

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.

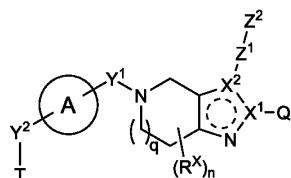
BACKGROUND

[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

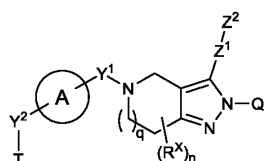
[0004] In one aspect, the present disclosure provides a compound of Formula (I):



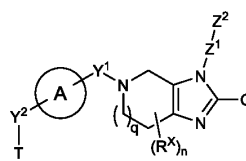
Formula (I),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

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



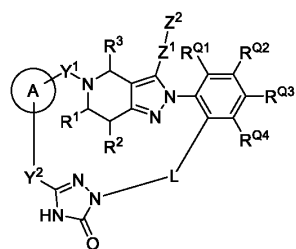
Formula (I-1),



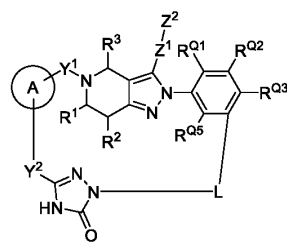
Formula (I-2),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

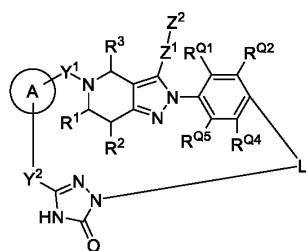
[0006] In one aspect, the present disclosure provides a compound of formula selected from:



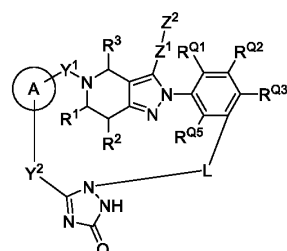
Formula (A-1),



Formula (A-2),



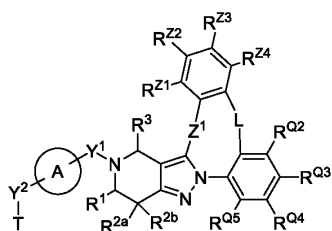
Formula (A-3) or



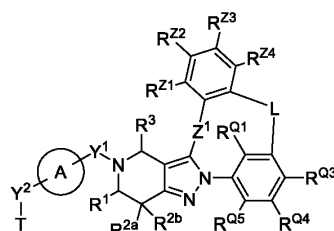
Formula (A-4),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

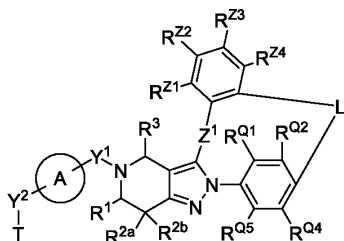
[0007] In one aspect, the present disclosure provides a compound of formula selected from:



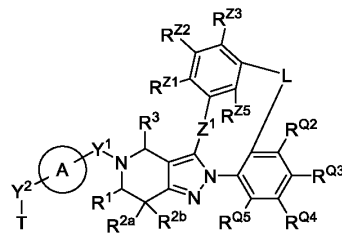
Formula (B-1),



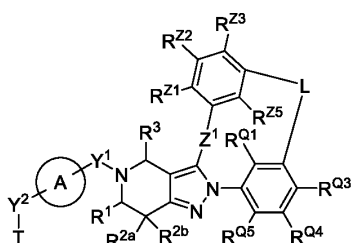
Formula (B-2),



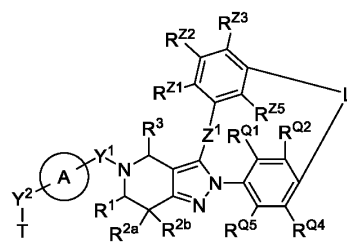
Formula (B-3),



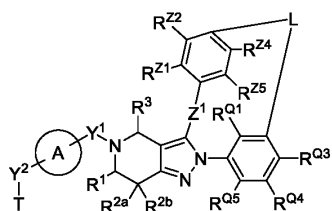
Formula (B-4),



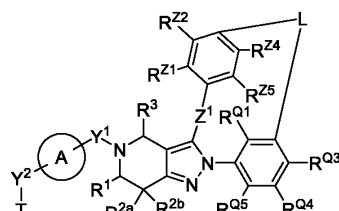
Formula (B-5),



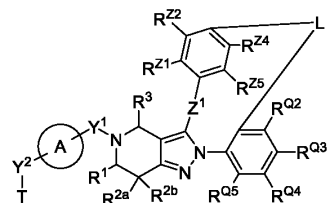
Formula (B-6),



Formula (B-7),



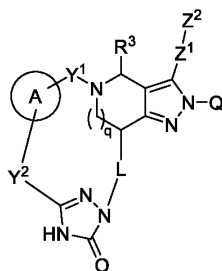
Formula (B-8) or



Formula (B-9),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

[0008] In one aspect, the present disclosure provides a compound of Formula (C-1):



Formula (C-1),

or a pharmaceutically acceptable salt thereof, as disclosed herein.

[0009] 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), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (B-1), Formula (B-2), Formula (B-3), Formula (B-4), Formula (B-5), Formula (B-6), Formula (B-7), Formula (B-8), Formula (B-9) or Formula (C-1), or a compound set forth in Table 1.1, Table 1.2, Table 2.1, Table 2.2, or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0010] 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), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (B-1), Formula (B-2), Formula (B-3), Formula (B-4), Formula (B-5), Formula (B-6), Formula (B-7), Formula (B-8), Formula (B-9) or Formula (C-1), or a compound set forth in Table 1.1, Table 1.2, Table 2.1, Table 2.2, or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein.

[0011] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (A-1), Formula (A-2), Formula (A-3), Formula

(A-4), Formula (B-1), Formula (B-2), Formula (B-3), Formula (B-4), Formula (B-5), Formula (B-6), Formula (B-7), Formula (B-8), Formula (B-9) or Formula (C-1), or a compound set forth in Table 1.1, Table 1.2, Table 2.1, Table 2.2, or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for activating GLP-1R in a subject.

[0012] Also disclosed herein is use of the compound disclosed herein (e.g., a compound of Formula (I), Formula (I-1), Formula (I-2), Formula (A-1), Formula (A-2), Formula (A-3), Formula (A-4), Formula (B-1), Formula (B-2), Formula (B-3), Formula (B-4), Formula (B-5), Formula (B-6), Formula (B-7), Formula (B-8), Formula (B-9) or Formula (C-1), or a compound set forth in Table 1.1, Table 1.2, Table 2.1, Table 2.2, or Table 3), or a pharmaceutically acceptable salt, or stereoisomer thereof, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof. In some embodiments, the disease or disorder is a GLP-1 associated disease or disorder.

INCORPORATION BY REFERENCE

[0013] 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

[0014] 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.

[0015] 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.

[0016] The terms below, as used herein, have the following meanings, unless indicated otherwise.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] When any variable (e.g., Rⁱ) 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 Rⁱ moieties, then the group may optionally be substituted with up to two Rⁱ moieties and Rⁱ at each occurrence is selected independently from the definition of Rⁱ. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0021] 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, C₁-C₆ 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 “C₁₋₁₂”

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.

[0022] “Oxo” refers to =O.

[0023] “Cyano” refers to -CN.

[0024] “Nitro” refers to -NO₂.

[0025] “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.

[0026] “Hydroxy” or “hydroxyl”, whether as part of another term or used independently, refers to -OH.

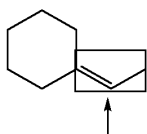
[0027] “Alkyl”, whether as part of another term or used independently, refers to a straight-chain, or branched-chain saturated hydrocarbon radical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁₋₆alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with one or more substituents, such as halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0028] “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 ($-\text{CH}=\text{CH}_2$), 1-propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), isopropenyl [$-\text{C}(\text{CH}_3)=\text{CH}_2$], 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.

[0029] “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.

[0030] “Alkylidenyl” is alkyl as defined above that is attached via the terminal divalent carbon. Exemplary alkylidenyls include, but are not limited to, methylidenyl ($\text{H}_2\text{C}=\text{}$), ethylidenyl ($\text{CH}_3\text{CH}=\text{}$), propylidenyl (such as $\text{=C}(\text{CH}_3)_2$ and $\text{=CHCH}_2\text{CH}_3$), hexylidenyl (such as $\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{}$), and the like. For example, in the compound below:



, the alkylidenyl group (i.e., ethylidenyl group), is enclosed by the box which is indicated by the arrow.

[0031] “Alkoxy” or “alkoxyl”, whether as part of another term or used independently, refers to a radical of the formula $-\text{OR}_a$ 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.

[0032] “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.

[0033] “Cycloalkyl”, whether as part of another term or used independently, refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (for example, fused with another cycloalkyl ring), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. In some embodiments, the cycloalkyl is partially saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C₃-C₁₅ fully saturated cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (C₃-C₁₀ fully saturated cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms

(C₃-C₈ fully saturated cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (C₃-C₆ fully saturated cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (C₃-C₅ fully saturated cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (C₃-C₄ fully saturated cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocyclyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -COOH, -COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with one or more substituents, such as oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0034] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0035] “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.

[0036] “Hydroxylalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyl radicals, as defined above, *e.g.*, hydroxylmethyl, 2-hydroxylethyl, 1,2-dihydroxylethyl, 1,2-dihydroxylpropyl, and the like.

[0037] “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.

[0038] “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.

[0039] “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.

[0040] “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.

[0041] “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.

[0042] “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.

[0043] “Heterocyclyl”, whether as part of another term or used independently, refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from 1 to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocyclyl is fully saturated. In some embodiments, the heterocyclyl is partially unsaturated. In some embodiments, the heterocyclyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocyclyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocyclyl comprises one to three nitrogens. In some embodiments, the heterocyclyl comprises one or two nitrogens. In some embodiments, the heterocyclyl comprises one nitrogen. In some embodiments, the heterocyclyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system. The polycyclic ring system may include fused (for example, a heterocyclyl ring fused with a cycloalkyl or another heterocyclyl ring), spiro, or bridged ring systems. The nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocyclyls include, but are not limited to, heterocyclyls having from two to fifteen carbon atoms (C₂-C₁₅ heterocyclyl), from two to ten carbon atoms (C₂-C₁₀ heterocyclyl), from two to eight carbon atoms (C₂-C₈ heterocyclyl), from two to seven carbon atoms (C₂-C₇ heterocyclyl), from two to six carbon atoms (C₂-C₆ heterocyclyl), from two to five carbon atoms (C₂-C₅ heterocyclyl), or two to four carbon atoms (C₂-C₄ heterocyclyl). Examples of such heterocyclyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, dihydrofuryl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl,

tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 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.

[0044] “Heteroaryl”, whether as part of another term or used independently, refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic or polycyclic (such as, bicyclic, tricyclic, or tetracyclic) ring system. The polycyclic ring system may include fused (for example, a heteroaryl ring fused with a cycloalkyl, heterocyclyl or aryl ring), bridged (for example, an aryl or heteroaryl ring fused with a bridged cycloalkyl or heterocyclyl ring) or spiro (for example, an aryl ring fused with a spiro heterocyclyl ring, or an heteroaryl ring fused with a spiro cycloalkyl or spiro heterocyclyl ring) ring systems. The nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some

embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (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, quinazoliny, 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.

[0045] 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-.

[0046] 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-.

[0047] 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.

[0048] 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., $-\text{CH}_2\text{CH}_3$), fully substituted (e.g., $-\text{CF}_2\text{CF}_3$), mono-substituted (e.g., $-\text{CH}_2\text{CH}_2\text{F}$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, $-\text{CFHCHF}_2$, 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.

[0049] 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.

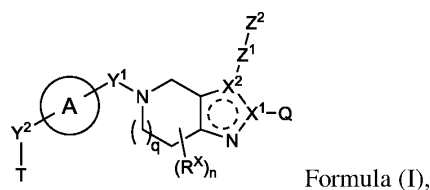
[0050] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0051] 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

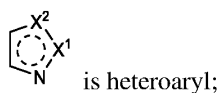
[0052] Described herein are compounds, or pharmaceutically acceptable salts thereof useful as GLP-1R agonists and in the treatment of diseases or disorders, such as cancer.

[0053] In one aspect, provided herein is a compound of 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, 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;

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, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)(R^d)$, $-S(=O)_2(R^d)$, 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, OCF_3 ;

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;

or one R^T together with one R^Q form a linking moiety L connecting T and Q;

or one R^Z together with one R^Q form a linking moiety L connecting Z^2 and Q;

or one R^T together with one R^X form a linking moiety L connecting T and R^X ;

each L is a bond or a linear C_{1-20} bivalent hydrocarbon chain optionally substituted with one or more R^y , wherein one or more methylene units of the chain are optionally and independently replaced

by cycloalkyl, heterocyclyl, $-C(R^L)=C(R^L)-$, $\begin{smallmatrix} \text{---} \end{smallmatrix}$, $-O-$, $-S-$, $-N(R^L)-$, $-C(=O)-$, $-OC(=O)-$, $-C(=O)O-$, $-S(=O)-$, $-S(=O)_2-$, $-N(R^L)C(=O)-$, $-C(=O)N(R^L)-$, $-N(R^L)S(=O)_2-$, or $-S(=O)_2N(R^L)-$;

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

each R^y is independently halogen, oxo, cyano, nitro, $-OR^{y1}$, $-OC(=O)R^{y1}$, $-OC(=O)OR^{y1}$, $-OC(=O)N(R^{y2})_2$, $-SR^{y1}$, $-S(=O)R^{y1}$, $-S(=O)_2R^{y1}$, $-S(=O)_2N(R^{y2})_2$, $-S(=O)(=NR^{y2})R^{y1}$, $-N(R^{y2})_2$, $-NR^{y2}C(=O)N(R^{y2})_2$, $-NR^{y2}C(=O)R^{y1}$, $-NR^{y2}C(=O)OR^{y1}$, $-NR^{y2}S(=O)_2R^{y1}$, $-N=S(=O)(R^{y1})_2$, $-C(=O)R^{y1}$, $-C(=O)OR^{y2}$, $-C(=O)N(R^{y2})_2$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, SF_5 , haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R^{y3} ;

each R^{y1} is independently hydrogen, alkyl, SF_5 , haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl or heterocyclyl, each optionally substituted with one or more R^{y3} ;

each R^{y2} is independently hydrogen, alkyl, SF_5 , haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-alkyl$ -cycloalkyl, or $-alkyl$ -heterocyclyl, optionally substituted with one or more R^{y3} ;

or two R^{y2} on the same atom are taken together with the atom to which they are attached to form a heterocyclcyl optionally substituted with one or more R^{y3} ; and

each R^{y3} is independently halogen, cyano, hydroxy, oxo, $-SF_5$, $-SH$, $-S(=O)$ -alkyl, $-S(=O)_2$ -alkyl, $-S(=O)_2NH_2$, $-S(=O)_2NH$ -alkyl, $-S(=O)_2N$ (alkyl) $_2$, $-S(=O)(=N$ -alkyl)(alkyl), $-NH_2$, $-NH$ -alkyl, $-N$ (alkyl) $_2$, $-N=S(=O)$ (alkyl) $_2$, $-C(=O)$ -alkyl, $-C(=O)OH$, $-C(=O)O$ -alkyl, $-C(=O)NH_2$, $-C(=O)NH$ -alkyl, $-C(=O)N$ (alkyl) $_2$, $-P(=O)$ (alkyl) $_2$, alkyl, alkoxy, SF_5 , haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, heteroalkyl or cycloalkyl;

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 heterocyclcyl;

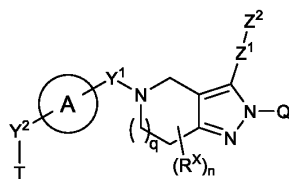
each R^d is independently hydrogen, alkyl, or cycloalkyl;

n is any integer of 0-6; and

q is any integer of 1-3;

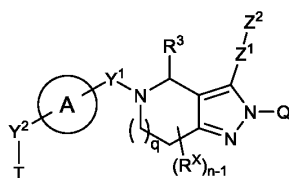
provided that the compound comprises at least one linking moiety L .

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



Formula (I-1).

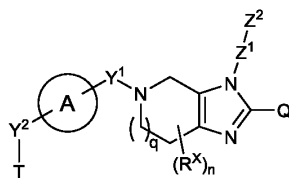
[0055] In some embodiments of Formula (I-1), the compound is of Formula (I-1-1):



Formula (I-1-1),

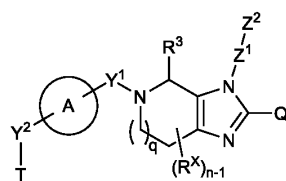
wherein R^3 is hydrogen or R^X , $n-1$ is any integer of 0-5. In some embodiments, R^3 is methyl. In some embodiments, $n-1$ is 0, 1, 2, or 3.

[0056] In some embodiments of Formula (I), the compound is of Formula (I-2):



Formula (I-2).

[0057] In some embodiments of Formula (I-2), the compound is of Formula (I-2-1):



Formula (I-2-1),

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

[0058] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), at least one linking moiety L exists. In some embodiments, one linking moiety L exists.

[0059] 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.

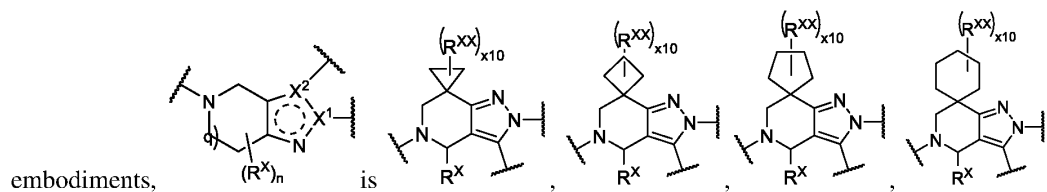
[0060] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2) or (I-1-2), two R^X taken together with the same atom to which they are attached form a C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, 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} .

[0061] 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} .

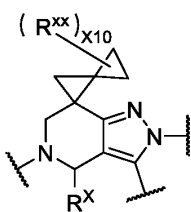
[0062] In some embodiments of Formula (I), (I-1), or (I-2), n is 1 and R^X is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, n is 1 and R^X is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0063] 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.

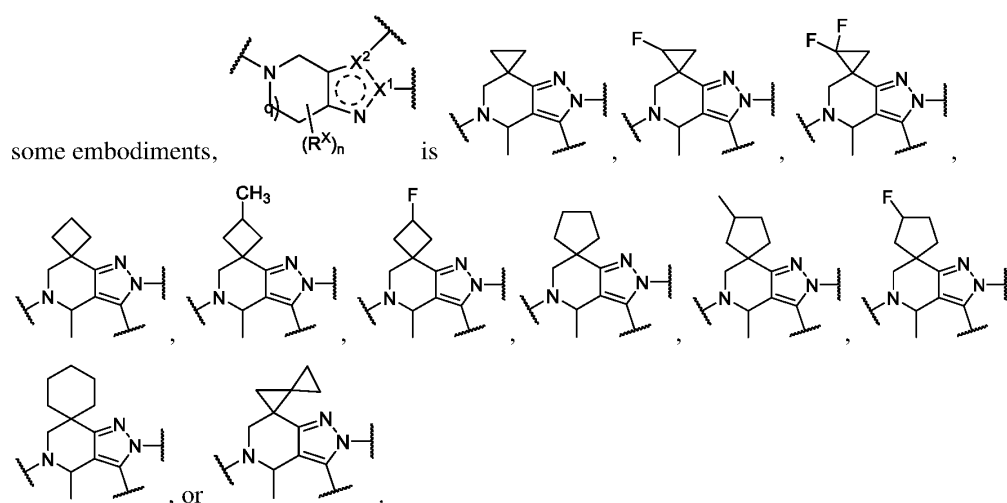
[0064] In some embodiments of Formula (I), (I-1) or (I-2), n is 3, one R^X is C_{1-6} alkyl and the other two R^X taken together with the same atom to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, n is 3, one 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



or

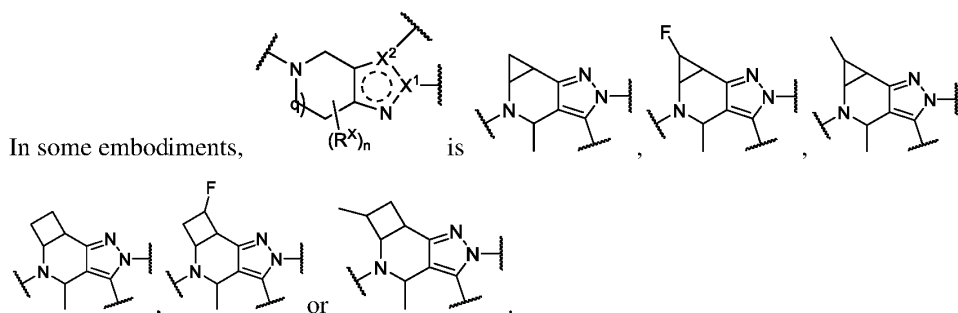


, X₁₀ is 0, 1, 2, or 3. In some embodiments, X₁₀ is 0, 1, or 2. In some embodiments, X₁₀ is 0, or 1. In some embodiments, X₁₀ is 0. In some embodiments, X₁₀ is 1. In



[0065] In some embodiments of Formula (I), (I-1) or (I-2), each R^{XX} is independently halogen, hydroxy, oxo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, C₁₋₆alkoxy or C₁₋₆alkoxyC₁₋₆alkyl. In some embodiments, each R^{XX} is independently halogen, hydroxy, oxo, or C₁₋₃alkyl.

[0066] In some embodiments of Formula (I), (I-1) or (I-2), n is 3, one R^X is C₁₋₆ 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 C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl and the other two R^X taken together with the adjacent atoms to which they are attached form a C₃₋₆ (e.g. C₃₋₄, C₃, C₄, C₅ or C₆, etc) cycloalkyl, C₃₋₅ cycloalkyl or C₃₋₄ cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX}.



[0067] 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} .

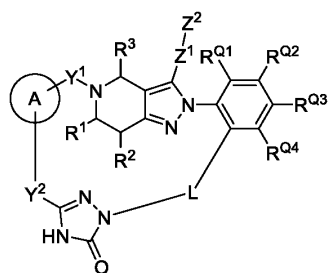
[0068] In some embodiments of Formula (I-1-1) or (I-2-1), $n-1$ is 2, two R^X taken together with the adjacent atoms to which they are attached form a cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more R^{XX} . In some embodiments, $n-1$ is 2, two R^X taken together with the 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} .

[0069] In some embodiments of Formula (I), (I-1) or (I-2), n is 0, 1, 2 or 3. In some embodiments, n is 0.

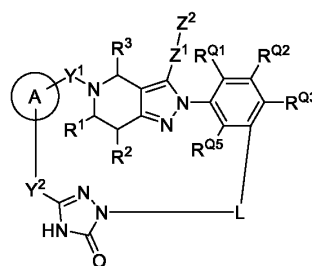
[0070] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), one R^T and one R^Q form a linking moiety L connecting T and Q .

[0071] 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 R^Q , T is heterocyclyl or heteroaryl optionally substituted with one or more R^T , and one R^T and one R^Q form a linking moiety L connecting T and Q .

