, 8.4, 4.1 Hz, 2H), 3.49 (td, <i>J</i> = 12.0, 4.7 Hz, 2H), 2.99 - 2.79 (m, 5H), 2.28 (d, <i>J</i> = 4.0 Hz, 3H), 1.84 - 1.68 (m, 6H), 1.45 (d, <i>J</i> = 8.0 Hz, 3H), 1.19 (dh, <i>J</i> = 12.0, 4.8 Hz, 2H), 1.13 - 1.05 (m, 2H).
62	int-17 & 18-2	LCMS: 915.3 [M+H] ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 80 °C) δ 7.72 - 7.37 (m, 6H), 7.21 - 7.06 (m, 3H), 6.92 - 6.84 (m, 1H), 6.55 (s, 1H), 5.71 - 5.53 (m, 1H), 5.39 - 5.19 (m, 1H), 4.44 - 4.20 (m, 1H), 4.14 - 4.03 (m, 2H), 4.02 - 3.94 (m, 2H), 3.82 - 3.58 (m, 1H), 3.55 - 3.43 (m, 2H), 2.97 - 2.92 (m, 1H), 2.88 - 2.81 (m, 2H), 2.77 - 2.70 (m, 2H), 2.31 - 2.18 (s, 4H), 2.08 - 1.92 (d, <i>J</i> = 16.9 Hz, 2H), 1.84 - 1.66 (m, 5H), 1.63 - 1.54 (m, 2H), 1.38 (d, <i>J</i> = 8.0 Hz, 3H), 1.22 - 1.66 (s, 2H), 1.12 - 1.08 (m, 2H).
63	int-18 & 18-2	LCMS: 929.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 80 °C) δ 11.91 (brs, 1H), 7.82 - 7.47 (m, 5H), 7.45 - 7.36 (m, 1H), 7.26 - 7.18 (m, 1H), 7.14 - 6.91 (m, 1H), 6.89 - 6.84 (m, 1H), 6.82 - 6.68 (m, 2H), 5.75 - 5.13 (m, 1H), 4.78 - 4.27 (s, 1H), 4.22 - 3.94 (m, 5H), 3.53 - 3.44 (m, 3H), 2.94 - 2.91 (m, 1H), 2.90 - 2.78 (m, 3H), 2.68 - 2.57 (m, 2H), 2.30 (d, <i>J</i> = 8.0 Hz, 3H), 1.80 - 1.70 (m, 9H), 1.58 - 1.50 (m, 2H), 1.45 - 1.35 (m, 3H), 1.19 - 1.15 (m, 2H), 1.10 - 1.06 (m, 2H).
64	int-1 & 18-2	LCMS: 867.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 8.23 (s, 1H), 7.60 - 7.53 (m, 1H), 7.52 - 7.48 (m, 2H), 7.43 - 7.31 (m, 1H), 7.22 (dd, <i>J</i> = 8.6, 1.7 Hz, 1H), 7.12 (d, <i>J</i> = 6.3 Hz, 2H), 6.98 - 6.78 (m, 2H), 6.70 (s, 1H), 5.87 - 5.31 (m, 1H), 4.10 (s, 3H), 4.01 - 3.77 (m, 4H), 3.51 - 3.44 (m, 2H), 2.88 - 2.82 (m, 1H), 2.25 - 2.22 (m, 6H), 1.81 - 1.68 (m, 8H), 1.50 - 1.38 (m, 5H), 1.00 - 0.89 (m, 2H).
65	int-19 & 18-2	LCMS: 867.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 80 °C) δ 11.82 (brs, 1H), 8.23 (s, 1H), 8.10 (d, <i>J</i> = 8.0 Hz, 1H), 7.58 (brs, 1H), 7.50 - 7.37 (m, 1H), 7.29 (s, 1H), 7.13 - 7.06 (m, 2H), 7.00 - 6.81 (m, 2H), 6.70 (d, <i>J</i> = 8.0 Hz, 1H), 6.36 (brs, 1H), 5.92 - 5.05 (m, 1H), 4.09 (s,