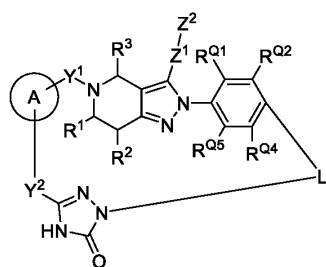
[0072] In some embodiments of Formula (I), (I-1) or (I-1-1), the compound is of formula selected from:



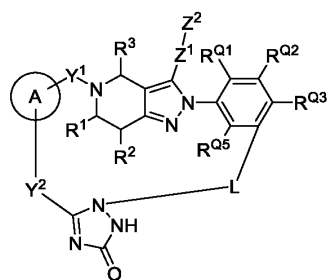
Formula (A-1),



Formula (A-2),



Formula (A-3) or



Formula (A-4),

wherein:

each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen or R^Q ;

or R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with the intervening atoms form a cycloalkyl, heterocyclyl, aryl, or heteroaryl, each optionally substituted with one or more group independently selected from halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxylalkyl, alkoxy or cycloalkyl;

each of R^1 , R^2 and R^3 is independently hydrogen or R^X .

[0073] In some embodiments of Formula (A-1), (A-2), (A-3) or (A-4), R^1 is hydrogen.

[0074] In some embodiments of Formula (A-1), (A-2), (A-3) or (A-4), R^2 is hydrogen.

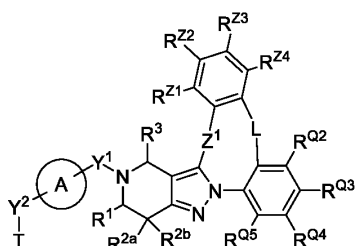
[0075] In some embodiments of Formula (A-1), (A-2), (A-3) or (A-4), R^3 is alkyl. In some embodiments, R^3 is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, R^3 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0076] In some embodiments of Formula (A-1), (A-2), (A-3) or (A-4), each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, halogen, alkyl or cycloalkyl. In some embodiments, each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, halogen, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl or C_{3-6} (e.g. C_{3-5} , C_3 , C_4 , C_5 or C_6 , etc) 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 the intervening atoms form a C_{3-6} (e.g. C_{3-5} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, C_6 aryl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more group independently selected from halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxylalkyl, alkoxy or cycloalkyl.

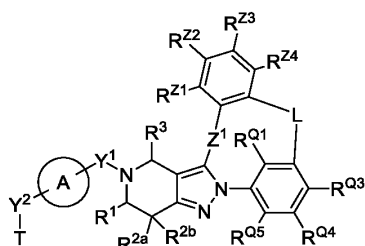
[0077] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), one R^Z and one R^Q form a linking moiety L connecting T and Q.

[0078] 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 R^Q , Z^2 is aryl optionally substituted with one or more R^Z , and one R^Z and one R^Q form a linking moiety L connecting Z^2 and Q.

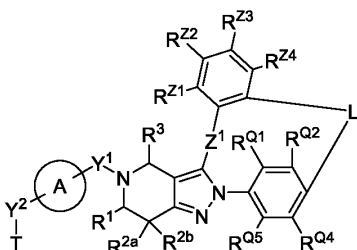
[0079] In some embodiments of Formula (I), (I-1), or (I-1-1), the compound is of formula selected from:



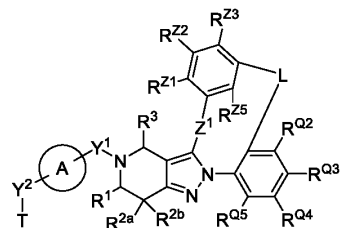
Formula (B-1),



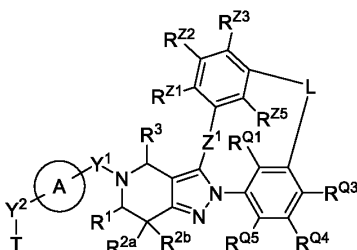
Formula (B-2),



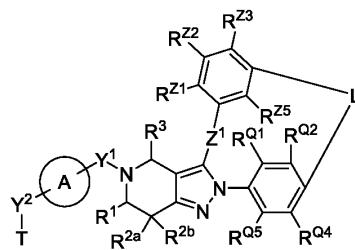
Formula (B-3),



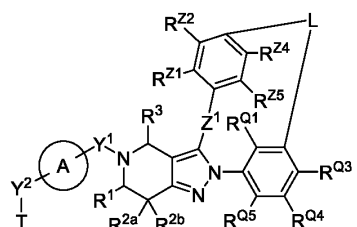
Formula (B-4),



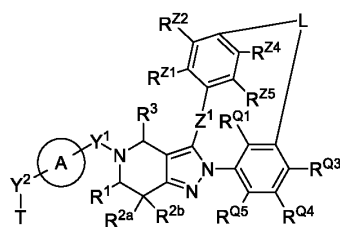
Formula (B-5),



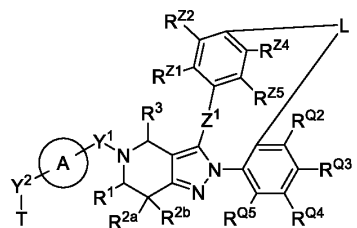
Formula (B-6),



Formula (B-7),



Formula (B-8) or



Formula (B-9),

wherein:

each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen or R^Q ;

each of R^{Z1} , R^{Z2} , R^{Z3} , R^{Z4} and R^{Z5} is independently hydrogen or R^Z ;

or R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , R^{Q4} and R^{Q5} , R^{Z1} and R^{Z2} , R^{Z2} and R^{Z3} , R^{Z3} and R^{Z4} , or R^{Z4} and R^{Z5} together with the 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; and

each of R^1 , R^{2a} , R^{2b} and R^3 is independently hydrogen or R^X .

[0080] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), R^1 is hydrogen.

[0081] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), R^1 and R^{2a} are taken together with the atoms they attached to form a cycloalkyl or heterocyclyl. In some embodiments, R^1 and R^{2a} are taken together with the atoms they attached to form a C_{3-6} cycloalkyl (such as C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl, or C_3 cycloalkyl) or 3- to 6-membered heterocyclyl (such as 6-membered heterocyclyl, 5-membered heterocyclyl, 4-membered heterocyclyl, or 3-membered heterocyclyl).

[0082] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), R^{2a} and R^{2b} are taken together with the atom they attached to form a cycloalkyl or heterocyclyl. In some embodiments, R^{2a} and R^{2b} are taken together with the atoms they attached to form a C_{3-6} cycloalkyl (such as C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl, or C_3 cycloalkyl) or 3- to 6-membered heterocyclyl (such as 6-membered heterocyclyl, 5-membered heterocyclyl, 4-membered heterocyclyl, or 3-membered heterocyclyl).

[0083] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, halogen, alkyl or cycloalkyl. In some embodiments, each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, halogen, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl or C_{3-6} (e.g. C_{3-5} , C_3 , C_4 , C_5 or C_6 , etc) 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 the intervening atoms form a C_{3-6} (e.g. C_{3-5} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, C_6 aryl, or 5- to 6- membered heteroaryl, each optionally substituted with one or more group independently selected from halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxylalkyl, alkoxy or cycloalkyl.

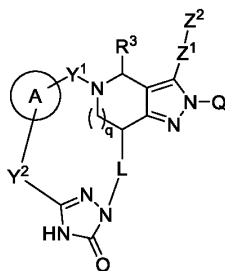
[0084] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), R^3 is alkyl. In some embodiments, R^3 is C_{1-6} alkyl, C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl. In some embodiments, R^3 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0085] In some embodiments of Formula (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8) or (B-9), each of R^{Z1} , R^{Z2} , R^{Z3} , R^{Z4} and R^{Z5} is independently hydrogen, halogen or alkyl. In some embodiments, each of R^{Z1} , R^{Z2} , R^{Z3} , R^{Z4} and R^{Z5} is independently hydrogen, -F or methyl.

[0086] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), one R^T together with one R^X form a linking moiety L connecting T and R^X .

[0087] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), or (I-2-1), n is an integer of 1 to 6, T is heterocyclyl or heteroaryl optionally substituted with one or more R^T , and one R^T and one R^X form a linking moiety L connecting T and R^X .

[0088] In some embodiments of Formula (I), (I-1), or (I-1-1), the compound is of Formula (C-1):



Formula (C-1),

wherein R^3 is hydrogen or R^X .

[0089] In some embodiments of Formula (C-1), R^3 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, R^3 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[0090] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), L is

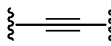
$\text{---}L^{11}\text{---}L^{12}\text{---}L^{13}\text{---}L^{14}\text{---}L^{15}\text{---}$, each of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is independently selected from a bond, S, ---C(=O)--- , O, NH, $\text{---S(=O)}_2\text{---}$, ---S(=O)--- , alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more (e.g. two, or three, etc) R^Y . In some embodiments, L^{11} is attaching to Q or Z^2 or R^X . In some embodiments, at least one of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is not a bond. In some embodiments, one of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is a bond. In some embodiments, two of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} are bonds. In some embodiments, three of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} are bonds. In some embodiments, four of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} are bonds. In some embodiments, the linker L^1 has a structure of $\text{---}L^{11}\text{---}L^{12}\text{---}$, $\text{---}L^{11}\text{---}L^{12}\text{---}L^{13}\text{---}$, $\text{---}L^{11}\text{---}L^{12}\text{---}L^{13}\text{---}L^{14}\text{---}$, $\text{---}L^{11}\text{---}L^{12}\text{---}L^{13}\text{---}L^{14}\text{---}L^{15}\text{---}$, $\text{---}L^{13}\text{---}L^{14}\text{---}L^{15}\text{---}$, or $\text{---}L^{11}\text{---}L^{15}\text{---}$. In some embodiments, the linker L^1 has a structure of $\text{---}L^{11}\text{---}L^{12}\text{---}$. In some embodiments, each of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is independently selected from a bond, S, ---C(=O)--- , O, NH, $\text{---S(=O)}_2\text{---}$, ---S(=O)--- , C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkynyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkynyl, C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, or 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more (e.g. two, or three, etc) R^Y . In some embodiments, each of L^{11} ,

L^{12} , L^{13} , L^{14} , and L^{15} is independently selected from a bond, S, $-C(=O)-$, O, NH, $-S(=O)_2-$, $-S(=O)-$, -

CH_2- , $-CH_2CH_2-$, $-CH=CH-$,  or , wherein NH, $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, or



are optionally substituted with one or more R^y .

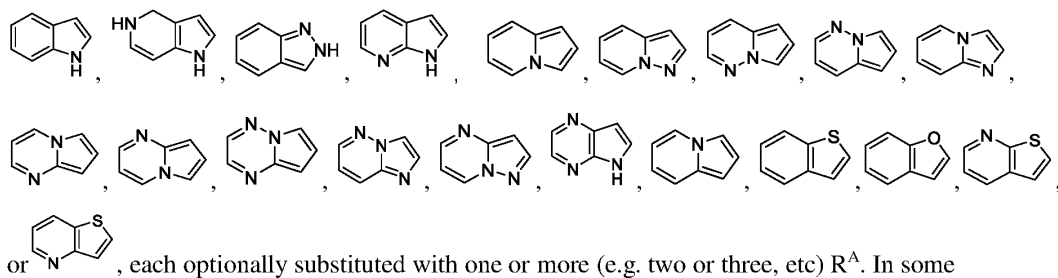
[0091] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), L is a bond or a linear C_{1-20} bivalent hydrocarbon chain optionally substituted with one or more R^y , wherein one or more methylene units of the chain are optionally and independently replaced by C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, $-C(R^L)=C(R^L)-$, , $-O-$, $-S-$, $-N(R^L)-$, $-C(=O)-$, $-OC(=O)-$, $-C(=O)O-$, $-S(=O)-$, $-S(=O)_2-$, $-N(R^L)C(=O)-$, $-C(=O)N(R^L)-$, $-N(R^L)S(=O)_2-$, or $-S(=O)_2N(R^L)-$. In some embodiments, each R^L is independently hydrogen, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl, or C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl.

[0092] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), each R^y is independently halogen, oxo, cyano, nitro, $-OR^{y1}$, $-OC(=O)R^{y1}$, $-OC(=O)OR^{y1}$, $-OC(=O)N(R^{y2})_2$, $-SR^{y1}$, $-S(=O)R^{y1}$, $-S(=O)_2R^{y1}$, $-S(=O)_2N(R^{y2})_2$, $-S(=O)(=NR^{y2})R^{y1}$, $-N(R^{y2})_2$, $-NR^{y2}C(=O)N(R^{y2})_2$, $-NR^{y2}C(=O)R^{y1}$, $-NR^{y2}C(=O)OR^{y1}$, $-NR^{y2}S(=O)_2R^{y1}$, $-N=S(=O)(R^{y1})_2$, $-C(=O)R^{y1}$, $-C(=O)OR^{y2}$, $-C(=O)N(R^{y2})_2$, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkynyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkynyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) haloalkyl, hydroxyalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) aminoalkyl, C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl or 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R^{y3} . In some embodiments, each R^{y1} is independently hydrogen, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) haloalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) hydroxyalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) aminoalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkynyl, C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl or 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, each optionally substituted with one or more R^{y3} . In some embodiments, each R^{y2} is independently hydrogen, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) haloalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) hydroxyalkyl, aminoalkyl, C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 or C_6 , etc) heteroalkyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkenyl, C_{2-6} (e.g. C_{2-3} , C_2 , C_3 , C_4 , C_5 or C_6 , etc) alkynyl, C_{3-6} (e.g. C_{3-4} , C_3 , C_4 , C_5 or C_6 , etc) cycloalkyl, 3- to 6- membered (e.g. 3-, 4-, 5- or 6-

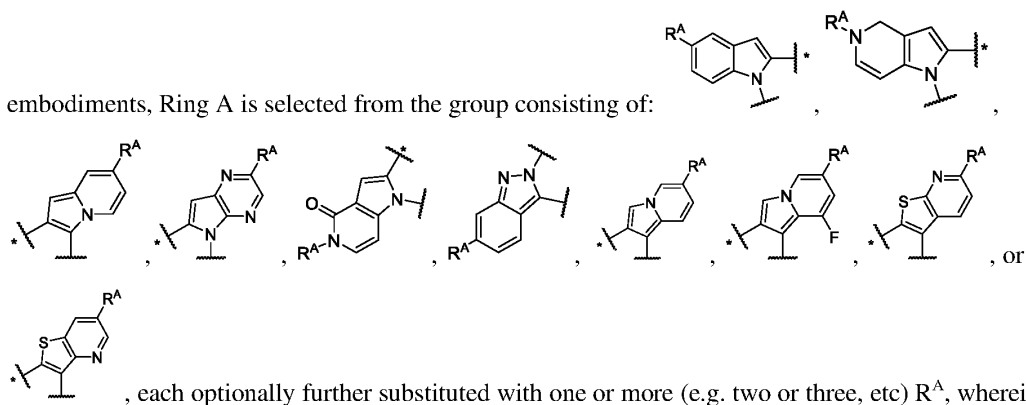
membered) heterocycloalkyl, C₆₋₁₂ (e.g. C₆₋₁₁ or C₆, etc) aryl, 5- to 12- membered (e.g. 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 5-to 6-, 7- to 8- or 10- to 12- membered) heteroaryl, -C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl-C₃₋₆ (e.g. C₃₋₄, C₃, C₄, C₅ or C₆, etc) cycloalkyl, or -C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl- 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl, optionally substituted with one or more R^{y3}. In some embodiments, two R^{y2} on the same atom are taken together with the atom to which they are attached to form a 3- to 6- membered (e.g. 3-, 4-, 5- or 6-membered) heterocyclyl optionally substituted with one or more R^{y3}. In some embodiments, each R^{y3} is independently halogen, cyano, hydroxy, oxo, -SF₅, -SH, -S(=O)-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -S(=O)₂-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -S(=O)₂NH₂, -S(=O)₂NH-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -S(=O)₂N(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)₂, -S(=O)(=N-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl), -NH₂, -NH-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -N(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)₂, -N=S(=O)(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)₂, -C(=O)-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -C(=O)OH, -C(=O)O-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, -C(=O)NH₂, -C(=O)NH-C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc)alkyl, -C(=O)N(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)₂, -P(=O)(C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl)₂, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkyl, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) alkoxy, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) haloalkyl, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) haloalkoxy, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) hydroxyalkyl, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) aminoalkyl, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅ or C₆, etc) heteroalkyl or C₃₋₆ (e.g. C₃₋₄, C₃, C₄, C₅ or C₆, etc)cycloalkyl.

[0093] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), L is -CH₂CH₂-#, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂C=CH-, -CH₂CH₂O-, -OCH₂CH₂-, -NHCH₂CH₂-# or -CH₂CH₂NH-, -CH₂CH₂CH₂O-, -OCH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂O-, -OCH₂CH₂CH₂CH₂-, -OCH₂CH₂O-, -OCH₂CH₂CH₂O-, -CH=CHCH₂O-, -OCH₂CH=CH-, -CH₂CH₂CH₂NH-, -NHCH₂CH₂CH₂-, -CH₂CH₂OCH₂CH₂-, -CH₂CH₂OCH₂-, -CH₂-cyclobutyl-O-, or -CH₂-cyclopropyl-O-, wherein# end of L is connected to Q or Z² or R^x.

[0094] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-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:



embodiments, Ring A is selected from the group consisting of:

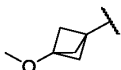


end of Ring A is connected to Y¹.

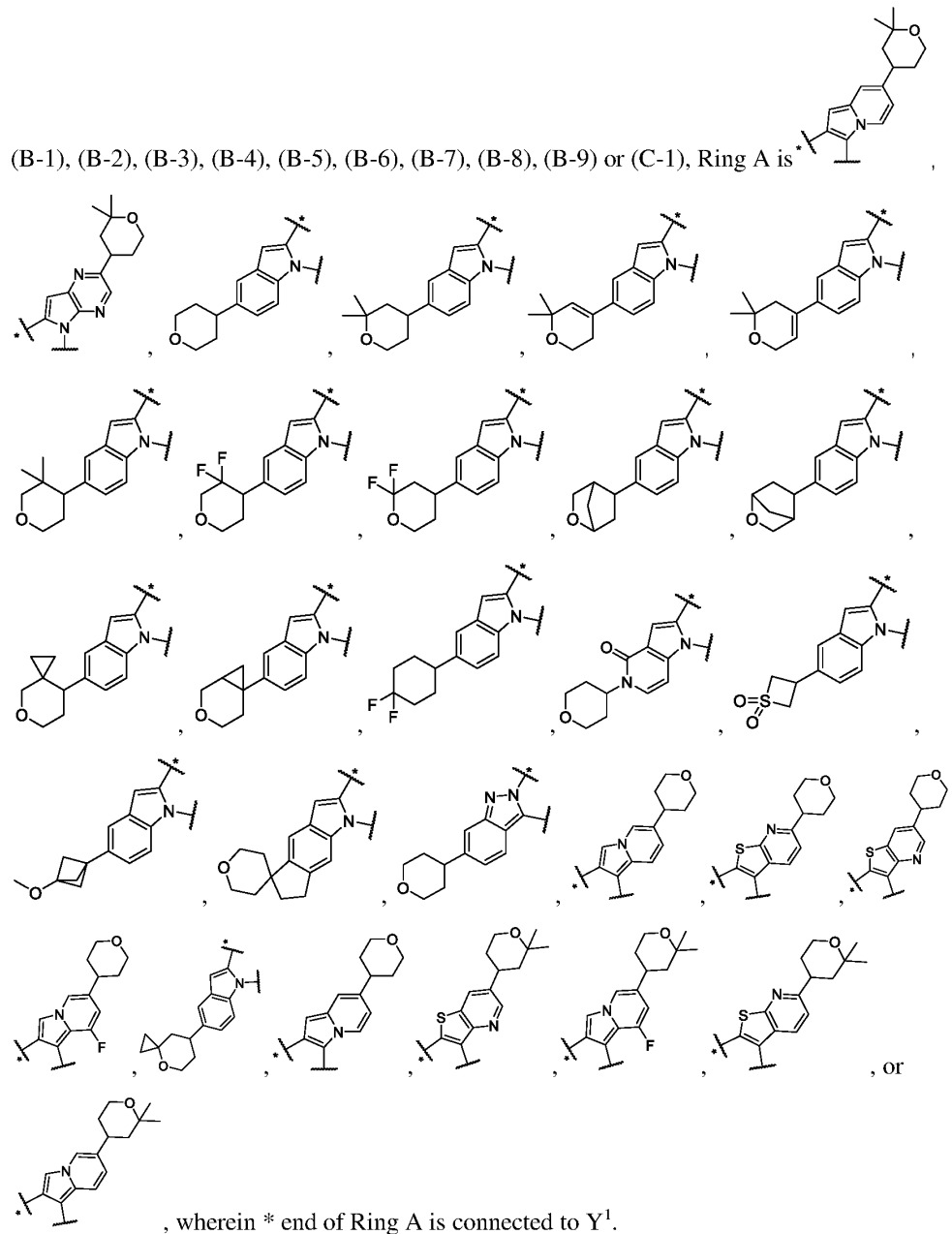
[0095] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), each R^A is independently halogen, hydroxy, oxo, cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl are optionally 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 C₃₋₈ cycloalkyl, C₄₋₈ cycloalkyl, C₅₋₈ cycloalkyl, C₅₋₇ cycloalkyl or C₅₋₆ 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 C₃ cycloalkyl, C₄ cycloalkyl, C₅ cycloalkyl, C₆ cycloalkyl, C₇ cycloalkyl or C₈ 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}.

[0096] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), each R^{Al} is independently oxo, alkyl or alkoxy. In some embodiments, each R^{Al} is independently oxo, C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅, C₆, etc) alkyl or C₁₋₆ (e.g. C₁₋₃, C₁, C₂, C₃, C₄, C₅, C₆, etc) alkoxy. In some embodiments, each R^{Al} is independently oxo, -CH₃, or -OCH₃.

[0097] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-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 .

[0098] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4),



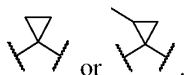
[0099] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), Y^1 is $-C(=O)-$, $-C(R^a)_2-$, or $-$

$S(=O)_2$ -. In some embodiments, Y^1 is $-C(=O)-$. In some embodiments, Y^1 is $-C(R^a)_2-$, and R^a is hydrogen or C_{1-6} (e.g. C_{1-3} , C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , etc) alkyl. In some embodiments, Y^1 is $-C(R^a)_2-$, and two R^a taken together with the same atom to which they are attached form a C_{3-6} (e.g. C_3 , C_4 , C_5 , or C_6 , etc) cycloalkyl or 3- to 6-membered (e.g. 3-, 4-, 5-, 6-, 3- to 4-, 4- to 5-, 5- to 6- membered, etc)



heterocyclyl. In some embodiments, Y^1 is $-S(=O)_2-$.