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		3H), 3.99 - 3.92 (m, 2H), 3.85 - 3.74 (m, 1H), 3.63 - 3.53 (m, 1H), 3.46 - 3.43 (m, 2H), 2.76 - 2.71 (m, 1H), 2.22 (s, 6H), 1.79 - 1.67 (m, 4H), 1.66 - 1.63 (m, 2H), 1.49 - 1.36 (m, 5H), 1.18 - 1.01 (m, 1H), 0.89 - 0.81 (m, 2H), 0.80 - 0.69 (m, 1H).
67	int-17 & int-64	LCMS: 878.4 [M-H] ⁺
96	Int-17 & int-44	LCMS: 968.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.58 (s, 1H), 7.78 - 7.41 (m, 3H), 7.38 (d, <i>J</i> = 8.5 Hz, 2H), 7.26 - 7.00 (m, 5H), 6.98 - 6.57 (m, 2H), 5.51 (d, <i>J</i> = 153.9 Hz, 1H), 4.31 - 3.45 (m, 4H), 3.06 - 2.96 (m, 1H), 2.18 (d, <i>J</i> = 2.1 Hz, 6H), 1.78 (s, 2H), 1.75 - 1.62 (m, 6H), 1.61 - 1.44 (m, 5H), 1.37 (d, <i>J</i> = 15.9 Hz, 3H), 1.15 - 1.03 (m, 2H), 1.00 - 0.90 (s, 1H).
99	Int-17 & int-67	LCMS: 950.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.59 (s, 1H), 7.54 (s, 2H), 7.39 (d, <i>J</i> = 8.6 Hz, 2H), 7.25 (d, <i>J</i> = 8.5 Hz, 2H), 7.18 (s, 1H), 7.10 (s, 2H), 6.94 (s, 1H), 6.76 (s, 1H), 5.93 (d, <i>J</i> = 53.7 Hz, 2H), 5.71 (s, 1H), 3.98 (s, 1H), 3.72 (d, <i>J</i> = 8.4 Hz, 3H), 3.08 - 2.96 (m, 1H), 2.20 (d, <i>J</i> = 2.1 Hz, 6H), 1.79 - 1.69 (m, 4H), 1.68 - 1.63 (m, 4H), 1.62 - 1.49 (m, 5H), 1.45 - 1.36 (m, 2H), 1.23 (d, <i>J</i> = 35.4 Hz, 9H), 1.14 - 1.02 (m, 2H), 1.00 - 0.90 (s, 1H).
105	Int-1 & int-67	LCMS: 908.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 7.66 - 7.42 (m, 3H), 7.34 (s, 1H), 7.25 - 7.11 (m, 3H), 7.09 (d, <i>J</i> = 6.3 Hz, 2H), 6.88 (s, 1H), 6.69 (s, 1H), 5.98 (s, 1H), 5.85 (s, 1H), 5.52 (d, <i>J</i> = 145.7 Hz, 1H), 4.24 - 3.60 (m, 4H), 3.51 - 3.41 (m, 2H), 2.91 - 2.78 (m, 1H), 2.18 (d, <i>J</i> = 2.2 Hz, 6H), 1.86 - 1.69 (m, 8H), 1.65 (q, <i>J</i> = 3.9, 3.2 Hz, 3H), 1.51 - 1.35 (m, 5H), 0.90 (d, <i>J</i> = 25.4 Hz, 1H), 1.02 - 0.85 (m, 2H).
107	Int-7-P2 & int-67	LCMS: 936.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.80 (brs, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.66 - 7.33 (m, 2H), 7.32 - 7.26 (m, 1H), 7.23 - 7.15 (m, 1H), 7.13 - 7.05 (m, 3H), 7.02 - 6.87 (d, <i>J</i> = 14.7 Hz, 1H), 6.70 (d, <i>J</i> = 8.0 Hz, 1H), 6.37 (brs, 1H), 6.07 - 5.92 (m, 1H), 5.91 - 5.80 (s, 1H), 5.19 - 4.15 (m, 1H), 3.894 - 3.79 (m, 1H), 3.71 (d, <i>J</i> = 8.0 Hz, 2H), 3.50 - 3.38 (m, 1H), 2.96 - 2.86 (m, 1H), 2.19 (s, 6H), 1.77 - 1.62 (m, 8H), 1.58 - 1.54 (m, 1H), 1.51 - 1.43 (m, 3H), 1.40 - 1.35 (m, 3H), 1.30 - 1.25 (m, 5H), 1.19 (s, 3H), 1.13 - 0.92 (m, 1H), 0.82 - 0.69 (m, 1H).
119	Int-7-P2 & int-44	LCMS: 954.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.82 (brs, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.77 - 7.42 (m, 2H), 7.40 - 7.14 (m, 4H), 7.13 - 6.91 (m, 3H), 6.75 - 6.61 (m, 1H), 6.36 (s, 1H), 5.89 - 5.02 (m, 1H), 4.34 - 3.74 (m, 1H), 3.70 (d, <i>J</i> = 8.0 Hz, 2H), 3.52 - 3.37 (m, 1H), 2.95 - 2.88 (m, 1H), 2.17 (s, 6H), 1.83 - 1.76 (m, 2H), 1.74 - 1.64 (m, 6H), 1.59 - 1.51 (m, 1H), 1.50 - 1.44 (m, 2H), 1.43 - 1.32 (m, 5H), 1.27 - 1.24 (m, 4H), 1.20 - 1.17 (m, 3H), 1.08 - 0.98 (m, 1H), 0.77 - 0.68 (m, 1H).
120	18-2 & int-50	LCMS: 891.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.88 (brs, 1H), 8.22 (s, 1H), 7.63 - 7.50 (m, 1H), 7.49 - 7.36 (m, 2H), 7.34 (s, 1H), 7.11 (d, <i>J</i> = 8.0 Hz, 2H), 7.01 - 6.75 (m, 2H), 6.72 - 6.63 (m, 1H), 5.99 - 5.29 (m, 1H), 4.08 (s, 3H), 3.96 - 3.71 (m, 4H), 3.57 (t, <i>J</i> = 12.0 Hz, 2H), 2.98 (t, <i>J</i> = 8.0 Hz, 2H), 2.23 (s, 6H), 2.17 - 2.09 (m, 2H), 1.96 - 1.62 (m, 6H), 1.54 - 1.35 (m, 7H), 1.03 - 0.87 (m, 2H).
133	Int-56 & Intermediate 59 of	LCMS: 841.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.25 (s, 1H), 8.12 (d, <i>J</i> = 8.0 Hz, 1H), 7.59 (brs, 1H), 7.42 (brs, 1H), 7.33 - 7.19 (m, 2H), 7.06 - 6.68 (m, 3H), 6.58 (brs, 1H), 6.51 (d, <i>J</i> = 8.0, 1H),

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
	WO2022017338	6.26 (s, 1H), 5.75 – 5.59 (m, 1H), 5.37 – 5.24 (m, 1H), 5.10 – 4.82 (m, 2H), 4.65 – 4.52 (m, 2H), 4.10 (s, 3H), 3.44 – 3.34 (m, 2H), 2.79 – 2.70 (m, 2H), 2.11 – 2.04 (m, 1H), 1.70 – 1.57 (m, 2H), 1.39 – 1.25 (m, 5H), 1.00 (d, <i>J</i> = 8.0 Hz, 2H), 0.73 – 0.60 (m, 2H).
143	Int-18 & int-58	LCMS: 855.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.76 (brs, 1H), 8.23 (s, 1H), 7.58 (d, <i>J</i> = 8.0 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.33 (m, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.11 (d, <i>J</i> = 8.0 Hz, 2H), 6.95 (brs, 1H), 6.91 – 6.80 (m, 1H), 6.77 (brs, 1H), 4.27 – 3.75 (m, 9H), 3.52 – 3.42 (m, 2H), 3.10 – 2.98 (m, 2H), 2.89 – 2.68 (m, 3H), 2.24 (s, 6H), 1.88 – 1.63 (m, 6H), 1.62 – 1.48 (m, 1H), 1.26 – 1.03 (m, 3H).