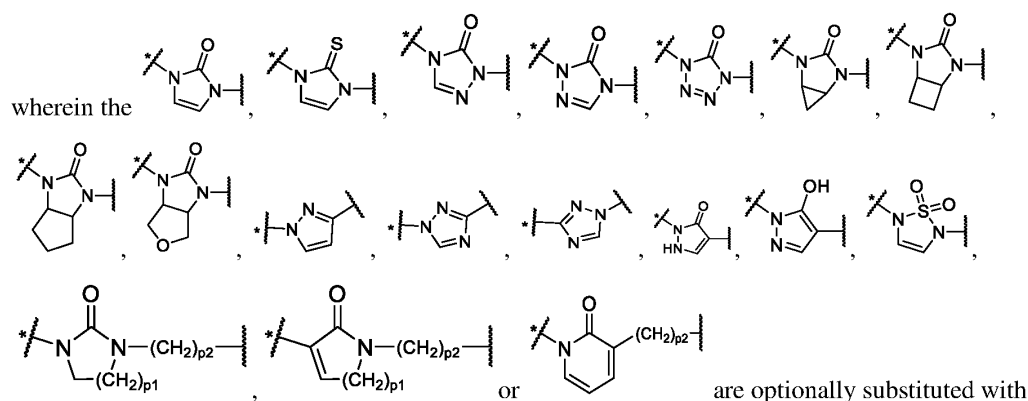
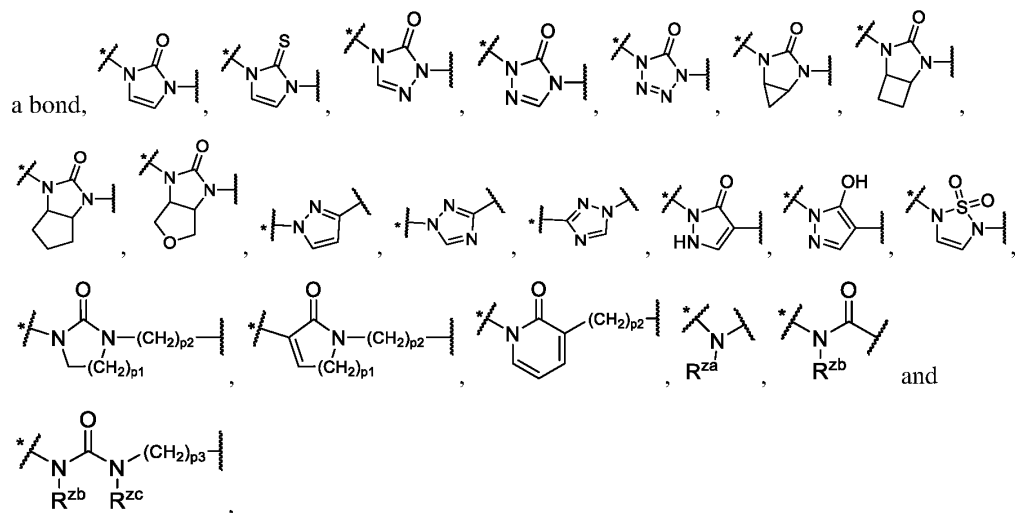
[0100] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), Y^2 is alkyl or cycloalkyl optionally substituted with alkyl. In some embodiments, Y^2 is C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, each optionally substituted with alkyl. In some embodiments, Y^2 is C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl, C_3 cycloalkyl, each optionally substituted with alkyl. In some embodiments, Y^2 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, Y^2 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl or C_2 alkyl or C_1 alkyl. In some embodiments, Y^2 is ,



[0101] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), 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. 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, etc) 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.

[0102] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), Z¹ is selected from the group consisting of:



one or more groups independently selected from halogen, hydroxy, oxo, alkyl or haloalkyl,

p1 is any integer of 1-3;

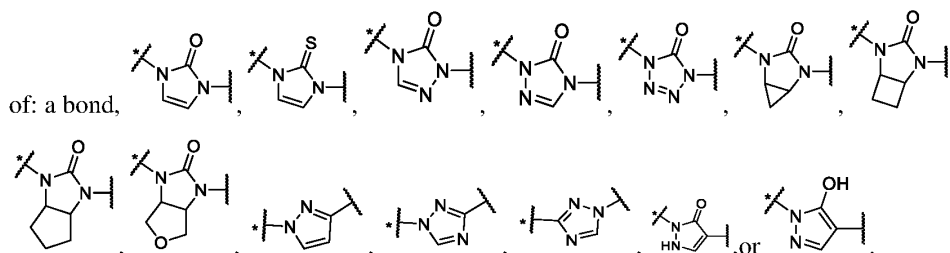
p2 is any integer of 0-10;

p3 is any integer of 0-10;

R^{2a} is hydrogen, C₁₋₆ alkyl, or (C₁₋₆ alkyl)carbonyl;

R^{zb} and R^{zc} are independently hydrogen or C₁₋₆ alkyl; and

* end of Z^1 is connected to X^2 . In some embodiments, Z^1 is selected from the group consisting



[0103] In some embodiments, p1 is 1, 2, or 3. In some embodiments, p2 is 0, 1, 2, 3, or 4. In some embodiments, p3 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.

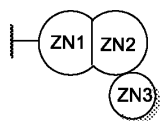
[0104] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z^2 is aryl or heteroaryl, each optionally substituted with one or more R^Z .

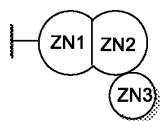
[0105] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z^2 is C_{6-12} (e.g. C_{12} , C_{11} , C_{10} , C_9 , C_8 , C_7 , or C_6) aryl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .

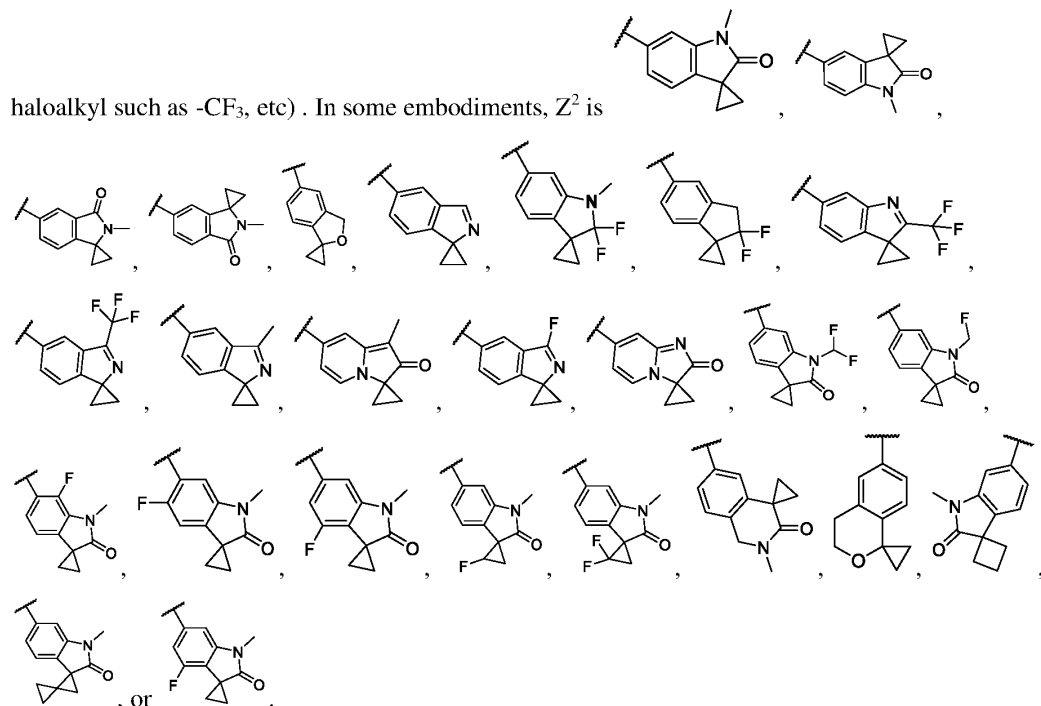
[0106] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z^2 is 5- to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heteroaryl, 6- to 14-membered heteroaryl, 7- to 14-membered heteroaryl, 8- to 14-membered heteroaryl, 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 .

[0107] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-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 .

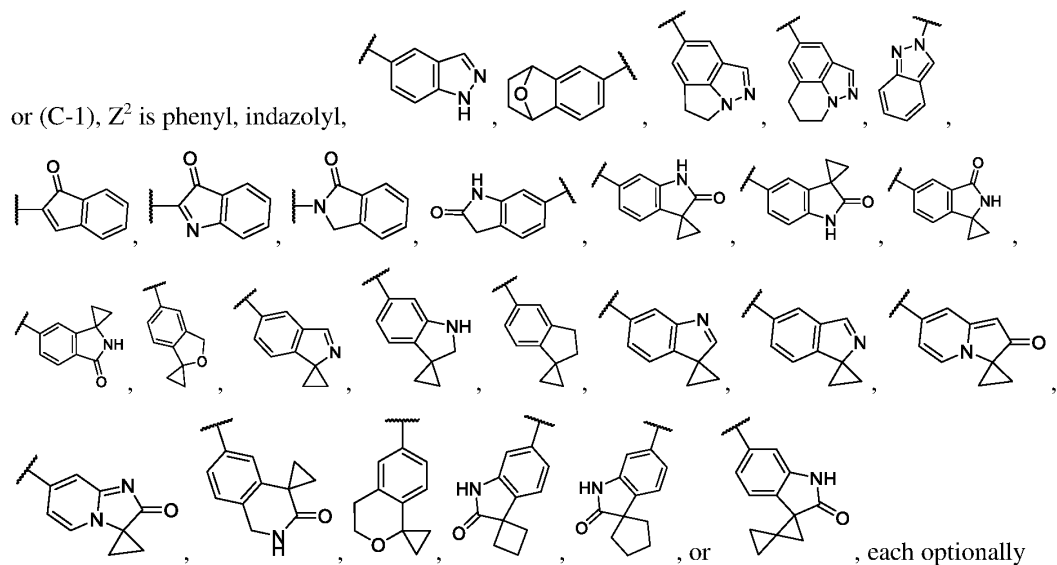
[0108] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z^2 is aryl or heteroaryl, each optionally substituted with one or more (e.g. two or three, etc)



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}



[0109] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4)



[0110] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z^2 is cycloalkyl or heterocyclyl, each optionally substituted with one or more (e.g. two or three, etc) R^Z .

[0111] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-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,

C₆₋₉ cycloalkyl or C₆₋₈ cycloalkyl, each optionally substituted with one or more (e.g. two or three, etc) R^Z.

[0112] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), Z² 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

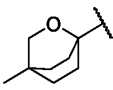
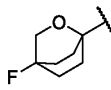
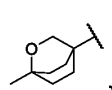
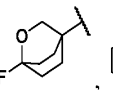
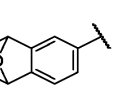
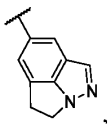
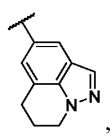
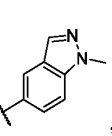
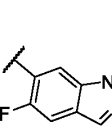
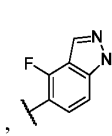
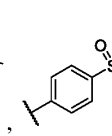
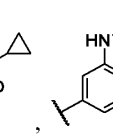
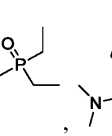
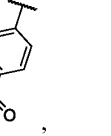
substituted with one or more (e.g. two or three, etc) R^Z. In some embodiments, Z² is  or , each optionally substituted with one or more (e.g. two or three, etc) R^Z.

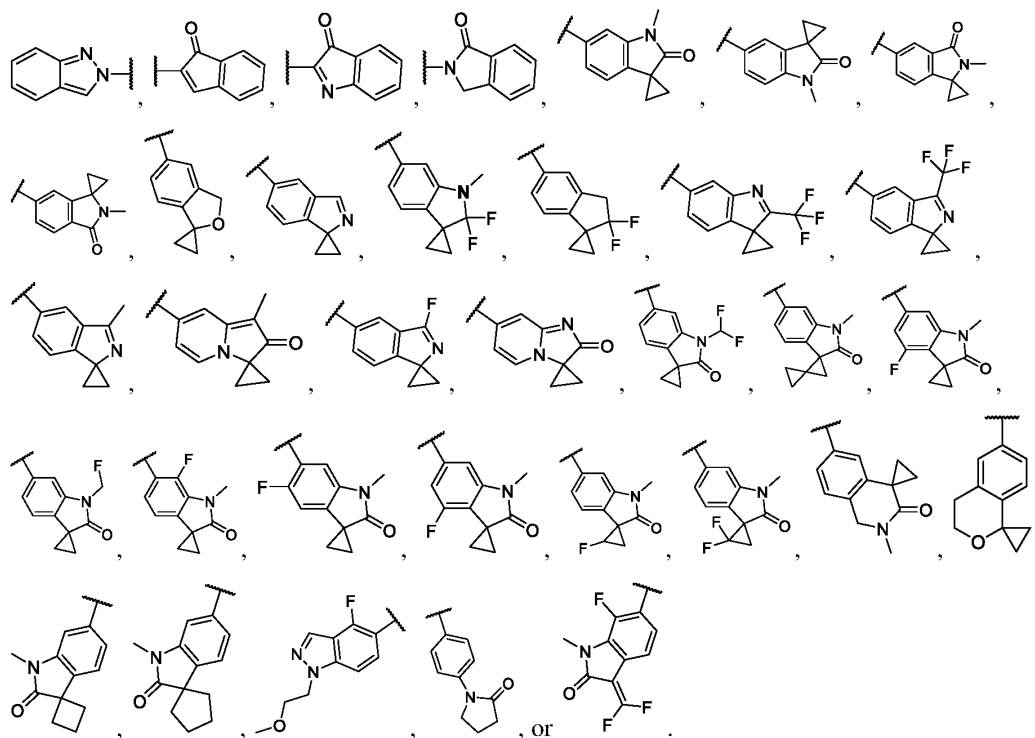
[0113] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4) or (C-1), each R^Z is independently halogen, alkyl, oxo, haloalkyl, -N(R^d)₂, -C(=O)N(R^d)₂, -S(=O)₂(R^d), -P(=O)(R^d)₂ or heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy. In some embodiments, each R^Z is independently halogen, C₁₋₆ alkyl, C₁₋₆ 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, -CHF₂, -CH₂F, -CF₃, -CH₂CH₂OCH₃, -NH(CH₃), -C(=O)N(CH₃)₂, -S(=O)₂(cyclopropyl) or -P(=O)(CH₂CH₃)₂. In some embodiments, 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 R. In some embodiments, 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 halogen. In some embodiments, two R^Z together with the same atom to which they are both attached form a C₂-C₄ 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 .

[0114] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4)

or (C-1), Z² is selected from , , , , , , , , , , , , , .



[0115] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-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

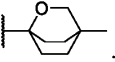
In some embodiments, Q is . In some embodiments, Q is , each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen or R^Q . In some embodiments, each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen, cyano, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl substituted 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, $-CH_3$, , , , , , or . 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 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.

[0116] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-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 .

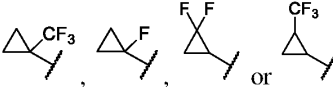
[0117] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-1), Q is heterocyclyl optionally substituted with one or more (e.g. two or three, etc) R^Q . In some embodiments, Q is 5- to 14-membered (e.g., 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered) heterocyclyl, 6- to 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 .

[0118] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-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.

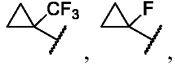
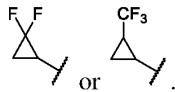
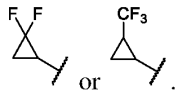
[0119] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-1), Q is aryl substituted with one or more R^Q , and one R^Q is C_{3-6} cycloalkyl, C_{3-5} cycloalkyl or C_{3-4} cycloalkyl, each substituted with one or more groups independently selected from halogen or haloalkyl. In 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.

[0120] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-1), Q is aryl

substituted with one or more R^Q , and one R^Q is , or

[0121] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (A-1), (A-2), (A-3), (A-4), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), each R^Q is independently

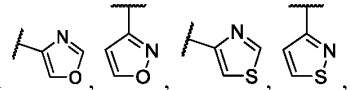
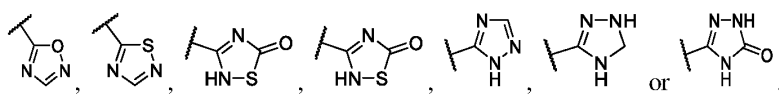
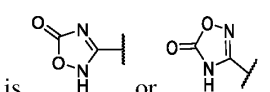
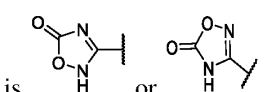
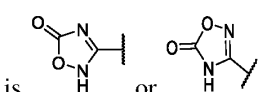
halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxyalkyl, alkoxy or cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more (e.g. two or three, etc) groups independently selected from halogen, haloalkyl, or alkyl. In some embodiments, each R^Q is independently halogen (e.g. F, Cl, 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 ,  or . 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.

[0122] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-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.

[0123] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), (B-1), (B-2), (B-3), (B-4), (B-5), (B-6), (B-7), (B-8), (B-9) or (C-1), T is selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, oxadiazolonyl, thiadiazolonyl, triazolyl, dihydrotriazolyl, or

dihydrotriazolonyl. In some embodiments, T is selected from ,  or . In some embodiments, T is  or .

[0124] In some embodiments of Formula (I), (I-1), (I-1-1), (I-2), (I-2-1), or (C-1), q is 1, 2 or 3. In some embodiments, q is 1. In some embodiments, q is 2 or 3.

[0125] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 1.1, Table 1.2, Table 2.1, Table 2.2 and Table 3.

TABLE 1.1 Exemplary Compounds

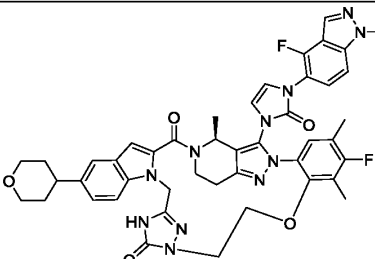
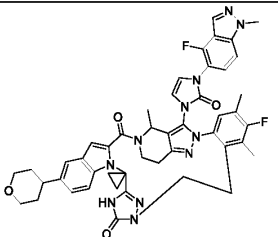
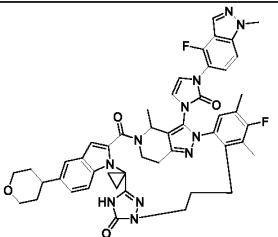
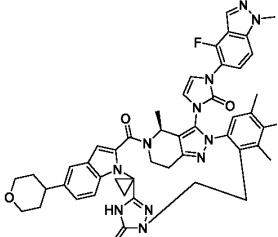
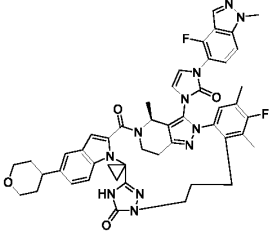
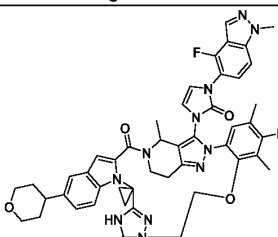
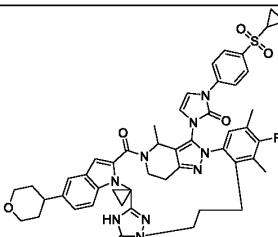
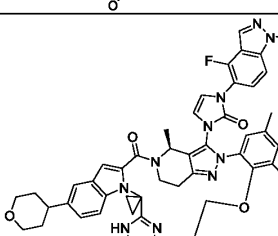
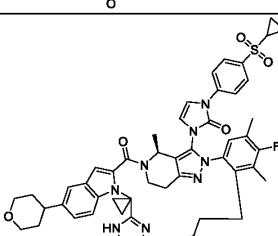
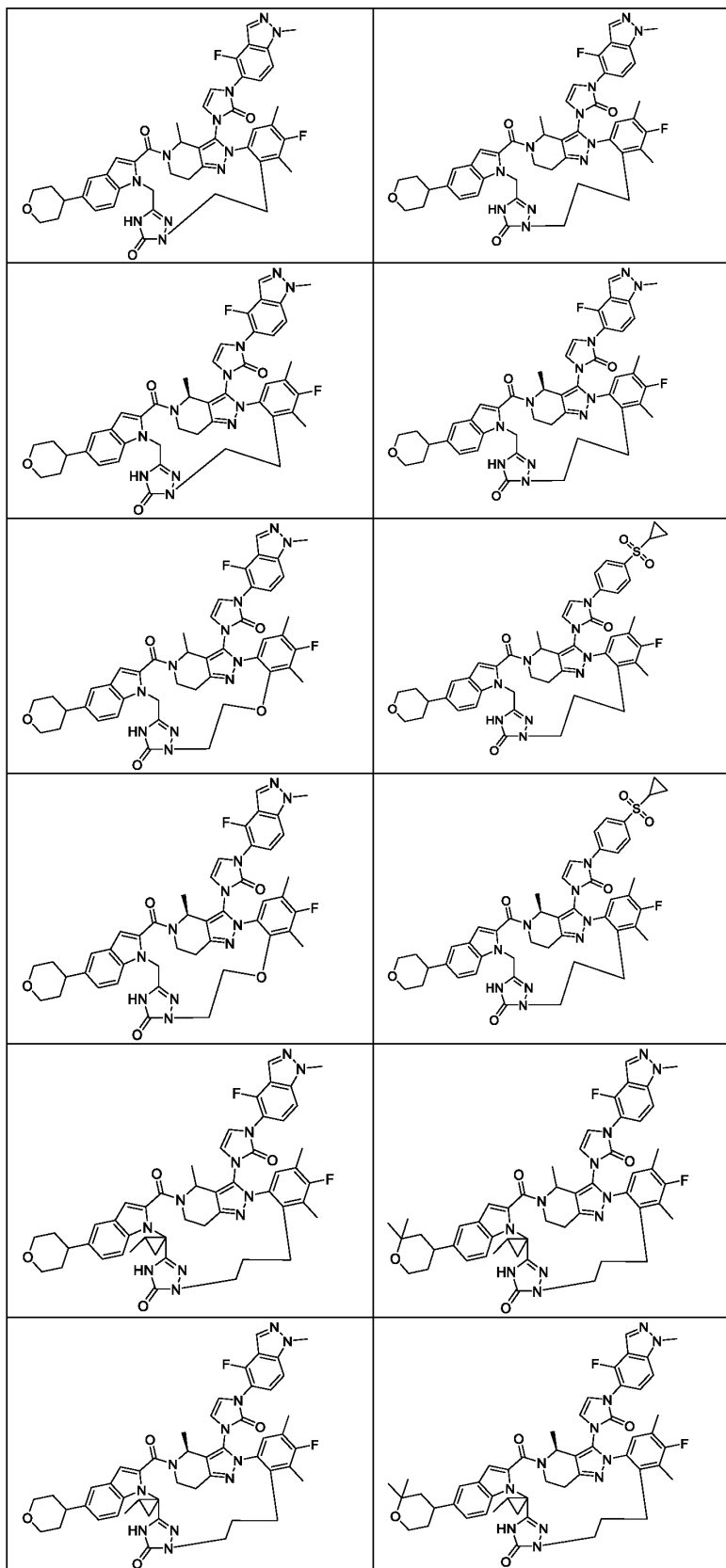
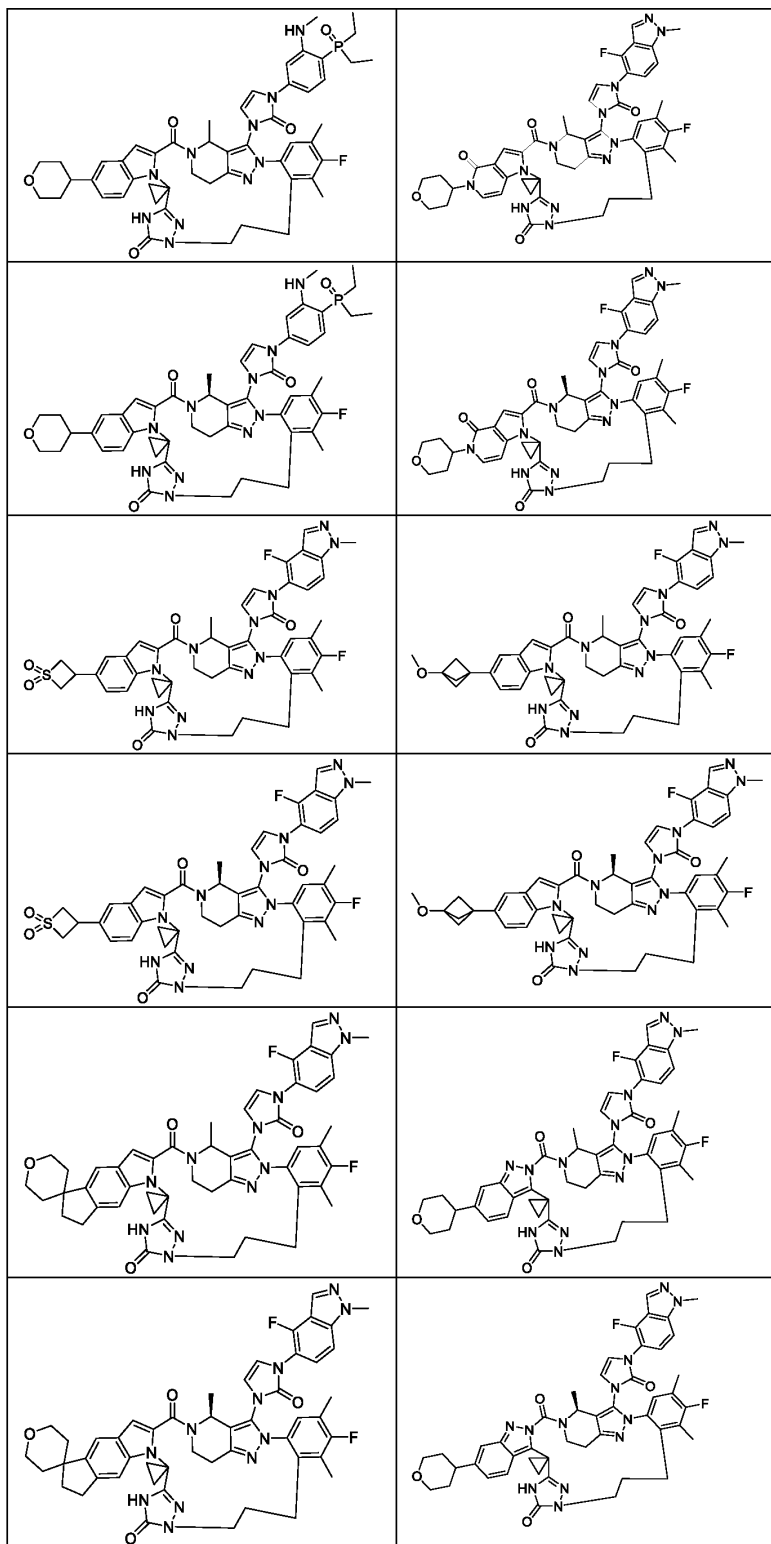
Compound No.	Structure	Compound No.	Structure
5			

TABLE 1.2 Exemplary Compounds





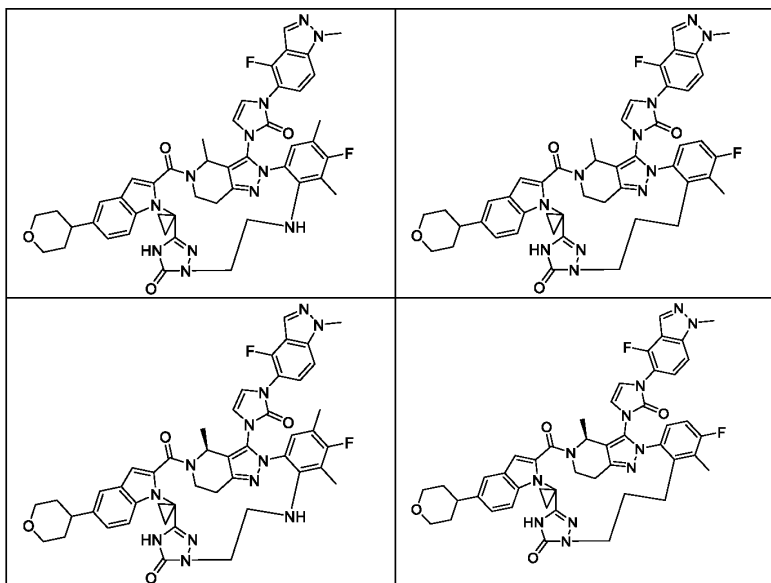
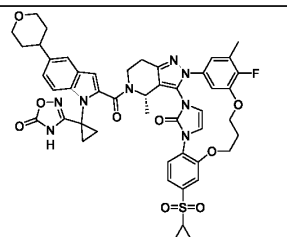
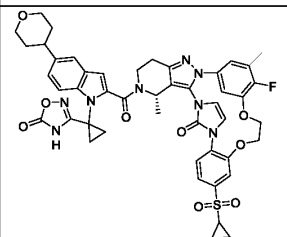
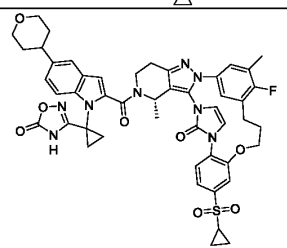
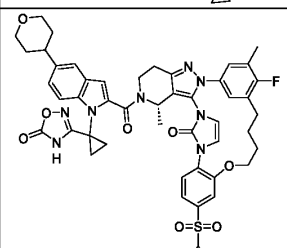
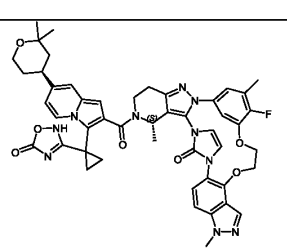
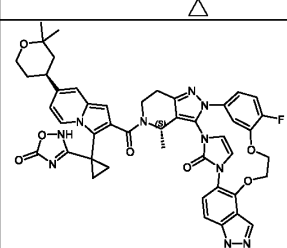
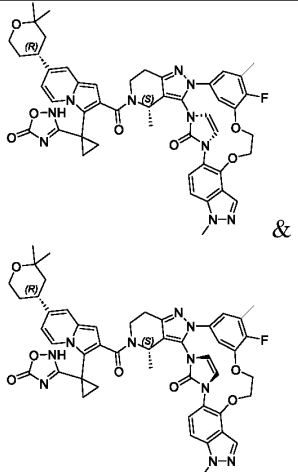
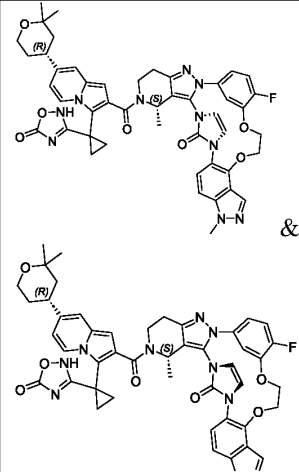
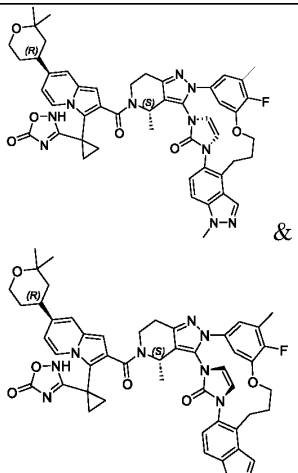
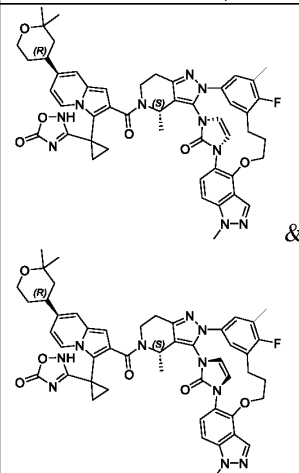
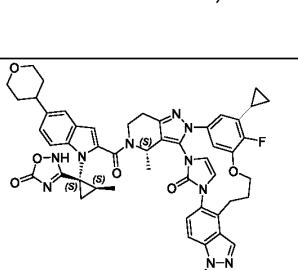
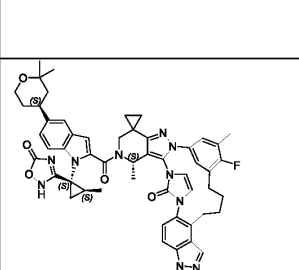
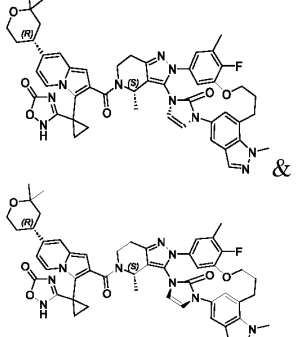
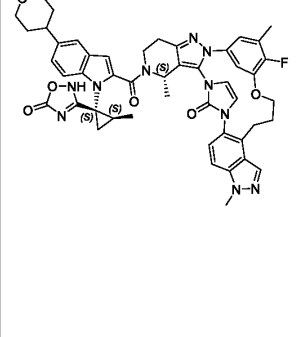
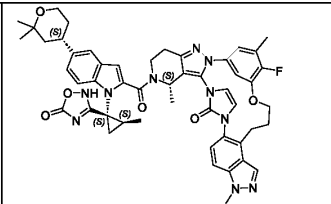
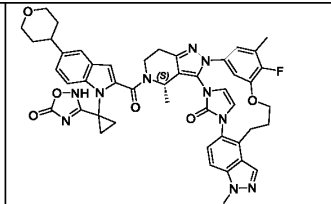
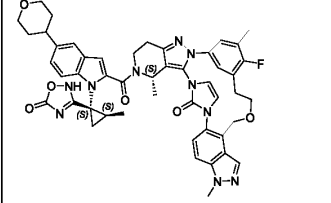
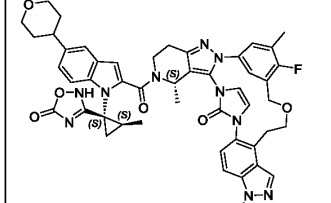
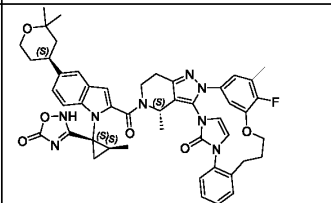
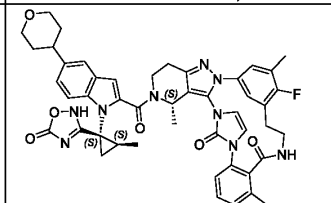
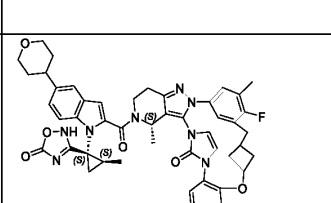
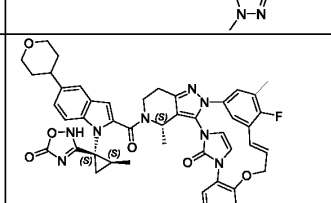
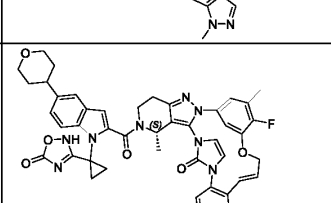
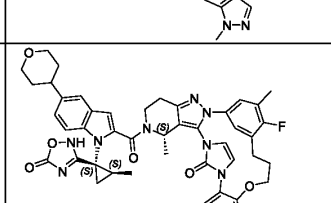
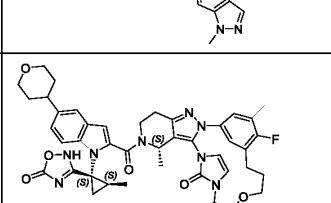
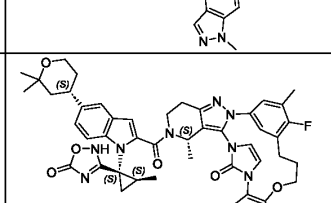
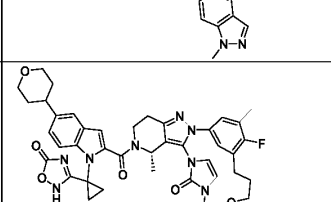
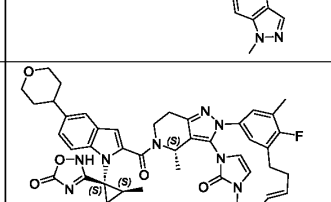
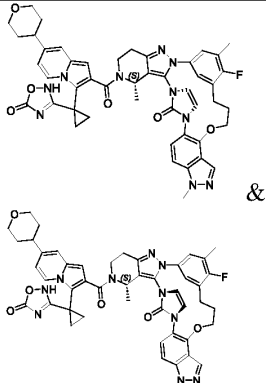
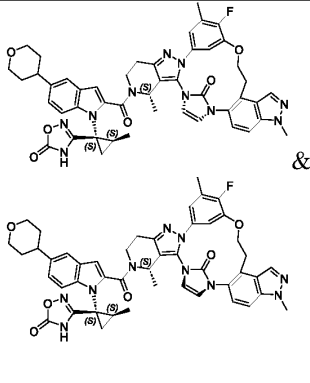
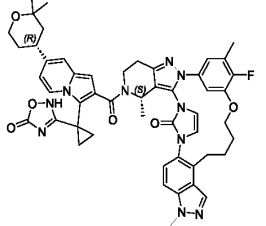
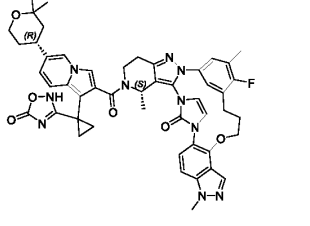
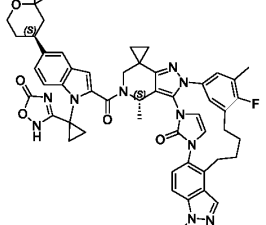
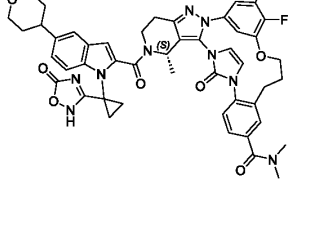
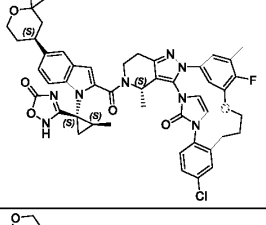
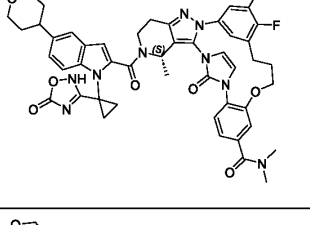
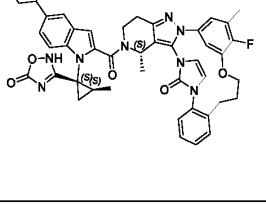
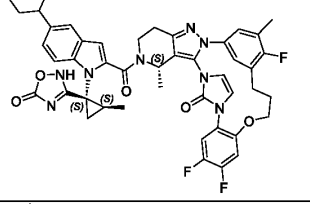
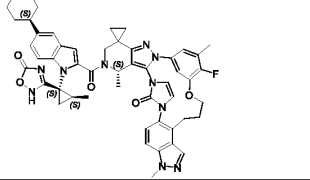


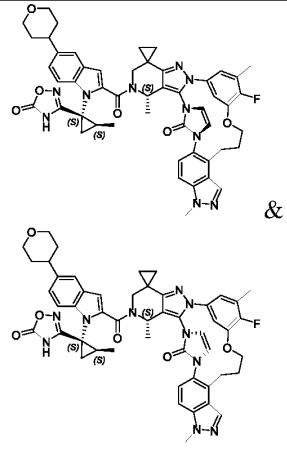
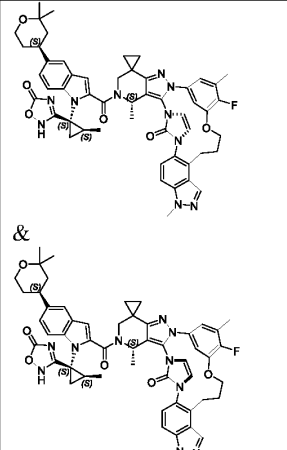
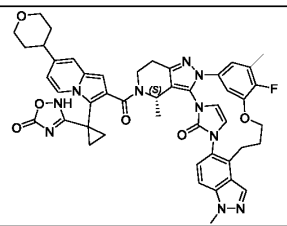
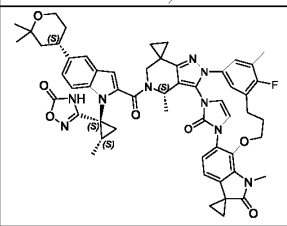
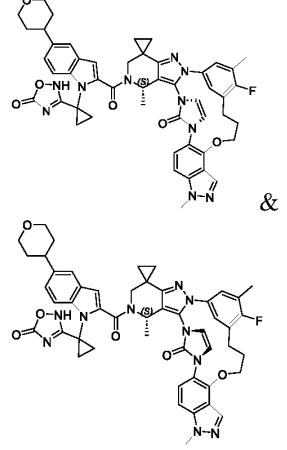
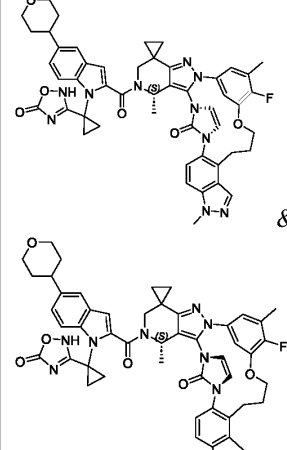
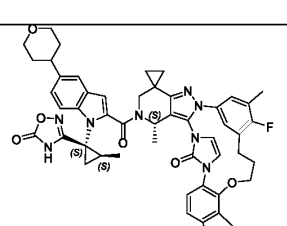
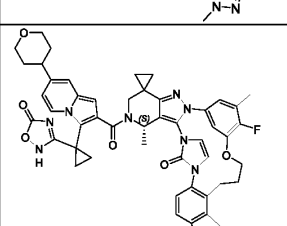
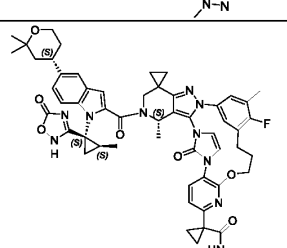
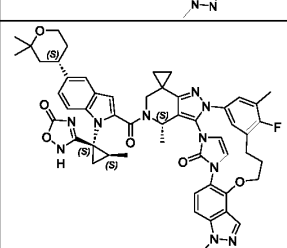
TABLE 2.1 Exemplary Compounds

Compound No.	Structure	Compound No.	Structure
1		2	
3		4	
19		20	

19-1 & 21		20-1 & 22	
24 & 25		26 & 27	
23		28	
29&30		31	

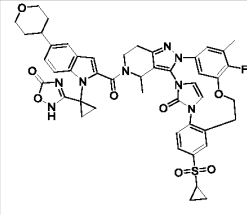
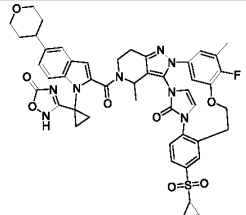
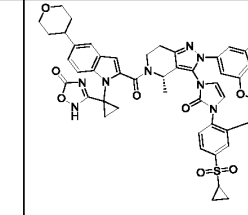
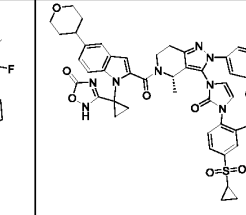
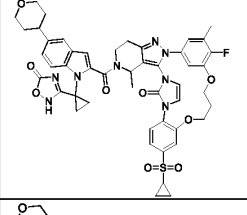
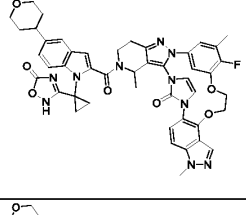
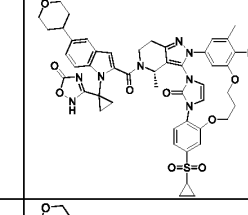
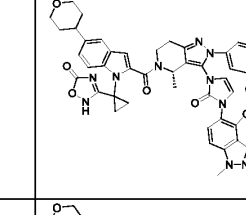
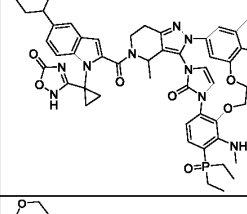
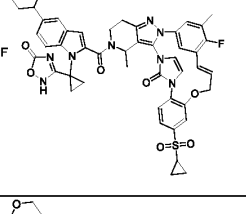
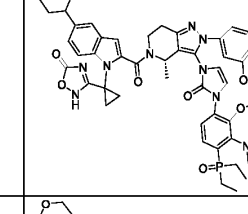
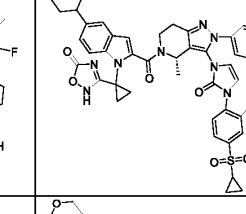
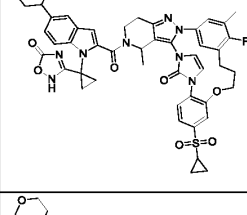
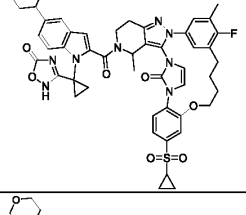
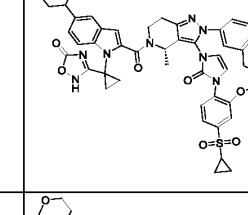
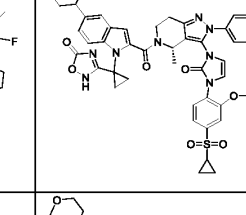
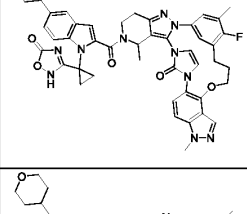
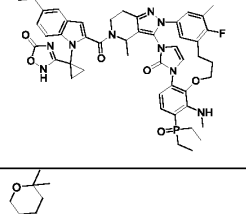
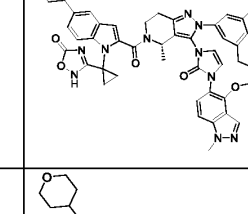
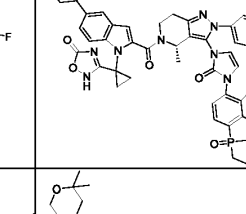
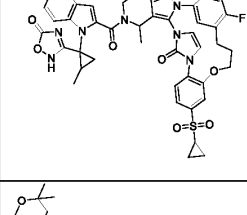
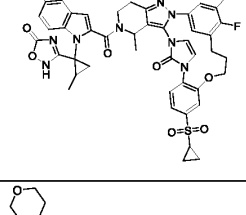
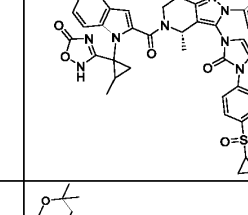
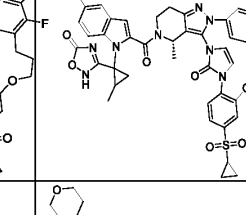
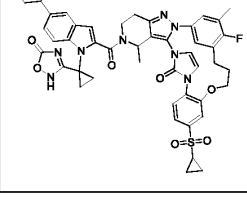
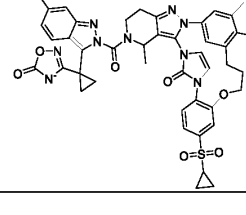
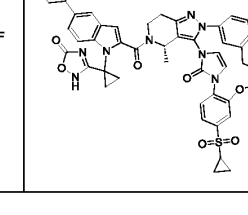
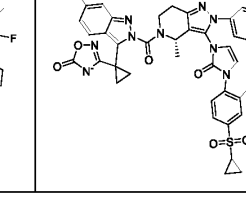
33		34	
35		36	
37		38	
39		40	
42		43	
44		45	
46		47	