Example 1.11: Synthesis of Compound 86



Step 1: 86-1

[0267] To a solution of (2, 3-dihydro-1H-inden-5-yl) hydrazine (8.7 g, 58.7 mmol) in EtOH (90 mL) were added H₂O (5.29 mL, 294 mmol) and tert-butyl (2S) -3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (8.39 g, 35.2 mmol) at 25 °C. After addition, the resulting mixture was stirred at 80 °C for 16 hrs. The reaction solution was added water (700mL) and extracted with EA (50 mL × 3) , washed with brine (700 mL × 2) . The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 86-1 (10 g, 27.1 mmol, 46.2 %yield) . LCMS: 369.3 [M+H]⁺. Step 2: 86-2

[0268] To a solution of 86-1 (5 g, 13.57 mmol) in DMF (50 mL) was added NaH (1.628 g, 40.7 mmol) at 0 °C. After addition, the mixture was stirred at 0 °C for 30 mins under N₂. And then N- (2, 2-dimethoxyethyl) -1H-imidazole-1-carboxamide (8.11 g, 40.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 2 hrs, afterward, was poured into ice water (500 mL) and filtered, extracted with EA (30mL × 3) , washed with brine (500mL) . The organic layer was dried over Na₂SO₄,

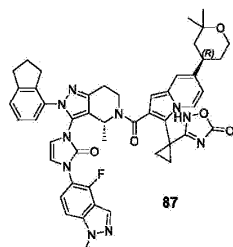
filtered, concentrated and purified by column chromatography to afford 86-2 (3.0 g, 6.00 mmol, 44.3 %yield) . LCMS: 500.2 [M+H]⁺. Step 2: 86-3

[0269] To a solution of 86-2 (3.0 g, 6.00 mmol) in THF (30 mL) were added Ts-OH (3.43 g, 18.01 mmol) at 25 °C. After addition, the resulting mixture was stirred at 60 °C for 1 hr. The reaction mixture was added water (100 mL) and filtered and extracted with EA (20mL × 3) , washed with brine (100 mL) . The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 86-3 (400 mg, 0.918 mmol, 15.30 %yield) . LCMS: 436.2 [M+H]⁺. Step 4: 86-4

[0270] To a solution of 6-bromo-7-fluoro-2-methyl-2H-indazole (182 mg, 0.794 mmol) in 1, 4-dioxane (5 mL) was added 86-3 (360 mg, 0.794 mmol) , Cs₂CO₃ (776 mg, 2.381 mmol) , CuI (30.2 mg, 0.159 mmol) and (1R, 2R) -N1, N2-dimethylcyclohexane-1, 2-diamine (45.2 mg, 0.318 mmol) . The reaction mixture was degassed and purged with N₂ for 3 mins. The mixture was stirred at 110 °C for 12 h. The reaction mixture was added water (20 mL) and extracted with EA (10mL × 3) , washed with brine (30 mL) . The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford 86-4 (140 mg, 0.240 mmol, 30.2 %yield) . LCMS: 584.4 [M+H]⁺ . LCMS: 436.2 [M+H]⁺. Step 5: 86-5

[0271] To a solution of 86-4 (140 mg, 0.240 mmol) in DCM (1 mL) was added EA/HCl (0.5 mL, 2 mmol) . The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to afford 86-5 (70 mg, 0.089 mol, 60.4 %yield) . LCMS: 484.3 [M+H]⁺. Step 6: Compound 86

[0272] To a solution of int-7-P2 (50 mg, 0.126 mmol) in DMF (2 ml) were added 86-5 (60.8 mg, 0.126 mmol) , DIEA (0.066 ml, 0.377 mmol) and HATU (57.4 mg, 0.151 mmol) at 25 °C. After addition, the resulting mixture was stirred at 25 °C for 1 hr. The reaction mixture was added water (20 mL) and extracted with EA (5mL × 3) , the combined organic layers were washed with brine (20 mL × 3) , dried over Na₂SO₄, filtered, concentrated and purified by Prep-TLC to afford 86 (14 mg, 0.016 mol, 12.9 %yield) . LCMS: 863.4 [M+H]⁺ . ¹HNMR (500 MHz, DMSO-d₆) δ 11.84 (s, 1H) , 8.32 –8.06 (m, 2H) , 7.51 (d, J = 68.4 Hz, 2H) , 7.35 –7.12 (m, 4H) , 7.06 –6.60 (m, 3H) , 6.43 (s, 1H) , 4.09 (s, 3H) , 3.71 (d, J = 8.6 Hz, 2H) , 3.39 (s, 1H) , 2.97 –2.66 (m, 7H) , 2.14 –2.02 (m, 2H) , 1.78 –1.10 (m, 19H) . Example 1.12: Synthesis of Compound 87