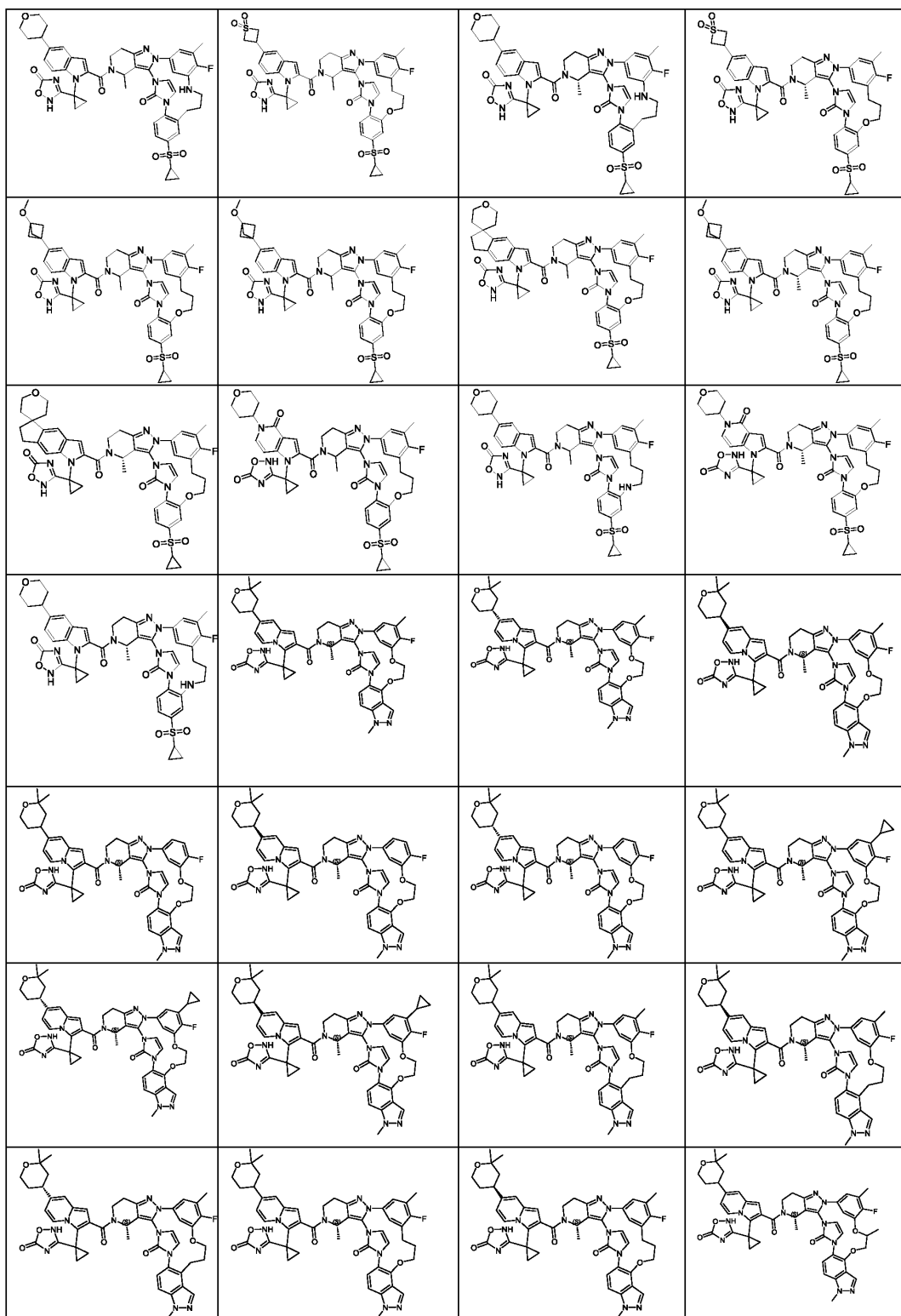
48&49		50&51	
52		53	
54		55	
56		57	
58		59	
		73	

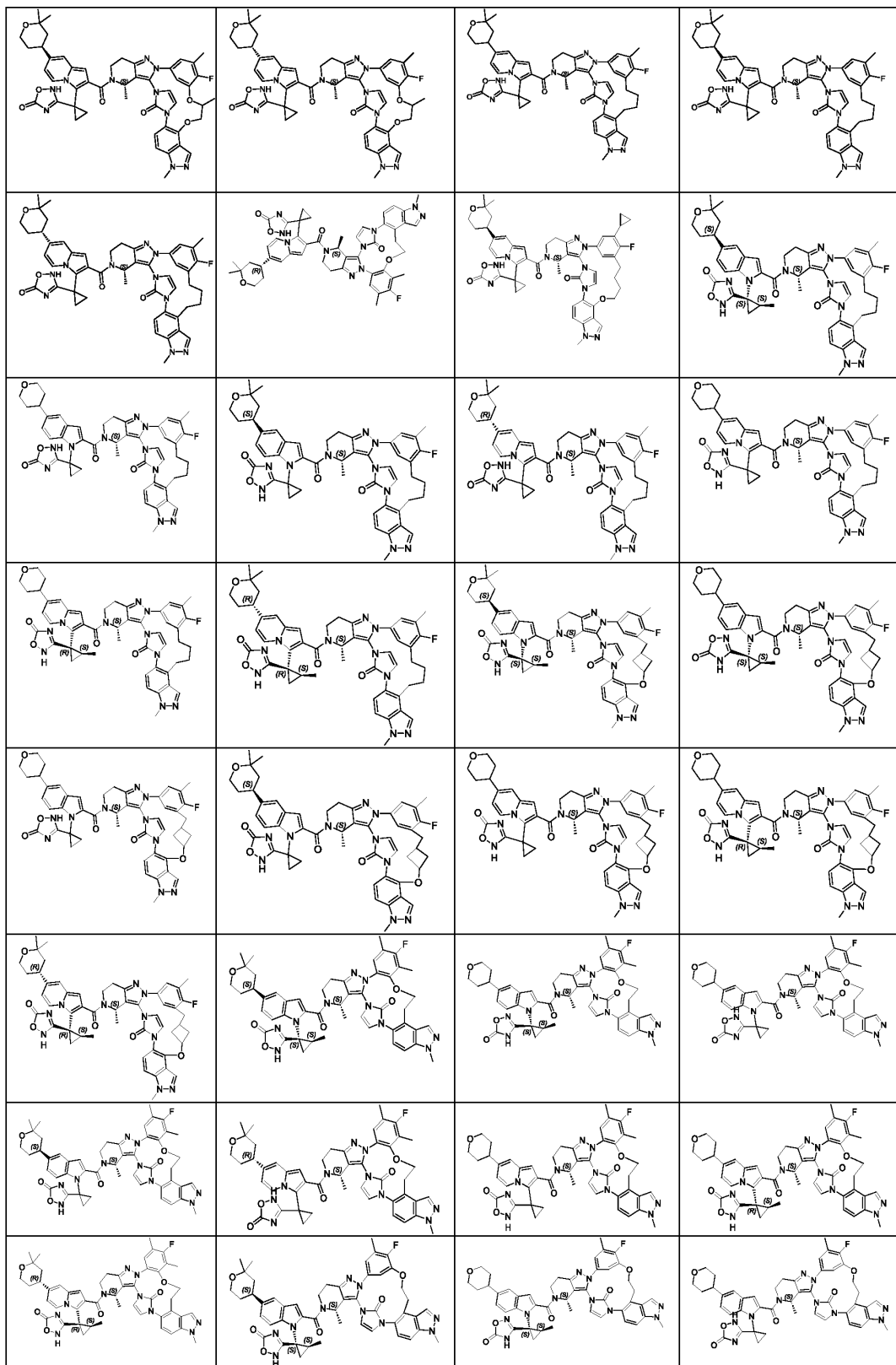
74&75		73-1 & 73-2	
76		133	
78 & 78-1		79 & 79-1	
77		109	
110		111	

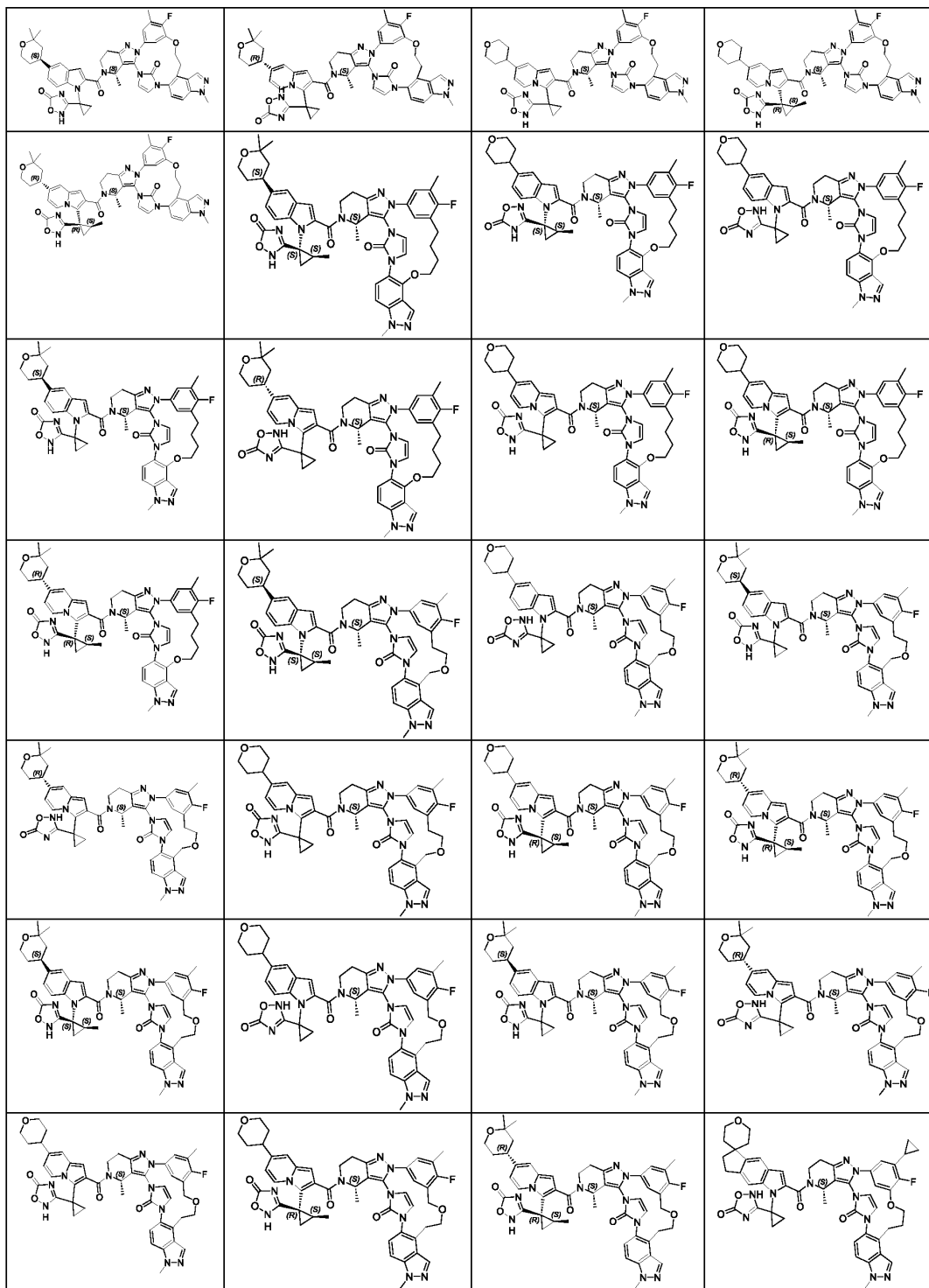
112		113	
114		115	
116		117	
118 & 118-1		111-1 & 111-2	
134		135	
136		142	

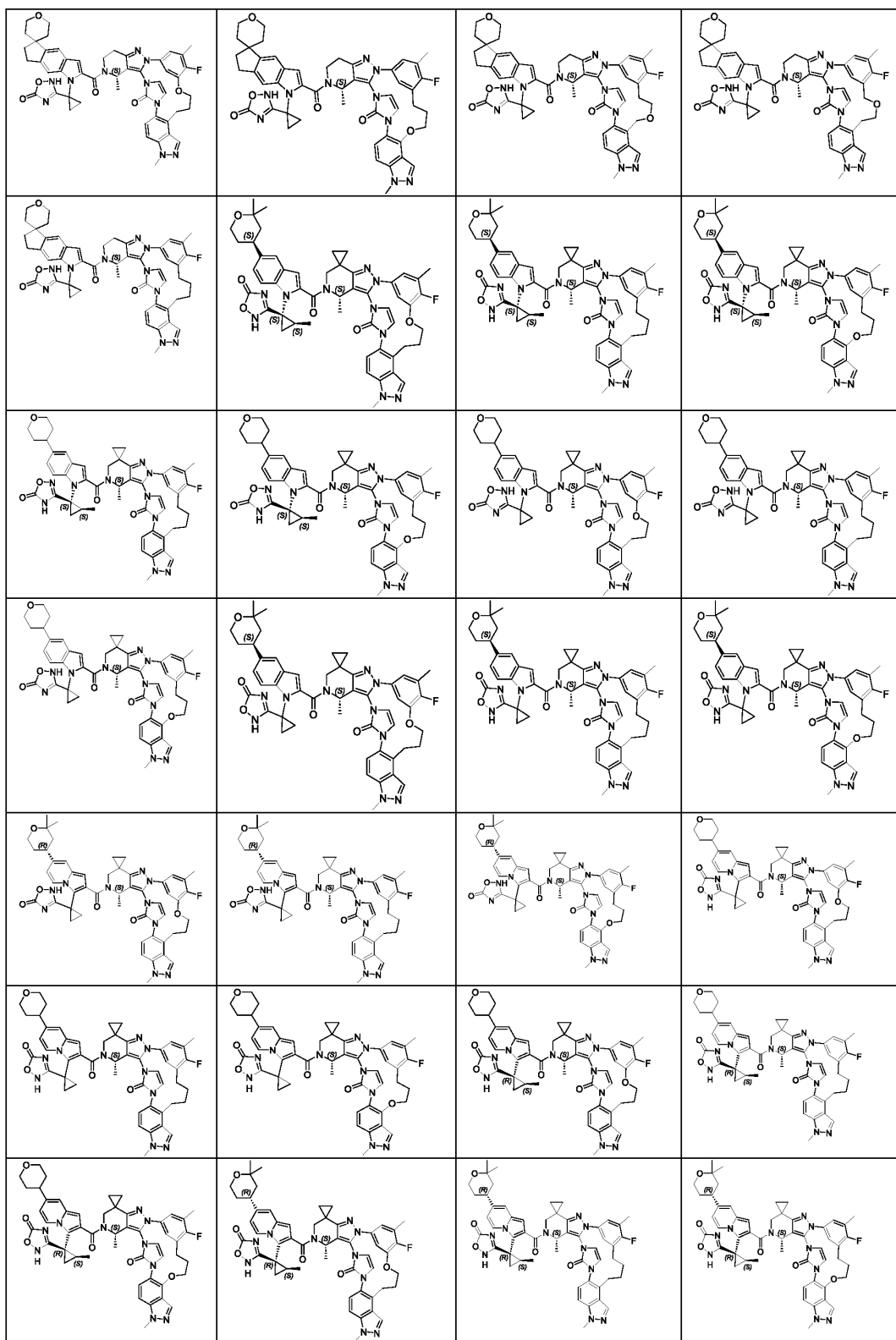
TABLE 2.2 Exemplary Compounds

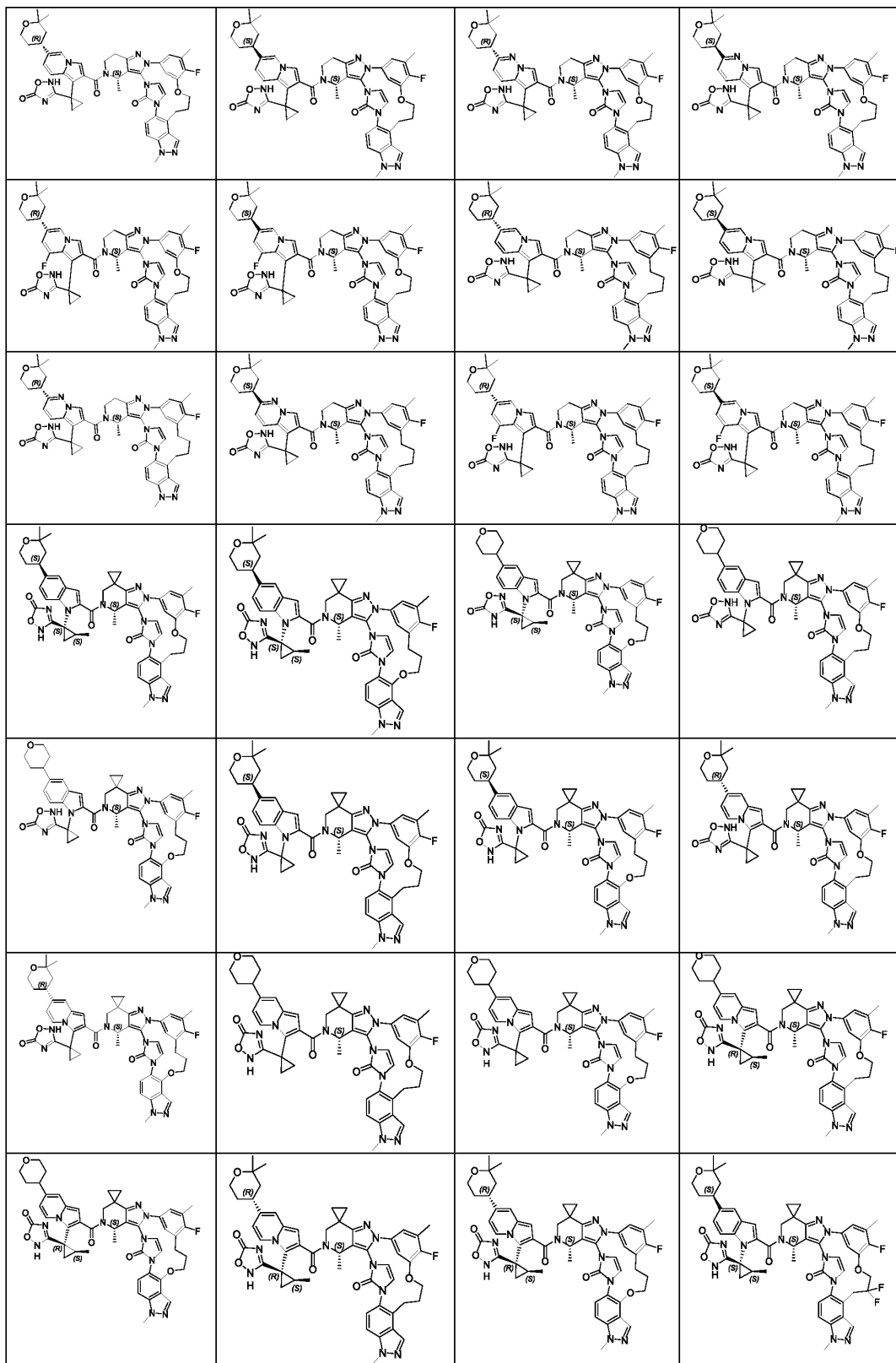
			
			
			
			
			
			
			