- [0273] Compound 87 was prepared in accordance with the synthetic sequence in Compound 86 using (2, 3-dihydro-1H-inden-4-yl) hydrazine instead of (2, 3-dihydro-1H-inden-5-yl) hydrazine. LCMS: 863.4 [M+H]⁺. ¹HNMR (500 MHz, DMSO-d₆) δ 13.02–11.09 (m, 1H), 8.52–7.90 (m, 2H), 7.64–7.03 (m, 6H), 6.90–6.66 (m, 2H), 6.45 (d, J = 4.9 Hz, 1H), 5.92–4.67 (m, 1H), 4.37–3.96 (m, 4H), 3.82–3.63 (m, 2H), 3.48–3.34 (m, 1H), 2.97–2.69 (m, 7H), 2.05–1.93 (m, 2H), 1.78–1.44 (m, 7H), 1.39–1.16 (m, 11H). Example 2.1: cAMP assay
- [0274] The changes of cAMP in human GLP-1 cells (cAMP HunterTM CHO-K1 GLP1R Gs Cell Line, Supplier: Eurofins, Catalog Number: 95-0062C2) were measured by LANCE Ultra cAMP Kit to evaluate the in vitro activity of compounds on human GLP-1 receptor. Experimental Methods:
- [0275] 1. Cell Thawing
- [0276] 1) Pre-warm complete medium (DMEM/F12+10%FBS+500 μg/mL G418) in a 37 °C water bath for 30 minutes.
- [0277] 2) Remove the GLP-1 cells from the liquid nitrogen tank, quickly thaw them in a 37 °C water bath, transfer the cell suspension to a 15 mL centrifuge tube with a pipette, and add 6 mL of complete culture medium.
- [0278] 3) After centrifugation at 1000 rpm for 4 minutes, the supernatant was discarded, cell precipitation was resuspended in 5 mL complete medium, and transferred to a T75 culture flask. 10 mL of the assay complete medium was added into a T75 flask and incubated at 37 °C and 5% CO₂.
- [0279] 4) Maintain the cells in culture until they are 80% confluent.
- [0280] 2. Cell Propagation
- [0281] 1) Remove the T75 flask from the cell culture incubator and place in a sterile tissue culture hood.
- [0282] 2) Gently aspirate media from the T75 flask.
- [0283] 3) Add 5 mL DPBS into the T75 flask, very gently tip the flask side to side allowing PBS to cover the entire surface of the flask to rinse the cells. Gently aspirate DPBS from flask.
- [0284] 4) Add 2 mL of 0.25% Trypsin-EDTA to the T75 flask. Gently rock the flask back and forth to ensure the surface of the flask is completely covered with trypsin.
- [0285] 5) Incubate the flask at 37 °C and 5% CO₂ for 2 to 3 minutes or until the cells have detached.
- [0286] 6) Add 5 mL of complete culture medium to the T75 flask. Using a pipette, gently rinse the cells from the surface of the flask with the added media.

- [0287] 7) Fill a new T75 flask with complete culture medium until the total volume equals 12 mL for T75 flasks, and add 1 mL cell suspension to the media in the flask. Transfer flask to a tissue culture incubator and incubate cells for 24 hours at 37°C and 5%CO₂.
- [0288] 8) The cells were passed for twice and then used for the cell experiment.
- [0289] 3. Compound Treatment
- [0290] Compounds were prepared with DMSO to a stock concentration of 10 mM. Reference compound Exendin-4 was prepared with DMSO to a stock concentration of 5 mM.
- [0291] The starting concentration of the compounds was 10 μM, 3-fold dilution, 10 concentration points, and duplicate. The 100 nL compounds were transferred to the 384-well plate using Echo.
- [0292] 4. Cell Culture
- [0293] 1) GLP-1 stable cell lines were removed from the incubator, and the cell status was observed. When the cell density reached 80%~90%, the medium was abandoned and the cells were washed with 5 mL DPBS.
- [0294] 2) DPBS was removed, followed by the addition of 2 mL 0.25% Trypsin-EDTA, then the cells was incubated in 37 °C for 2-5 min.
- [0295] 3) 10 mL complete culture medium was added into plates, and then the cells were collected by centrifugation at 1000 rpm for 4 min, followed by the remove of the supernatant.
- [0296] 4) The density of cell suspension was adjusted to 1000 cells/well by Stimulation Buffer. TABLE 5 Stimulation Buffer

Reagents	Stock (mM)	Work (mM)	Dil fold	V (μL)
HEPES	1000	5	200	60.0
IBMX	50	0.01	5000	2.40
BSA	7.5%	0.1%	75	160.0
1X HBSS				11,778
Total				12,000

- [0297] 5. Reaction
- [0298] 1) Transfer 10μl of cell solution to 384-well plate.
- [0299] 2) Centrifuge at 600 rpm for 3 minutes and incubate 60 minutes at room temperature.
- [0300] 3) Add 5μL 4X Eu-cAMP tracer solution and 5μL 4X ULIGHT™-anti-cAMP solution to 384-well plate. TABLE 6 Detection reagent

Reagents	Dilution fold	Volume (μL)
4X Eu-cAMP tracer solution	100	24.0
4X ULight™-anti-cAMP solution	300	8.0
cAMP Detection Buffer	-	2368.0
Total	-	2400

- [0301] 4) Centrifuge at 600rpm for 3 minutes and incubate 60 minutes at room temperature.
- [0302] cAMP signal was detected with Envision. GraphPad Prism (version 6.0) was used for the data analysis.
- [0303] 6. Detection of agonist activity in vitro:
- [0304] Plot the concentration value of the compound as the abscissa and the activity as the ordinate. Fit the data in GraphPad 6.0 to obtain EC50 values. $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{-(\text{LogEC50} - X) * \text{HillSlope}})$ Table 7

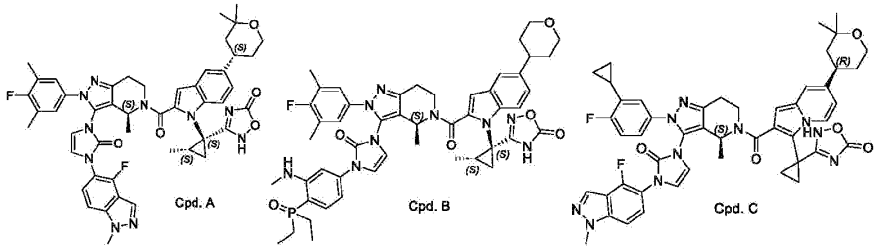
Compound No.	EC ₅₀
7	D
8	C
9	C
10	A
11	C
12	B
13	B
14	C
15	B
16	B
18	A
61	A
62	A
63	A
64	A
65	A
66	A
68	A
69	A
70	A
71	A
72	A
80	A
81	A
82	A
83	A
84	D
85	B

86	B
87	B
88	A
89	A
90	B
91	A
92	A
93	B
94	B
95	A
96	A
97	A
98	B
99	A
100	B
101	B
102	A
103	B
104	B
105	A
106	A
107	A
108	A
119	B
120	A
121	A
122	A
123	A
123-P2	A
124	A
125	A
126	B
127	A
128	B
129	A
130	B
131	A

132	A	EC ₅₀ : 0 < A ≤ 10 nM; 10 nM < B ≤ 50 nM; 50 nM < C ≤ 100 nM; 100 nM < D ≤ 200 nM
137	A	
138	D	
139	A	
140	A	
141	A	

- [0305] Other compounds disclosed herein also show GLP-1R agonist activity.Example 3.1: Pharmacokinetic profile evaluation
- [0306] Three cynomolgus monkeys were intravenously administrated with given compounds or orally gavage administrated with given compounds. The blood samples were taken at timepoints 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after intravenous (iv) administration or at timepoints 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6h, 8 h, and 24 h after oral gavage administration. Blood samples were placed in tubes containing K2-EDTA and stored on ice until centrifuged. The blood samples were centrifuged within 1 h after collected and stored frozen at approximately -80 °C. The analytical results were confirmed using quality control samples for intra-assay variation. The accuracy of >66.7%of the quality control samples should be between 80 -120%of the known value (s) . Standard set of parameters including Area Under the Curve (AUC_(0-t)) , maximum plasma concentration (C_{max}) , elimination half-life (T_{1/2}) will be calculated using non-compartmental analysis modules in FDA certified pharmacokinetic program Phoenix WinNonlin 7.0 (Pharsight, USA) .
- [0307] The data for Example C is shown in Table 8.Table 8. Monkey PK profile

Example	Dose (mg/kg)	PO T _{1/2} (h)	AUC _{0-t} (ng*h/mL)	Oral F%
Cpd. A	IV 0.5, PO 1.5	6.2	1154	22
Cpd. B	IV 0.5, PO 1.5	4.8	161	17
Cpd. C	IV 0.5, PO 1.5	1	104	8
68	IV 0.5, PO 1.5	15.6	1821	20
92	IV 0.5, PO 1.5	21.1	6320	28
97	PO 0.1	4.2	294	
127	IV 0.5, PO 1.5	15.6	2230	23

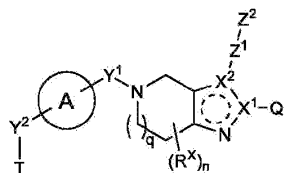


- [0308] Compared to reference compounds Cpd. A, Cpd. B and Cpd. C, examples disclosed herein showed better monkey pharmacokinetic profiles.

Claims

[Claim 1]

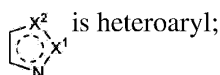
A compound of Formula (I) :



Formula (I),

or a pharmaceutically acceptable salt thereof,

wherein:

 X^1 is N and X^2 is C;or X^1 is C and X^2 is N; Y^1 is $-C(=O)-$, $-C(R^A)_2-$, or $-S(=O)_2-$;Ring A is heteroaryl optionally substituted with one or more R^A ;each R^A is independently halogen, hydroxy, oxo, SF_5 , alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the alkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more R^{A1} ;each R^{A1} is independently halogen, hydroxy, oxo, alkyl or alkoxy; Y^2 is $-Y^{2a}-Y^{2b}-Y^{2c}-$;each of Y^{2a} and Y^{2c} is a bond or alkyl; Y^{2b} is alkyl, SF_5 , haloalkyl or cycloalkyl, wherein the alkyl, haloalkyl and cycloalkyl are optionally substituted with one or more groups independently selected from alkyl, haloalkyl or cycloalkyl; T is $-C(=O)O(R^b)$, $-C(=O)N(R^b)$ -alkyl, $-C(=O)N(R^b)C(=O)(R^b)$, $-C(=O)N(R^b)-S(=O)(R^b)$, $-C(=O)N(R^b)-S(=O)_2(R^b)$, heterocyclyl or heteroaryl, wherein the alkyl, heterocyclyl and heteroaryl are optionally substituted with one or more R^T ;each R^X is independently halogen, hydroxyl, cyano, alkyl, SF_5 , haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy or alkoxyalkyl;or two R^X taken together with the intervening atom (s) form a cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl are optionally substituted with one or more R^{XX} ;each R^{XX} is independently halogen, hydroxy, oxo, alkyl, SF_5 , haloalkyl, hydroxyalkyl, alkoxy or alkoxyalkyl;

Q is cycloalkyl, aryl, heterocyclyl or heteroaryl, each optionally substituted with one or more R^Q ;

Z^1 is a bond, $-N(R^c)-$, $-N(R^c)-alkyl-$, $-N(R^c)-C(=O)-$, $-N(R^c)-C(=O)-N(R^c)-$, heterocyclyl, heteroaryl, heterocyclalkyl or heteroarylalkyl, wherein the alkyl, heterocyclyl, heteroaryl, heterocyclalkyl and heteroarylalkyl are optionally substituted with one or more groups independently selected from halogen, hydroxy, cyano, oxo, alkyl, haloalkyl, hydroxyalkyl, or alkoxy;