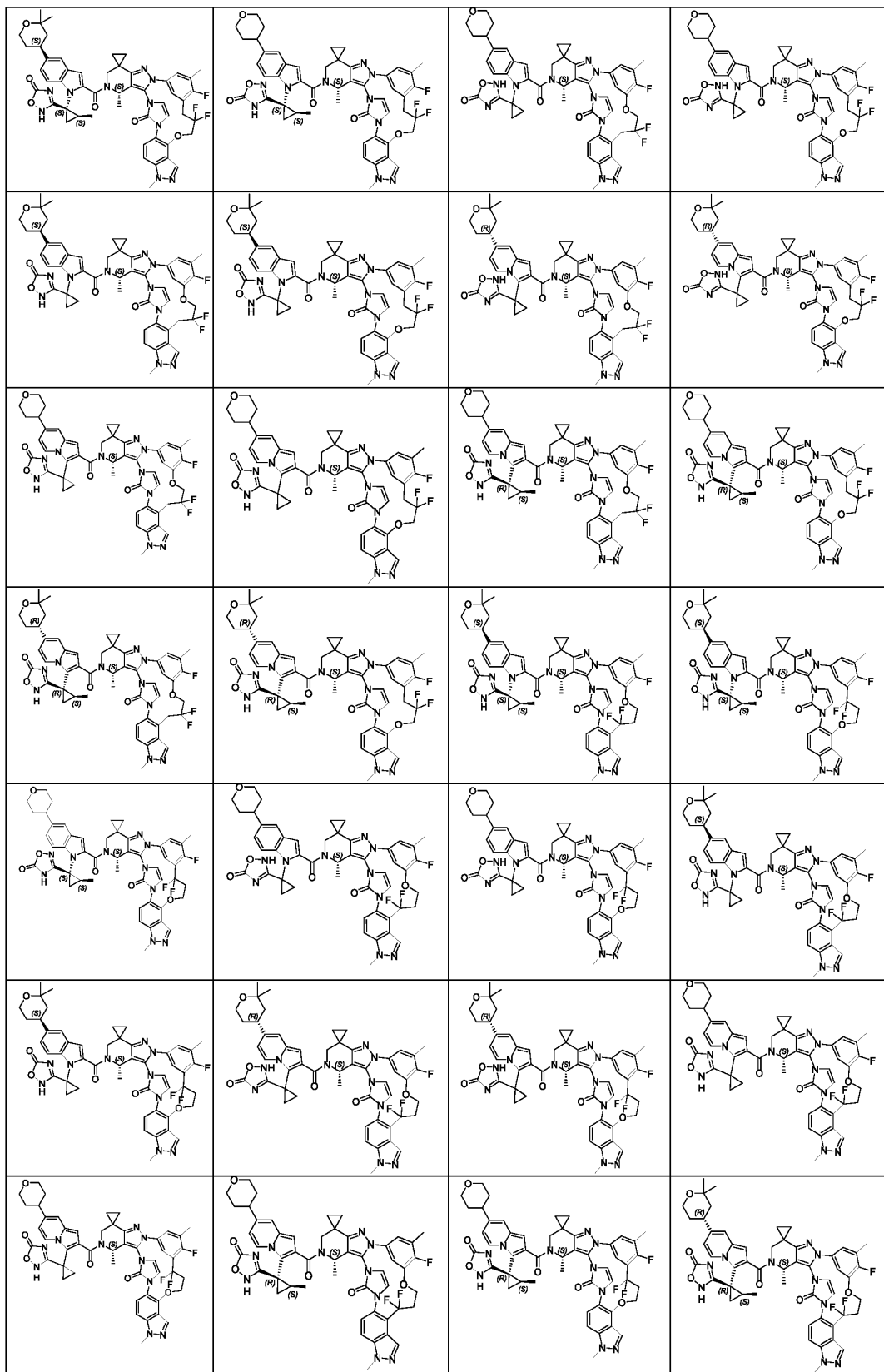


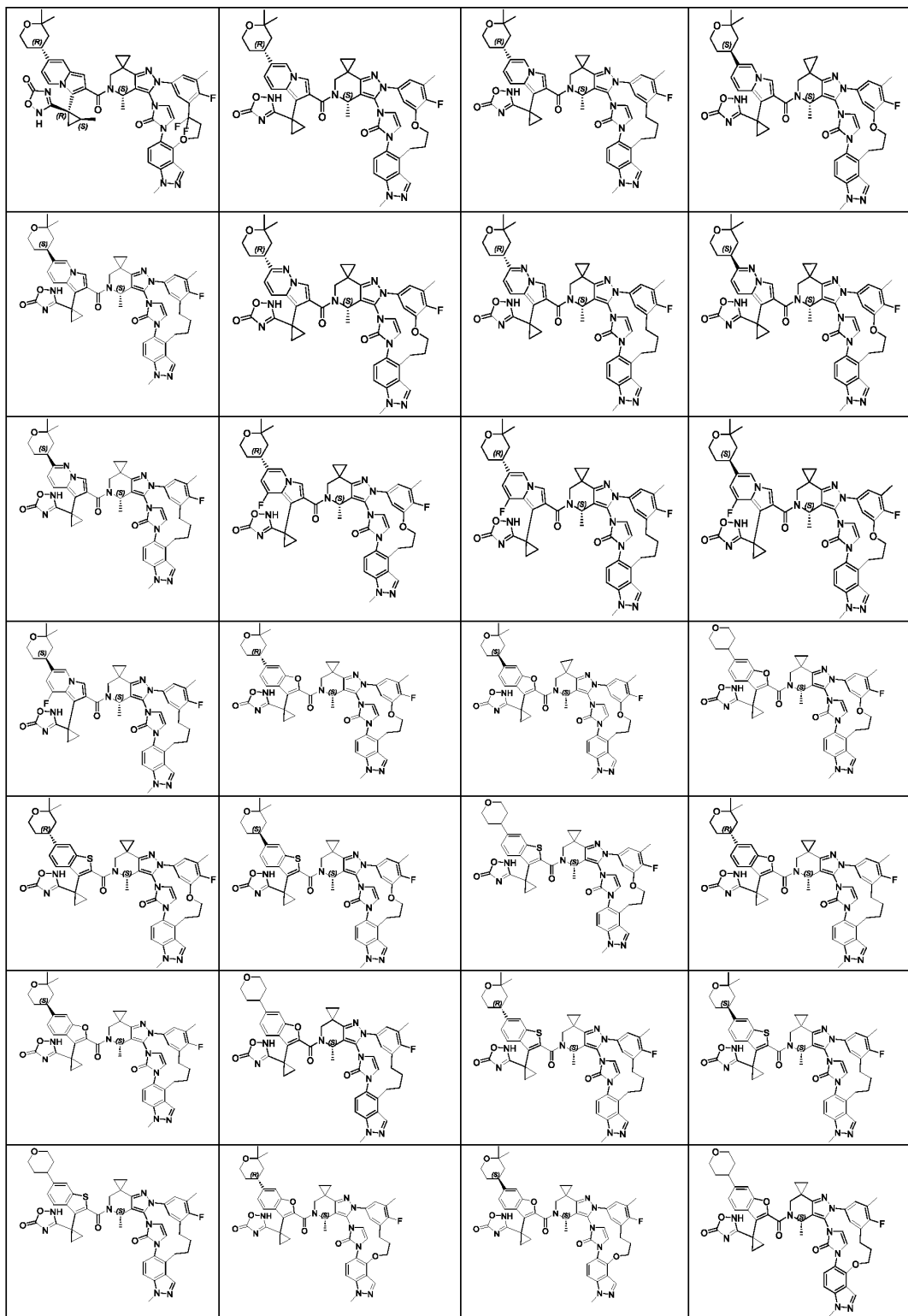


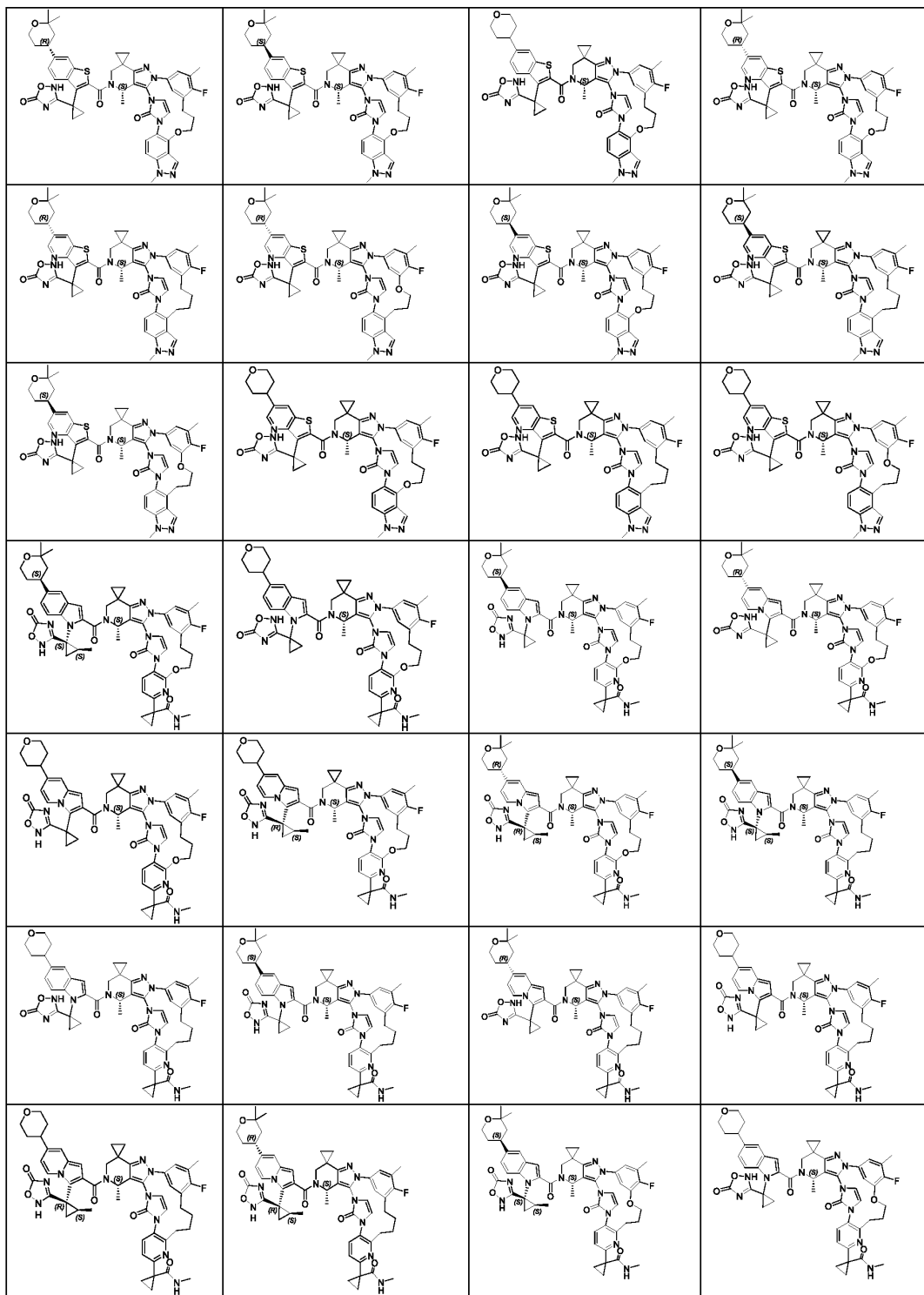


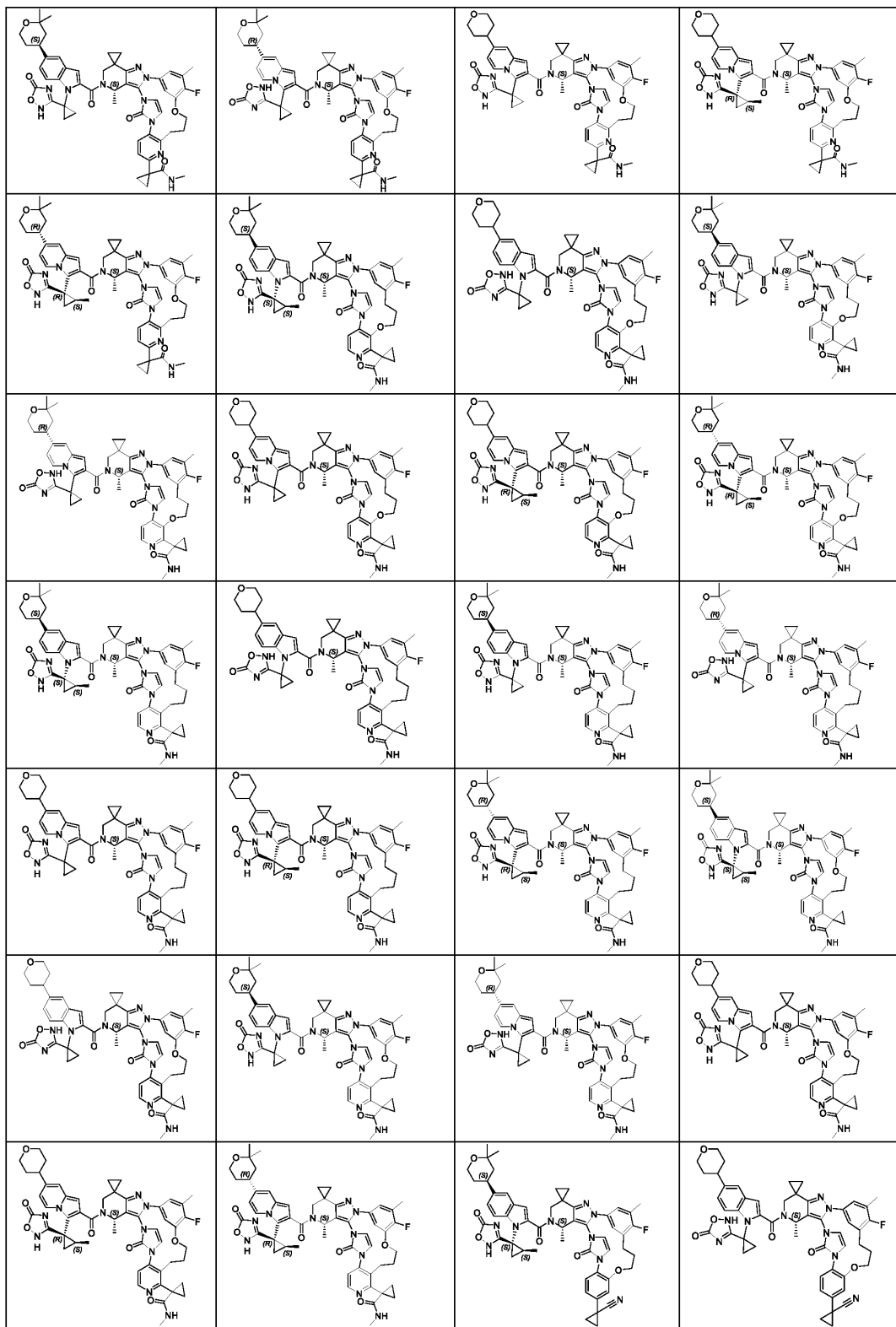


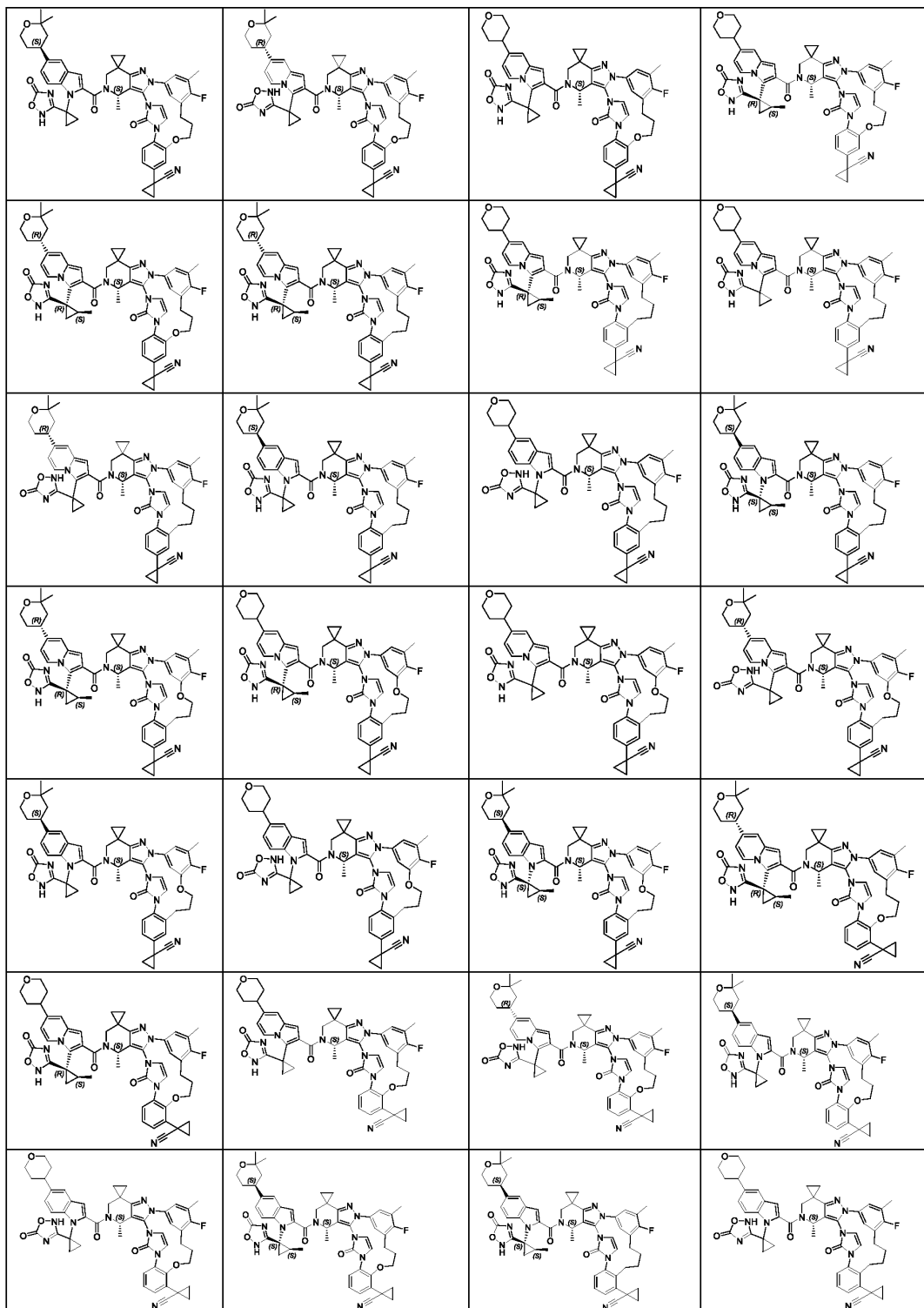


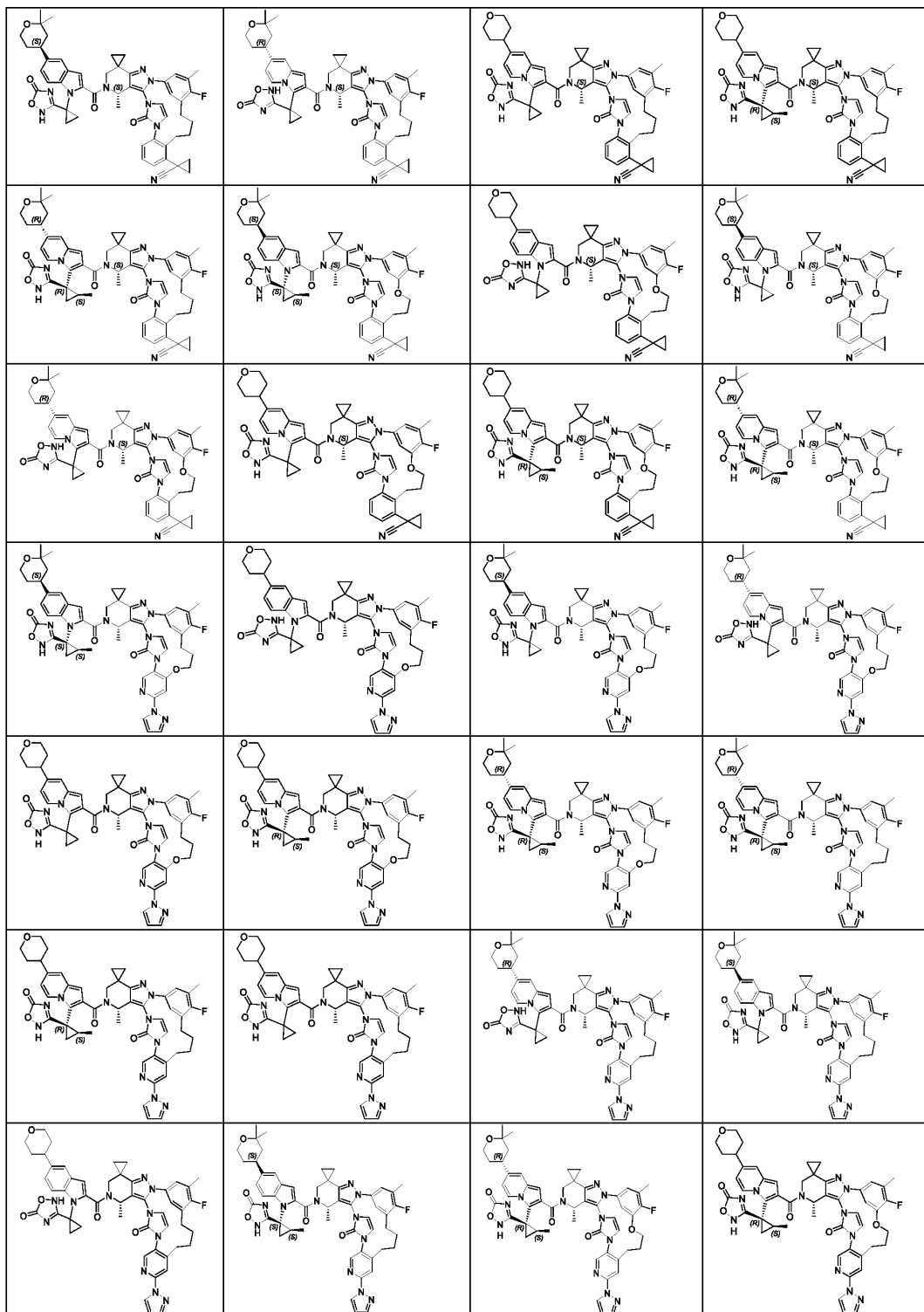


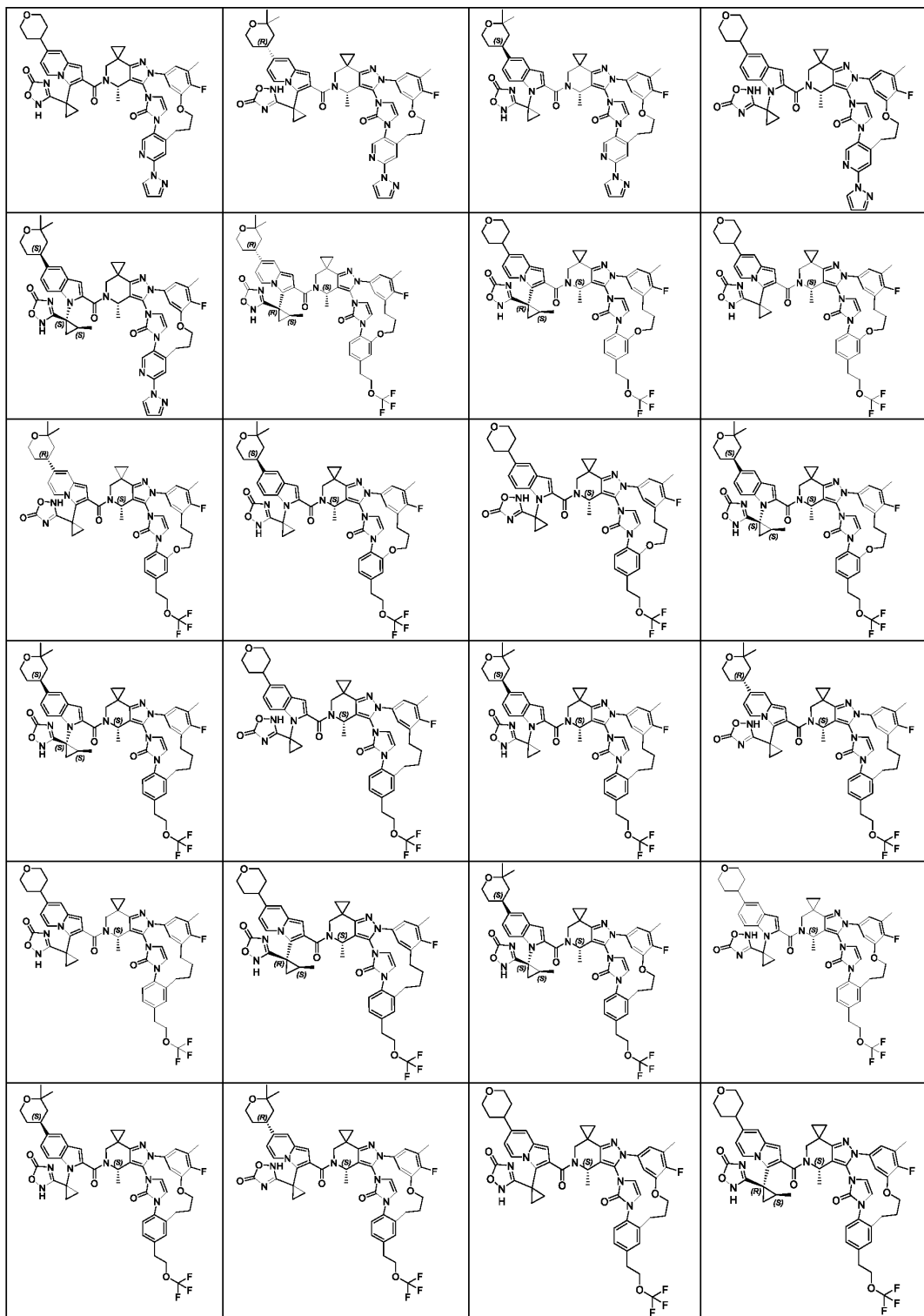


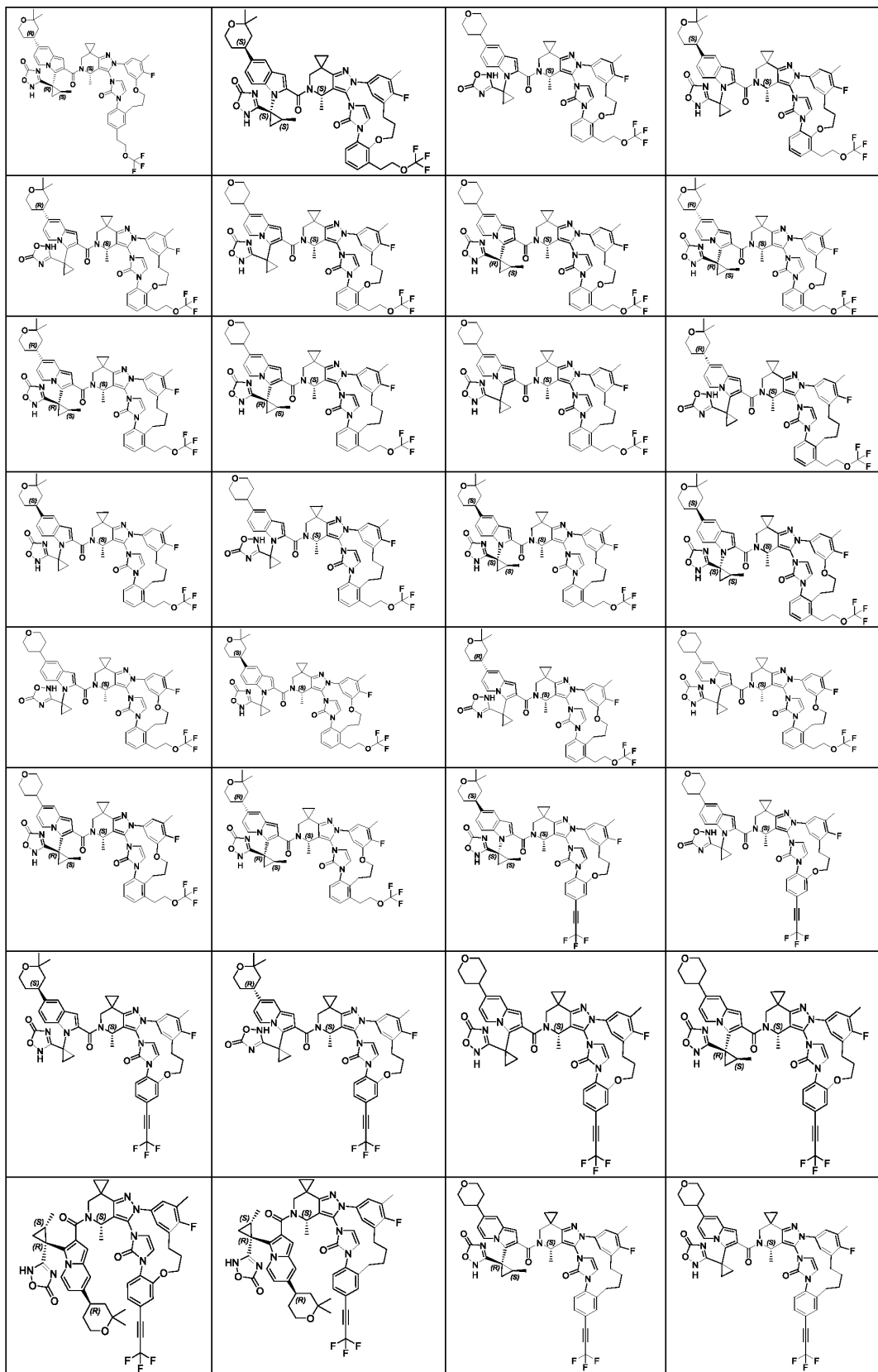


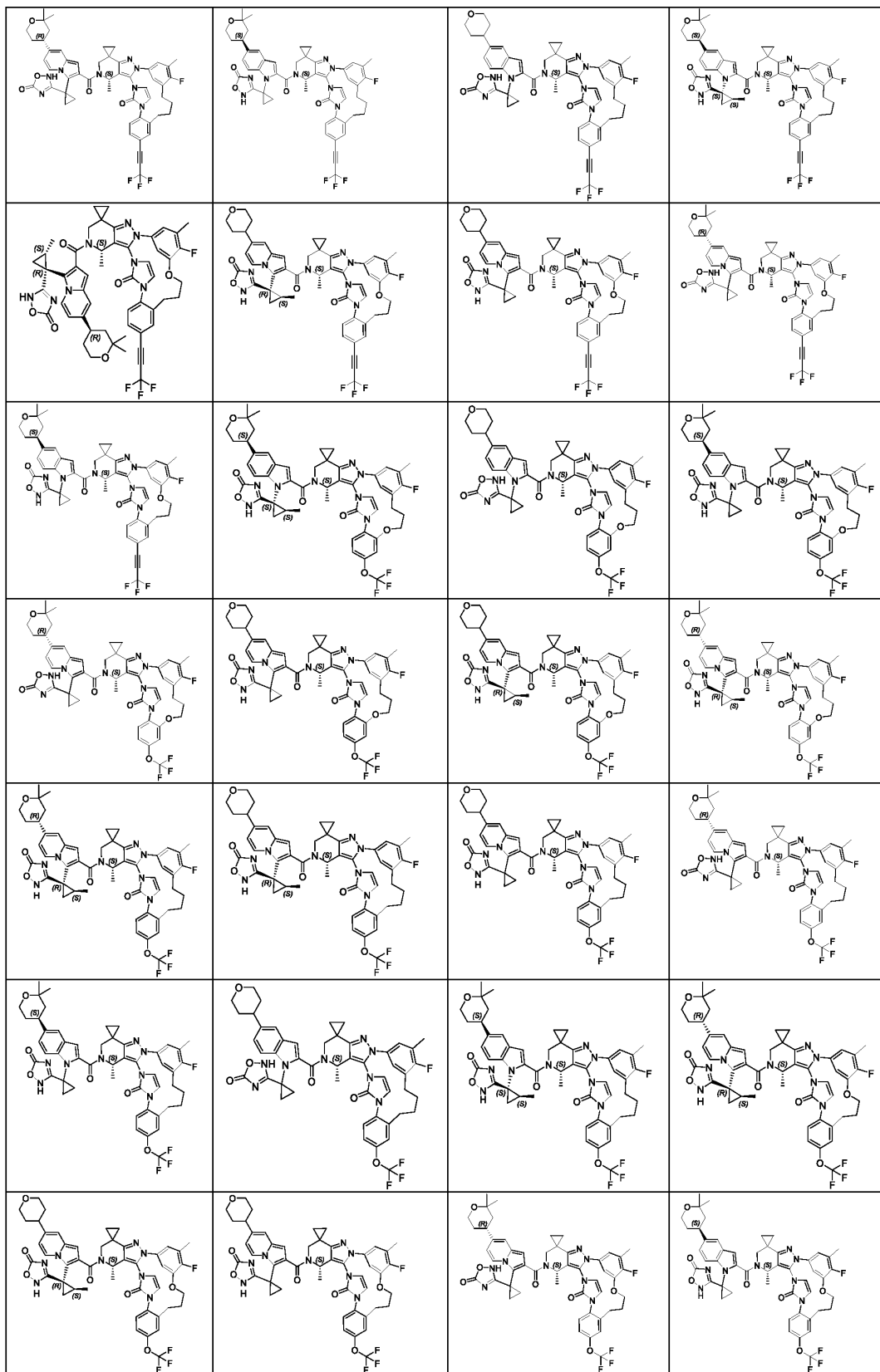


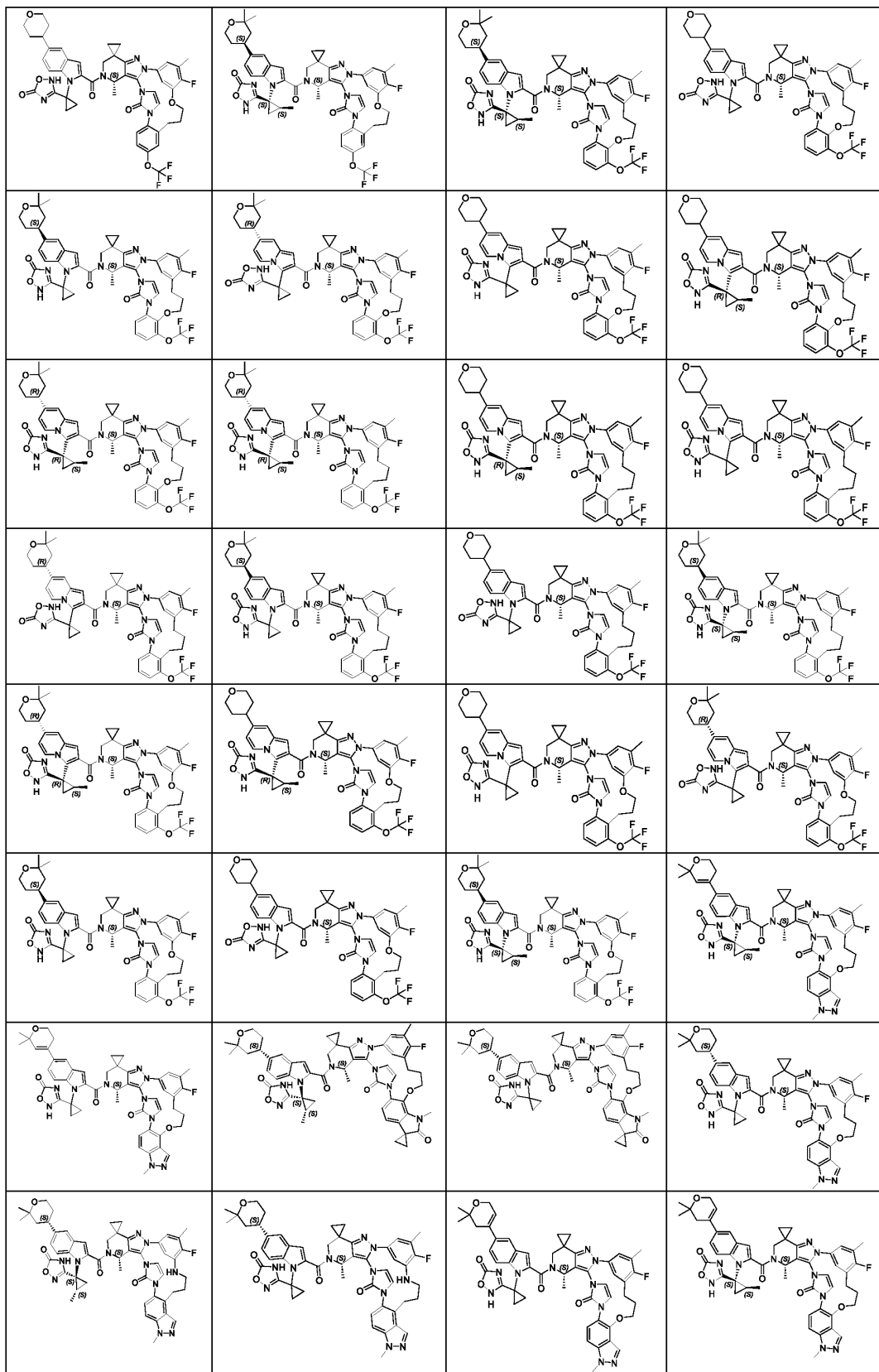












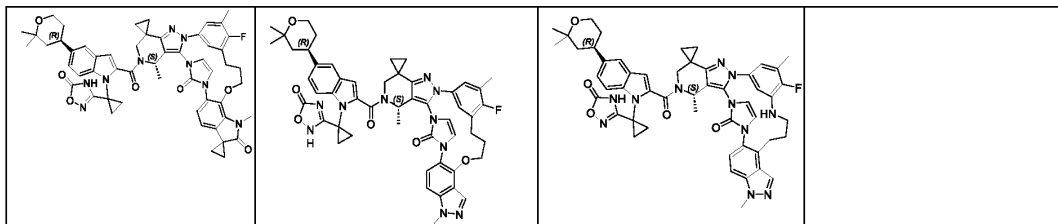
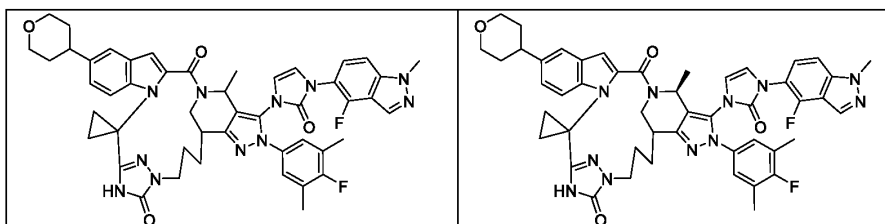


TABLE 3 Exemplary Compounds

**Further Forms of Compounds Disclosed Herein***Isomers/Stereoisomers*

[0126] 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

[0127] 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.

[0128] 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

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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

[0134] 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.

[0135] 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.

[0136] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[0137] 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.

[0138] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[0139] 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

[0140] 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.

[0141] 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.

[0142] Disclosed herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically affective 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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

[0148] 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.

[0149] 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

[0150] 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

[0151] 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.

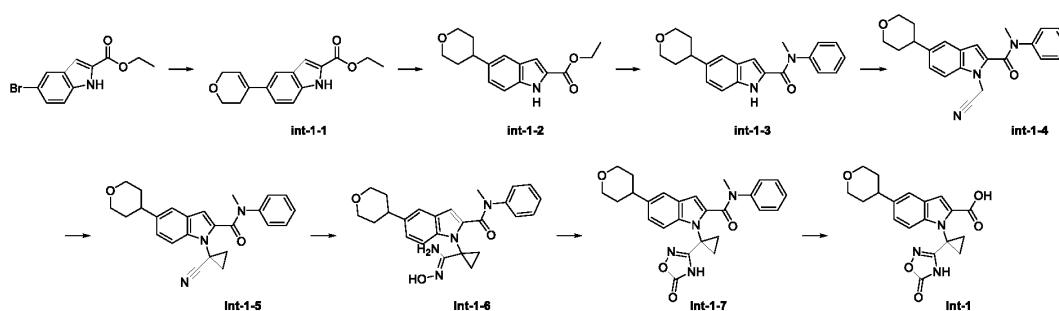
[0152] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel 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

[0153] 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



[0154] Step 1: int-1-1

[0155] 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-*d*₆) 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).

[0156] Step 2: int-1-2

[0157] 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]⁺.

[0158] Step 3: int-1-3

[0159] 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]⁺.

[0160] Step 4: int-1-4

[0161] 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]⁺.

[0162] Step 5: int-1-5

[0163] 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-*d*₆) 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).

[0164] Step 6: int-1-6

[0165] 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-*d*₆) 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).

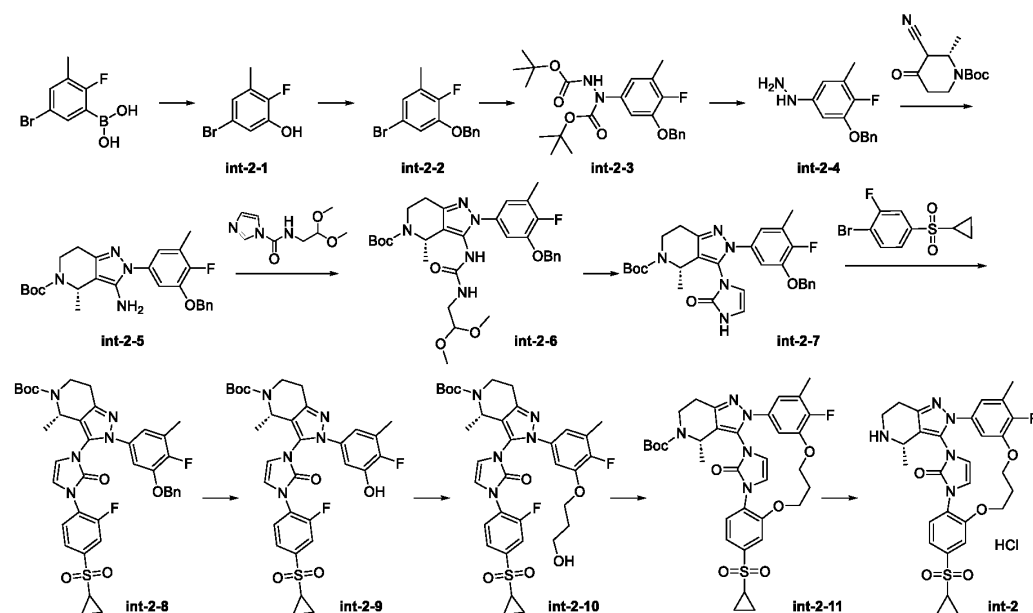
[0166] Step 7: int-1-7

[0167] 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-*d*₆) 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).

[0168] **Step 8: int-1**

[0169] 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 b: Synthesis of int-2



[0170] **Step 1: int-2-1**

[0171] To a solution of (5-bromo-2-fluoro-3-methylphenyl)boronic acid (78.0 g, 0.34 mol) in THF (780 mL) was added H₂O₂ (68 mL, 670 mmol, 30%) at 5 °C. The resulting mixture was stirred at 25 °C for 3 hrs and was poured into H₂O (1 L), extracted with EtOAc (500 mL × 3). Combined organic layers were washed with brine (1 L), dried over Na₂SO₄, filtered and concentrated to afford