Z^2 is alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, each optionally substituted with one or more R^Z ;

each R^T is independently halogen, hydroxy, oxo, alkyl, SF_5 , haloalkyl, hydroxyalkyl, alkoxy or alkoxyalkyl;

each R^Q is independently halogen, hydroxy, cyano, alkyl, SF_5 , haloalkyl, hydroxyalkyl, alkoxy or cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups independently selected from halogen, haloalkyl, or alkyl;

each R^Z is independently halogen, hydroxyl, cyano, oxo, alkyl, SF_5 , haloalkyl, alkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)(R^d)_2$, $-S(=O)_2(R^d)_2$, or $-P(=O)(R^d)_2$, wherein the alkyl, alkoxy, cycloalkyl, aryl, heterocyclyl and heteroaryl are optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy;

or two R^Z together with the same atom to which they are both attached form a C_2-C_6 alkylidenyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, SF_5 , haloalkyl, alkyl or alkoxy;

each of R^a , R^b and R^c is independently hydrogen or alkyl;

or two R^a taken together with the same atom to which they are attached form a cycloalkyl or heterocyclyl;

each R^d is independently hydrogen, alkyl, or cycloalkyl;

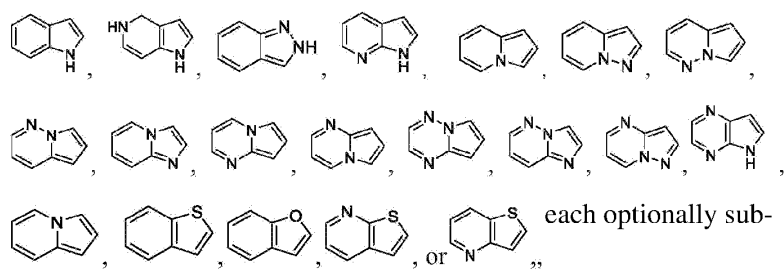
n is any integer of 0-6; and

q is any integer of 1-3.

[Claim 2]

The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is aryl optionally substituted with one or more R^Q .

- [Claim 3] The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Q is phenyl optionally substituted with one or more R^Q .
- [Claim 4] The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein T is heterocyclyl or heteroaryl, each optionally substituted with one or more R^T .
- [Claim 5] The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein T is selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, oxadiazolonyl, thiadiazolonyl, triazolyl, dihydrotriazolyl, or dihydrotriazolonyl.
- [Claim 6] The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is cycloalkyl or heterocyclyl, each are optionally substituted with one or more R^Q .
- [Claim 7] The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein Q is
-
- [Claim 8] The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is aryl substituted with one or more R^Q , and one R^Q is cycloalkyl substituted with one or more groups independently selected from halogen or haloalkyl.
- [Claim 9] The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein Q is aryl substituted with one or more R^Q , and one of R^Q is
-
- [Claim 10] The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein q is 2 or 3.
- [Claim 11] The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring A is a bicyclic heteroaryl optionally substituted with one or more R^A .
- [Claim 12] The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from the group consisting of:



[Claim 13]

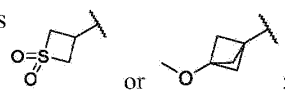
The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein each R^A is independently halogen, hydroxy, oxo, cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl are optionally substituted with one or more R^{A1} .

[Claim 14]

The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein each R^{A1} is independently oxo, alkyl or alkoxy.

[Claim 15]

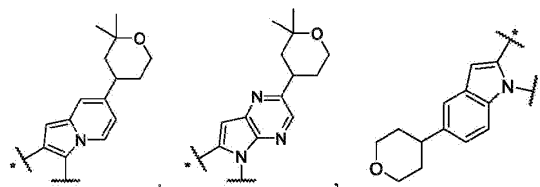
The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is a bicyclic heteroaryl substituted with one or more R^A , and one of R^A is

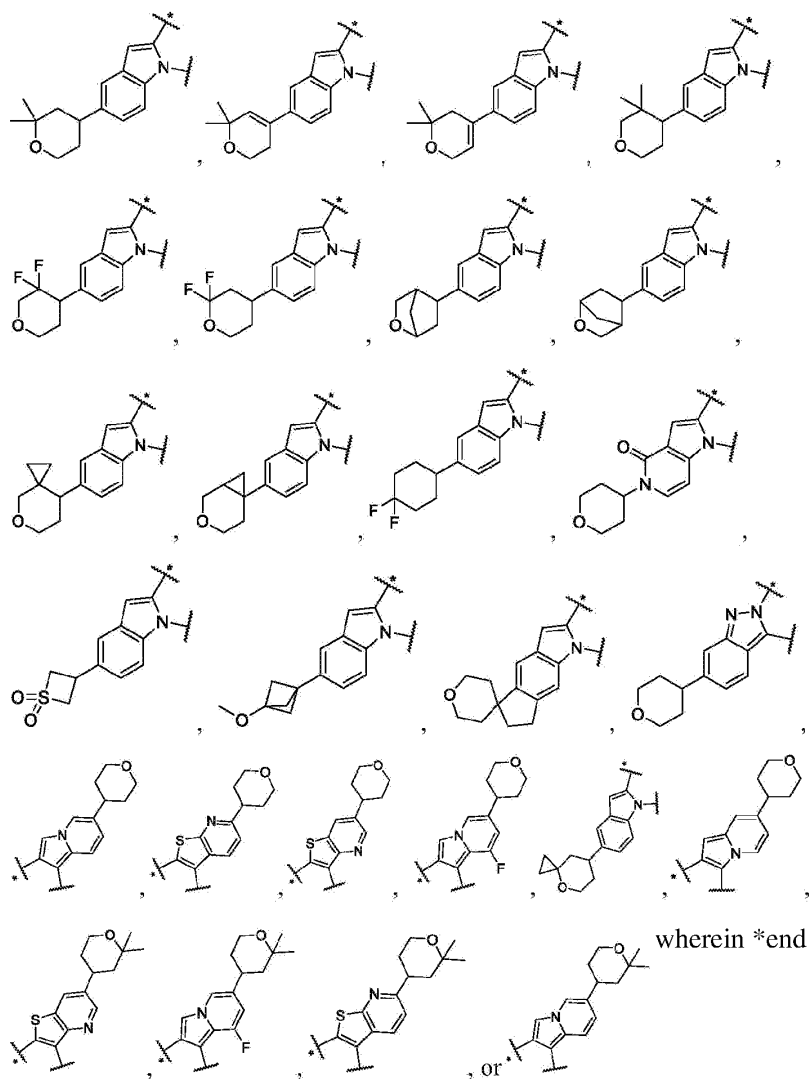


tricyclic or tetracyclic heteroaryl optionally substituted with one or more R^A .

[Claim 16]

The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Ring A is





of Ring A is connected to Y¹.

[Claim 17]

The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein Y¹ is -C(=O)- or ,



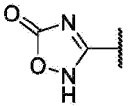
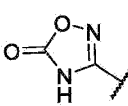
[Claim 18]

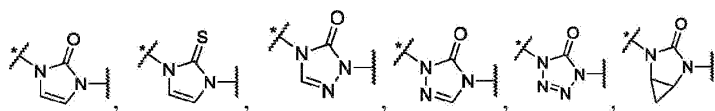
The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein Y² is alkyl or cycloalkyl optionally substituted with one or more alkyl.

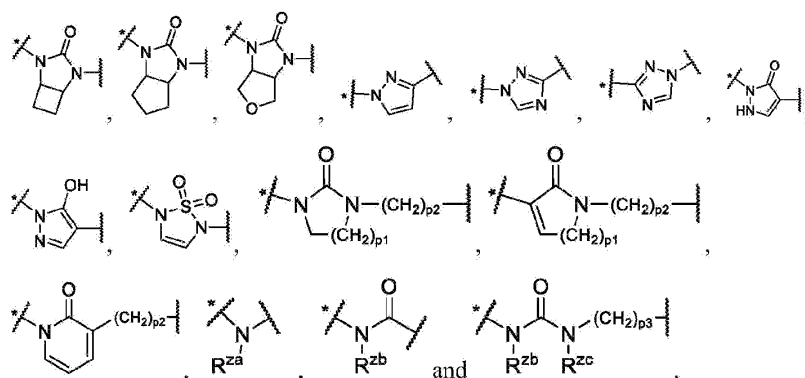
[Claim 19]

The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein Y² is

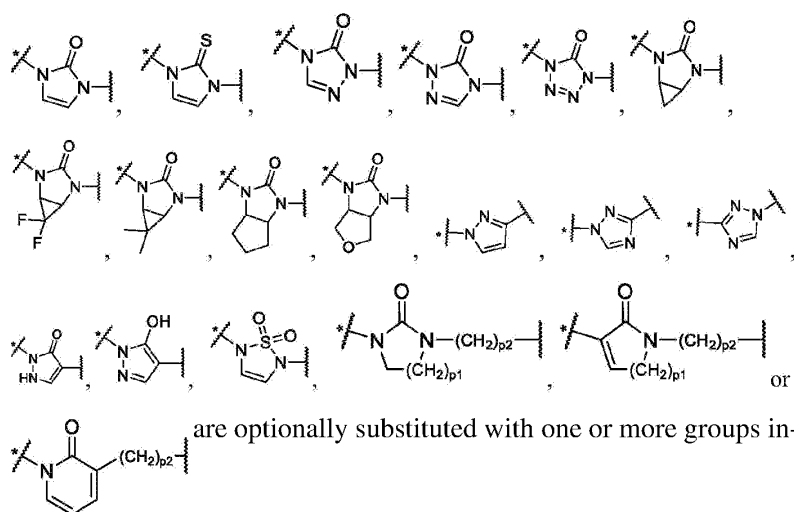


- [Claim 20] The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein T is heterocyclyl or heteroaryl, each optionally substituted with one or more R^T .
- [Claim 21] The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein each R^T is independently oxo, halogen or alkyl.
- [Claim 22] The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein T is  or .
- [Claim 23] The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^X is C_{1-6} alkyl.
- [Claim 24] The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein n is 3, one R^X is C_{1-6} alkyl and the other two R^X taken together with the same atom to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} .
- [Claim 25] The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein n is 3, one R^X is C_{1-6} alkyl and the other two R^X taken together with the adjacent atoms to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} .
- [Claim 26] The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Z^1 is a bond, $-N(R^c)-$, $-N(R^c)-C(=O)-$, $-N(R^c)-C(=O)-N(R^c)-$, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl, wherein the heterocyclyl or heteroaryl, heterocyclylalkyl or heteroarylalkyl are optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl.
- [Claim 27] The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein Z^1 is selected from the group consisting of: a bond,





wherein the



dependently selected from halogen, hydroxy, oxo, alkyl or haloalkyl,

p_1 is any integer of 1-3;

p_2 is any integer of 0-10;

p_3 is any integer of 0-10;

R^{za} is hydrogen, C_{1-6} alkyl, or $(C_{1-6}$ alkyl) carbonyl;

R^{zb} and R^{zc} are independently hydrogen or C_{1-6} alkyl; and

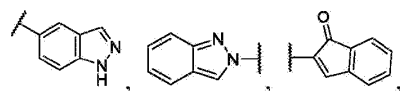
*end of Z^1 is connected to X^2 .