int-2-1 (84.0 g, 287 mmol, 86% yield). ¹HNMR (400 MHz, DMSO-*d*₆) δ 10.28 (s, 1H), 6.93 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.18 (s, 3H).

[0172] Step 2: int-2-2

[0173] To a solution of **int-2-1** (84.0 g, 0.29 mol) in DMF (840 mL) was added K₂CO₃ (59.5 g, 0.43 mol) and (bromomethyl)benzene (27.3 mL, 0.23 mol). The resulting mixture was stirred at 15 °C for 16 hrs, and was poured into 4 L of water, extracted with EtOAc (500 mL $\times$ 3). Combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated to afford **int-2-2** (85.0 g, 0.23 mol, 80% yield). ¹HNMR (400 MHz, Chloroform-*d*) δ 7.51 - 7.29 (m, 5H), 6.97 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.92 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.08 (s, 2H), 2.25 (s, 3H).

[0174] Step 3: int-2-3

[0175] To a solution of **int-2-2** (65.0 g, 220 mmol) in THF (900 mL) was added *n*-BuLi (106 mL, 0.26 mol) at -65 °C, the mixture was stirred for 0.5 hrs, then a solution of di-*tert*-butyl azodicarboxylate (65.9 g, 286 mmol) in THF (80 mL) was added dropwise. After stirring at -65 °C under N₂ for 1 hr, the reaction mixture was poured into ice-water (1 L), extracted with EtOAc (500 mL $\times$ 3). Combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-2-3** (36.0 g, 81 mmol, 36.6% yield). LCMS: 469.3 [M+ Na]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 7.47 - 7.33 (m, 7H), 2.20 (s, 3H), 1.43 (s, 9H), 1.41 (s, 9H).

[0176] Step 4: int-2-4

[0177] To a solution of **int-2-3** (36.0 g, 81.0 mmol) in a solution of HCl (4 M in dioxane) (360 mL) was stirred at 20 °C for 7 hrs. The reaction mixture was concentrated to afford **int-2-4** (21 g, HCl salt, crude). LCMS: 247.3 [M+ H]⁺.

[0178] Step 5: int-2-5

[0179] To a solution of **int-2-4** (21.0 g, 85.00 mmol) in EtOH (210 mL) was added *tert*-butyl (2*S*)-3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (16.3 g, 68.2 mmol) and Py*HCl (0.98 g, 8.53 mmol), the mixture was stirred at 85 °C for 2 hrs, poured into H₂O (600 mL), extracted with EtOAc (500 mL $\times$ 2). Combined organic layers were washed with brine (800 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-2-5** (9.0 g, 19.29 mmol, 22.62% yield). LCMS: 467.3 [M+ H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.58 - 7.26 (m, 7H), 7.17 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.19 (s, 2H), 5.17 - 5.06 (m, 1H), 4.11 - 3.89 (m, 1H), 3.12 - 2.88 (m, 2H), 2.49 - 2.38 (m, 2H), 2.26 (d, *J* = 4.0 Hz, 3H), 1.43 (s, 9H), 1.28 - 1.21 (m, 3H).

[0180] Step 6: int-2-6

[0181] To a solution of **int-2-5** (5 g, 10.72 mmol) in DMA (120 mL) was added NaH (1.72 g, 42.9 mmol, 60%) at 0 °C for 30 mins, then *N*-(2,2-dimethoxyethyl)-1*H*-imidazole-1-carboxamide (4.27 g, 21.43 mmol) was added in portions. The mixture was stirred at 20 °C for 2 hrs and was poured into H₂O (600mL) and extracted with EtOAc (500 mL $\times$ 3). The combined organic layers were washed

with brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-2-6** (1.70 g, 2.84 mmol, 26.5% yield). LCMS: 598.4 [M+ H]⁺.

[0182] Step 7: int-2-7

[0183] To a solution of **int-2-6** (7.0 g, 11.71 mmol) in THF (210 mL) was added pTSA (6.68 g, 35.1 mmol). The mixture was stirred at 60 °C for 2 hrs. After cooling to r.t., the mixture was poured into water (600 mL) and extracted with EtOAc (400 mL × 3). Combined organic layers were washed with brine (400 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-2-7** (4.50 g, 8.43 mmol, 72.0% yield). LCMS: 534.4 [M+ H]⁺.