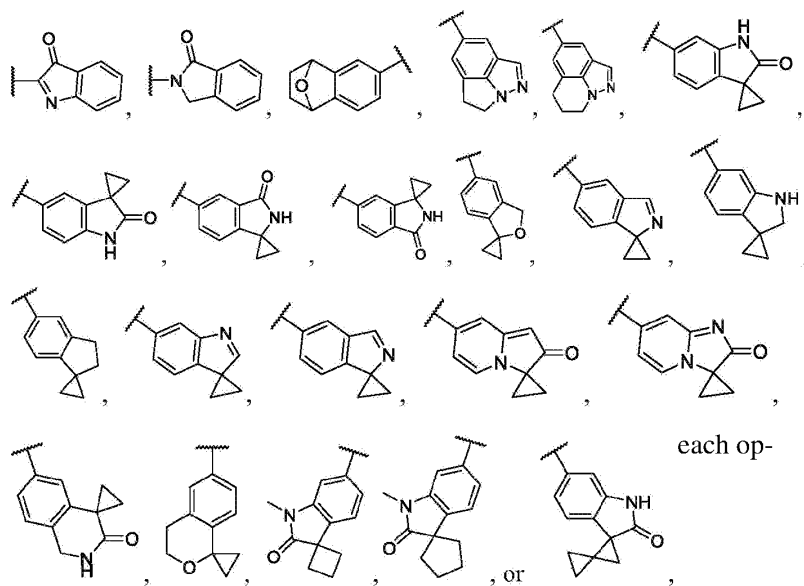
[Claim 28]

The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein Z^2 is aryl or heteroaryl, each optionally substituted with one or more R^Z .

[Claim 29]

The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein Z^2 is selected from phenyl, indazolyl,





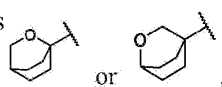
tionally substituted with one or more R^Z .

[Claim 30]

The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein Z^2 is cycloalkyl or heterocyclyl, each optionally substituted with one or more R^Z .

[Claim 31]

The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein Z^2 is



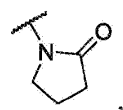
with one or more R^Z .

[Claim 32]

The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, alkyl, oxo, haloalkyl, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)_2(R^d)$, $-P(=O)(R^d)_2$ or heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy.

[Claim 33]

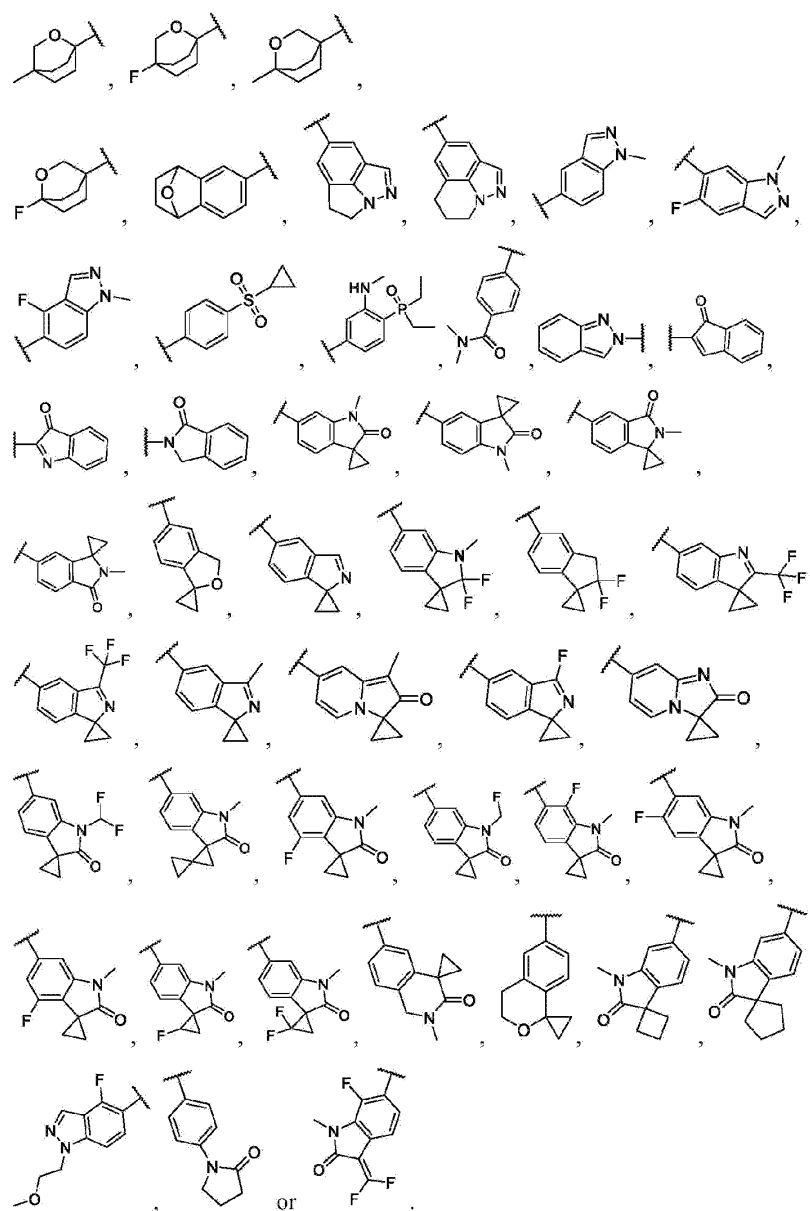
The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently



$NH(CH_3)$, $-C(=O)N(CH_3)_2$, $-S(=O)_2$ (cyclopropyl) or $-P(=O)(CH_2CH_3)_2$.

[Claim 34]

The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein Z^2 is selected from



[Claim 35]

The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from any compound set forth in Table 4.1 or Table 4.2.

[Claim 36]

A pharmaceutical composition comprising the compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

- [Claim 37] A method of treating or preventing a GLP-1 associated 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 1-35 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 36.
- [Claim 38] The method of claim 37, wherein the GLP-1 associated disease or disorder is non-insulin-dependent diabetes mellitus (Type 2 diabetes) , hyperglycemia, impaired glucose tolerance, insulin dependent diabetes mellitus (Type 1 diabetes) , diabetic complication, obesity, hypertension, hyperlipidemia, arteriosclerosis, coronary heart disease, brain infarction, non-alcoholic steatohepatitis, Parkinson's disease or dementia.