[0184] Step 8: int-2-8

[0185] A mixture of **int-2-7** (1.00 g, 1.87 mmol), 1-bromo-4-(cyclopropylsulfonyl)-2-fluorobenzene (0.628 g, 2.249 mmol), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (0.14 g, 0.94 mmol), copper(I) iodide (0.18 g, 0.94 mmol) and K₂CO₃ (0.52 g, 3.73 mmol) in NMP (20 mL) was degassed and purged with N₂. The mixture was stirred at 110 °C for 2 hrs under N₂ atmosphere. After cooling to r.t., the mixture was poured into H₂O (120 mL) and extracted with EtOAc (50 mL × 3). Combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-2-8** (1.40 g, 1.91 mmol, 90% yield). LCMS: 732.3 [M+ H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.92 - 7.78 (m, 2H), 7.41 - 7.32 (m, 5H), 7.22 - 1.17 (m, 1H), 7.14 - 6.99 (m, 2H), 6.91 - 6.84 (m, 1H), 5.15 (brs, 1H), 5.05 (s, 2H), 4.22 (brs, 1H), 3.23 - 3.07 (m, 1H), 3.02 - 2.92 (m, 1H), 2.78 - 2.72 (m, 1H), 2.68 - 2.57 (m, 1H), 2.23 (d, *J* = 4.0 Hz, 3H), 1.44 (s, 9H), 1.24 - 1.19 (m, 3H), 1.18 - 1.15 (m, 2H), 1.11 - 1.04 (m, 2H).

[0186] Step 9: int-2-9

[0187] To a mixture of **int-2-8** (1.20 g, 1.64 mmol) in THF (35 mL) was added Pd/C (120 mg, 10% purity), the mixture was degassed and purged with H₂ for 3 times, was stirred at 15 °C for 3 hrs under H₂ atmosphere (15 Psi). The mixture was filtered and the cake was washed with MeOH (15 mL × 2). Combined organic layers were concentrated and purified by column chromatography to afford **int-2-9** (630.0 mg, 0.98 mmol, 59.9% yield). LCMS: 642.3 [M+ H]⁺.

[0188] Step 10: int-2-10

[0189] To a solution of **int-2-9** (100 mg, 0.09 mmol) in DMF (2 mL) were added 3-bromopropan-1-ol (78 mg, 0.56 mmol) and K₂CO₃ (78 mg, 0.56 mmol). Resulting mixture was stirred at 15 °C for 6 hrs and was poured into water (5 mL). After being filtered, the cake was rinsed with MeOH (1 mL × 2) and concentrated to afford **int-2-10** (50 mg, 0.06 mmol, 61.1% yield). LCMS: 700.5 [M+ H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.06 - 7.98 (m, 1H), 7.89 - 7.81 (m, 2H), 7.20 - 7.15 (m, 1H), 7.06 (brs, 1H), 6.96 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.85 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.14 (brs, 1H), 4.58 (t, *J* = 4.0 Hz, 1H), 4.30 - 4.12 (m, 1H), 4.06 - 3.96 (m, 2H), 3.53 - 3.48 (m, 2H), 3.21 - 3.07 (m, 1H), 3.01 - 2.95 (m, 1H), 2.70 - 2.62 (m, 1H), 2.22 (s, 3H), 1.83 (p, *J* = 8.0 Hz, 2H), 1.44 (s, 9H), 1.23 - 1.17 (m, 5H), 1.13 - 1.05 (m, 2H).

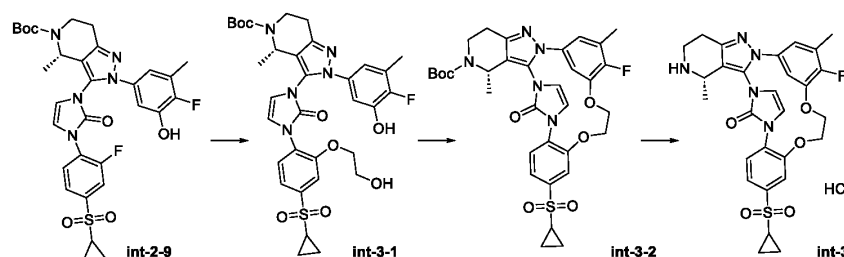
[0190] Step 11: int-2-11

[0191] To a solution of **int-2-10** (42 mg, 0.06 mmol) in DMA (4 mL) was added *t*-BuOK (39 mg, 0.34 mmol) and was stirred at 80 °C for 3 hrs. After cooling to r.t., the mixture was poured into water (10 mL), extracted with EtOAc (10 mL × 3). Combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered, concentrated, and purified by pre-TLC to afford **int-2-11** (20 mg, 0.03 mmol, 50.7% yield). LCMS: 680.4 [M+ H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.83 - 7.64 (m, 2H), 7.58 (td, *J* = 8.0, 4.0 Hz, 1H), 7.20 - 7.03 (m, 2H), 7.03 - 6.90 (m, 1H), 6.89 - 6.65 (m, 1H), 5.16 (brs, 1H), 4.41 - 4.05 (m, 5H), 3.18 (brs, 1H), 3.04 - 2.96 (m, 1H), 2.80 - 2.60 (m, 2H), 2.26 (brd, *J* = 4.0 Hz, 3H), 2.23 - 1.99 (m, 2H), 1.45 (s, 9H), 1.30 - 1.14 (m, 5H), 1.13 - 1.05 (m, 2H).

[0192] **Step 11: int-2**

[0193] To a solution of **int-2-11** (20 mg, 0.03 mmol) in EtOAc (5 mL) was added HCl in dioxane (4M, 2 mL) and stirred at r.t. for 2 hrs. Resulting mixture was filtered and concentrated to give crude **int-2** (22mg, crude). LCMS: 580.4 [M+ H]⁺.

Example c: Synthesis of int-3



[0194] **Step 1: int-3-1**

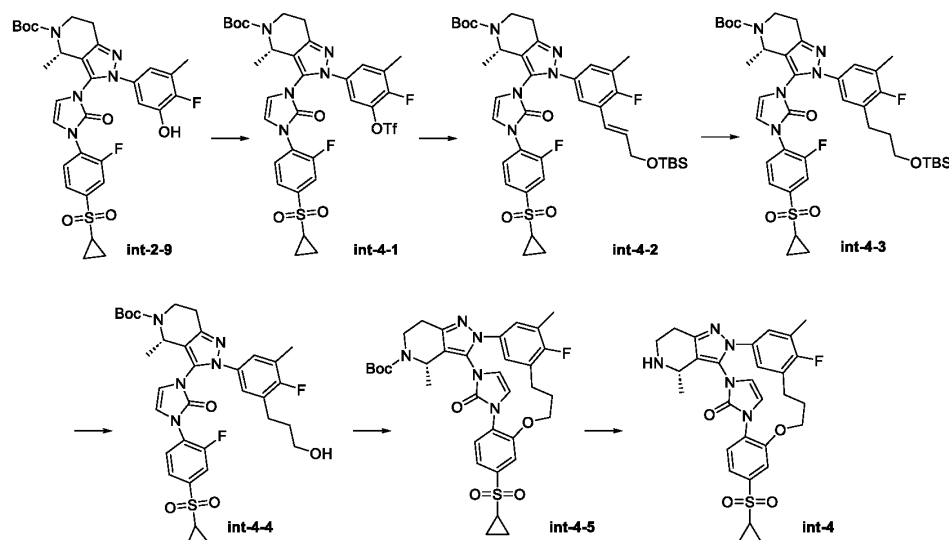
[0195] To a solution of **int-2-9** (200 mg, 0.31 mmol) in DMA (2 mL) were added 2-((*tert*-butyldimethylsilyl)oxy)ethan-1-ol (165 mg, 0.94 mmol), *t*-BuOK (84 mg, 0.75 mmol). The resulting mixture was stirred at 50 °C for 16 hrs. After being quenched by water (100 mL), the mixture was extracted with EtOAc (100 mL × 2). Combined organic layers were washed with water (200 mL) and brine (200 mL), dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography to afford **int-3-1** (130 mg, 0.19 mmol, 61.0% yield). LCMS: 684.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H), 7.65 (s, 1H), 7.64 - 7.61 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.10 (s, 1H), 6.89 (brs, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.64 (brs, 1H), 5.11 (brs, 1H), 4.84 (d, *J* = 4.0 Hz, 1H), 4.29 - 4.13 (m, 3H), 3.68 (d, *J* = 4.0 Hz, 2H), 3.16 - 3.08 (m, 1H), 2.98 - 2.94 (m, 1H), 2.73 - 2.64 (m, 2H), 2.18 (s, 3H), 1.43 (s, 9H), 1.25 - 1.19 (m, 3H), 1.16 - 1.14 (m, 2H), 1.08 - 1.04 (m, 2H).

[0196] **Step 2: int-3-2**

To a solution of **int-3-1** (100 mg, 0.15 mmol) in THF (2 mL) was added PPh₃ (58 mg, 0.22 mmol), followed by DIAD (0.05 mL, 0.22 mmol). The mixture was stirred at 40 °C for 2 hrs under N₂. After cooling to room temperature, the reaction was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography to afford **int-3-2** (170 mg, 0.11 mmol, 71.9% yield). LCMS: 666.3 [M+H]⁺.

[0197] Step 3: int-3

A mixture of **int-3-2** (170 mg, 0.11 mmol) in HCl solution (4 M in dioxane, 2 mL) was stirred at 10 °C for 1 hr. The reaction was concentrated to afford **int-3** (100 mg, crude), and was used for next step directly. LCMS: 566.3 [M+H]⁺.

Example d: Synthesis of int-4**[0198] Step 1: int-4-1**

[0199] To a solution of **int-2-9** (600 mg, 0.94 mmol) in DCM (12 mL) was added TEA (0.37 mL, 2.62 mmol) dropwise and then 2,2,2-trifluoro-*N*-phenyl-*N*-((2,2,2-trifluoroethyl)sulfonyl)ethane-1-sulfonamide (396 mg, 1.03 mmol) was added dropwise at 0 °C. After addition, the resulting mixture was stirred at 15 °C for 3 hrs. Then the reaction mixture was quenched by water (50 mL) and extracted with DCM (100 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-4-1** (630 mg, 0.81 mmol, 87.0% yield). LCMS: 774.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.87 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.58 - 7.51 (m, 1H), 7.47 - 7.41 (m, 1H), 7.26 - 7.21 (m, 1H), 7.11 (brs, 1H), 5.28 - 4.98 (m, 1H), 4.41 - 4.14 (m, 1H), 3.23 - 3.10 (m, 1H), 3.03 - 2.93 (m, 1H), 2.81 - 2.74 (m, 1H), 2.72 - 2.63 (m, 1H), 2.36 (s, 3H), 1.44 (s, 9H), 1.20 - 1.18 (m, 3H), 1.17 - 1.15 (m, 2H), 1.12 - 1.06 (m, 2H).

[0200] Step 2: int-4-2

[0201] A mixture of **int-4-1** (630 mg, 0.81 mmol), (*E*)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (486 mg, 1.63 mmol), K₂CO₃ (338 mg, 2.44 mmol), PdCl₂(dppf)·CH₂Cl₂ (66 mg, 0.08 mmol) in dioxane (12 mL) and water (1.2 mL) was degassed and purged with N₂ for 3 times and the mixture was stirred at 100 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with (100 mL), followed by brine (100 mL),

dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-4-2** (500 mg, 0.63 mmol, 77.0% yield). LCMS: 796.4 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.94 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.85 - 7.70 (m, 2H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.12 - 7.08 (m, 1H), 7.02 (brs, 1H), 6.67 - 6.58 (m, 1H), 6.33 - 6.21 (m, 1H), 5.16 - 5.00 (m, 1H), 4.26 - 4.24 (m, 2H), 4.22 - 4.08 (m, 1H), 3.15 - 3.05 (m, 1H), 2.95 - 2.88 (m, 1H), 2.72 - 2.58 (m, 2H), 2.19 (s, 3H), 1.39 (s, 9H), 1.18 - 1.14 (m, 3H), 1.13 - 1.09 (m, 2H), 1.06 - 1.02 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

[0202] Step 3: int-4-3

[0203] To a solution of **int-4-2** (490 mg, 0.62 mmol) in THF (15 mL) was added Pd/C (50 mg, 10% w/w). The reaction mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 3 hrs under H₂ atmosphere (15 psi). The reaction mixture was filtered through a silica gel pad and the cake was rinsed with MeOH (50 mL $\times$ 3). The combined organic layers were concentrated to afford **int-4-3** (500 mg, 0.56 mmol, 92.0% yield). LCMS: 798.4 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.05 - 8.00 (m, 1H), 7.92 - 7.84 (m, 2H), 7.21 - 7.15 (m, 2H), 7.14 - 7.00 (m, 2H), 5.33 - 5.04 (m, 1H), 4.29 - 4.20 (m, 1H), 3.59 (t, *J* = 8.0 Hz, 2H), 3.20 (s, 1H), 3.02 - 2.98 (m, 1H), 2.81 - 2.68 (m, 2H), 2.66 (t, *J* = 8.0 Hz, 2H), 2.25 (s, 3H), 1.71 - 1.68 (m, 2H), 1.47 (s, 9H), 1.27 - 1.20 (m, 5H), 1.14 - 1.08 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H).

[0204] Step 4: int-4-4

[0205] To a solution of **int-4-3** (500 mg, 0.63 mmol) in THF (15 mL) was added TBAF (1.25 mL, 1.25 mmol, 1 M in THF). The resulting mixture was stirred at 15 °C for 2 hrs. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (100 mL $\times$ 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-4-4** (350 mg, 0.51 mmol, 82.0% yield). LCMS: 684.3 [M+H]⁺.

[0206] Step 5: int-4-5

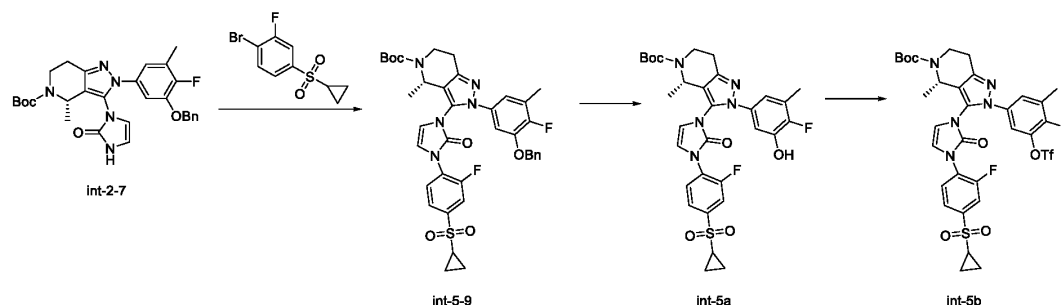
[0207] To a solution of **int-4-4** (200 mg, 0.29 mmol) in DMA (8 mL) was added potassium *tert*-butoxide (39 mg, 0.35 mmol). The resulting mixture was stirred at 10 °C for 1 hr. After completion, the mixture was poured into 20 mL of water and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-4-5**. LCMS: 664.3 [M+H]⁺.

[0208] Step 6: int-4

A mixture of **int-4-5** (25 mg, 0.04 mmol) and HCl (4 M in Dioxane, 2 mL, 8.0 mmol) was stirred at 15 °C for 1 hr. The mixture was concentrated, diluted with DCM (10 mL), and concentrated again. This was repeated 3 times to afford **int-4** (15 mg, 0.03 mmol, 70.7% yield). LCMS: 564.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.80 - 7.26 (m, 4H), 7.15 - 6.96 (m, 1H), 6.86 - 6.71 (m, 1H), 6.70 - 6.57 (m, 1H), 4.66 - 4.52 (d, *J* = 6.7 Hz, 1H), 4.20 - 4.02 (m, 2H), 3.70 - 3.58 (m, 1H), 3.53 - 3.37 (m, 2H), 3.36

- 3.24 (s, 1H), 3.04 - 2.89 (m, 3H), 2.87 - 2.75 (m, 1H), 2.30 - 2.16 (m, 3H), 2.07 - 1.88 (m, 2H), 1.60 - 1.40 (m, 3H), 1.22 - 1.13 (m, 2H), 1.12 - 1.06 (m, 2H).

Example e: Synthesis of int-5a and int-5b



[0209] Step 1: int-5-9

[0210] A mixture of **int-2-7** (1.0 g, 1.87 mmol), 1-bromo-4-(cyclopropylsulfonyl)-2-fluorobenzene (0.63 g, 2.25 mmol), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (0.14 g, 0.94 mmol), copper(I) iodide (0.18 g, 0.94 mmol) and K₂CO₃ (0.52 g, 3.73 mmol) in NMP (20 mL) was degassed and purged with N₂ for 3 times. The resulting mixture was stirred at 110 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into H₂O (120 mL) and extracted with EtOAc (50 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-5-9** (1.40 g, 1.91 mmol, 90% yield). LCMS: 732.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.92 - 7.78 (m, 2H), 7.41 - 7.32 (m, 5H), 7.22 - 1.17 (m, 1H), 7.14 - 6.99 (m, 2H), 6.91 - 6.84 (m, 1H), 5.15 (brs, 1H), 5.05 (s, 2H), 4.22 (brs, 1H), 3.23 - 3.07 (m, 1H), 3.02 - 2.92 (m, 1H), 2.78 - 2.72 (m, 1H), 2.68 - 2.57 (m, 1H), 2.23 (d, *J* = 4.0 Hz, 3H), 1.44 (s, 9H), 1.24 - 1.19 (m, 3H), 1.18 - 1.15 (m, 2H), 1.11 - 1.04 (m, 2H).

[0211] Step 2: int-5a

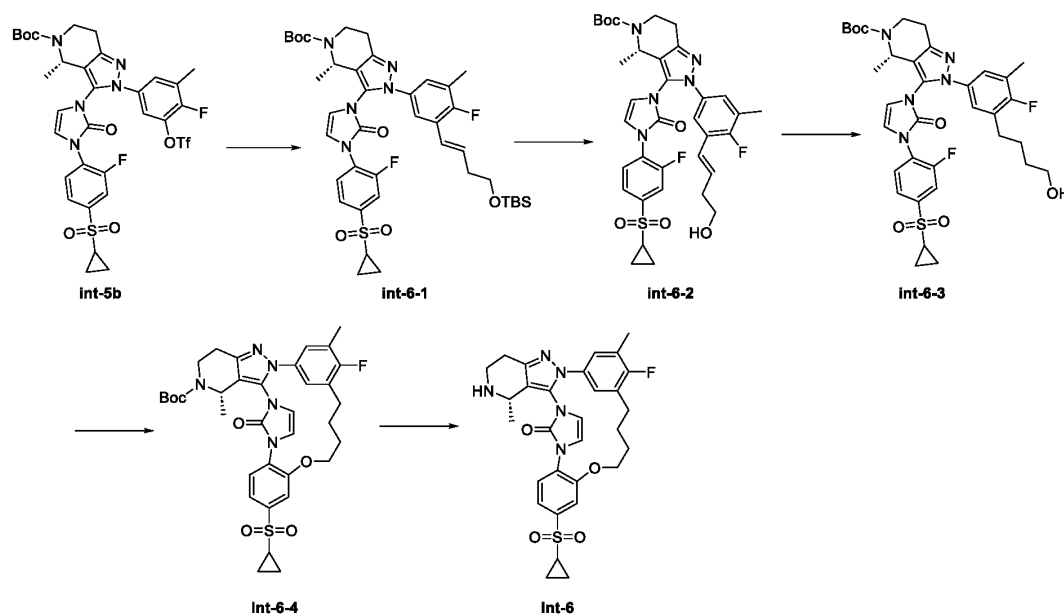
[0212] To a mixture of **int-5-9** (1.20 g, 1.64 mmol) in THF (35 mL) was added Pd/C (120 mg, 10% purity, 50% wet), the mixture was degassed and purged with H₂ for 3 times. The resulting mixture was stirred at 15 °C for 3 hrs under H₂ atmosphere (15 psi). The reaction mixture was filtered, concentrated and washed with MeOH (15 mL × 2). The combined organic layers were concentrated and purified by column chromatography to afford **int-5a** (630 mg, 0.98 mmol, 59.9% yield). LCMS: 642.3 [M+H]⁺.

[0213] Step 3: int-5b

[0214] To a solution of **int-5a** (600 mg, 0.94 mmol) in DCM (12 mL) was added TEA (0.3 mL, 2.6 mmol) dropwise and 2,2,2-trifluoro-*N*-phenyl-*N*-((2,2,2-trifluoroethyl)sulfonyl)ethane-1-sulfonamide (396 mg, 1.03 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 15 °C for 3 hrs. The reaction mixture was quenched by water (50 mL) and extracted with DCM (100 mL × 2). 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-5b** (630 mg, 0.81 mmol, 87.0% yield). LCMS: 774.3 $[\text{M}+\text{H}]^+$.

Example f: Synthesis of int-6



[0215] Step 1: int-6-1

[0216] A mixture of **int-5b** (900 mg, 1.16 mmol), (*E*)-*tert*-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)silane (727 mg, 2.32 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (95 mg, 0.11 mmol) and K_2CO_3 (482 mg, 3.49 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was degassed and purged with N_2 for 3 times, the mixture was stirred at 100 °C for 2 hrs under N_2 atmosphere. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (150 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-6-1** (560 mg, 0.69 mmol, 59.4% yield). LCMS: 810.3 $(\text{M}+\text{H})^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99 (d, J = 8.0 Hz, 1H), 7.88 - 7.79 (m, 2H), 7.31 (dd, J = 8.0, 4.0 Hz, 1H), 7.20 - 7.13 (m, 2H), 7.05 (brs, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.23 (dt, J = 16.0, 8.0 Hz, 1H), 5.14 (brs, 1H), 4.22 (brs, 1H), 3.65 (t, J = 8.0 Hz, 2H), 3.22 - 3.05 (m, 1H), 3.02 - 2.92 (m, 1H), 2.78 - 2.61 (m, 2H), 2.36 (q, J = 8.0 Hz, 2H), 2.23 (s, 3H), 1.44 (s, 9H), 1.24 - 1.16 (m, 5H), 1.12 - 1.07 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

[0217] Step 2: int-6-2

[0218] To a solution of **int-6-1** (300 mg, 0.37 mmol) in NMP (4.5 mL) was added Cs_2CO_3 (241 mg, 0.74 mmol). The mixture was stirred at 100 °C for 2 hrs. After cooling to room temperature, the

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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-6-2** (260 mg, 0.30 mmol, 81.0% yield). LCMS: 696.3 (M+H)⁺.

[0219] Step 3: int-6-3

[0220] To a solution of **int-6-2** (230 mg, 0.33 mmol) in THF (7 mL) was added Pd/C (23 mg, 10% w/w). The reaction mixture was degassed and purged with H₂ for 3 times, then stirred at 15 °C under H₂ atmosphere (15 Psi) for 2 hrs. After being filtered through Celite, the filter cake was rinsed with MeOH (20 mL $\times$ 3). The combined organic layers were concentrated and purified by column chromatography to afford **int-6-3** (130 mg, 0.18 mmol, 56.4% yield). LCMS: 698.3 (M+H)⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.01 (dd, *J* = 12.0 Hz, 1H), 7.90-7.83 (m, 2H), 7.18-7.14 (m, 2H), 7.10-6.99 (m, 2H), 5.14 (s, 1H), 4.22 (s, 1H), 3.32 (s, 1H), 3.20-3.08 (m, 1H), 3.02-2.95 (m, 1H), 2.79-2.54 (m, 5H), 2.24 (s, 3H), 1.55-1.48 (m, 2H), 1.44 (s, 9H), 1.42-1.36 (m, 2H), 1.25-1.15 (m, 6H), 1.12-1.07 (m, 2H).

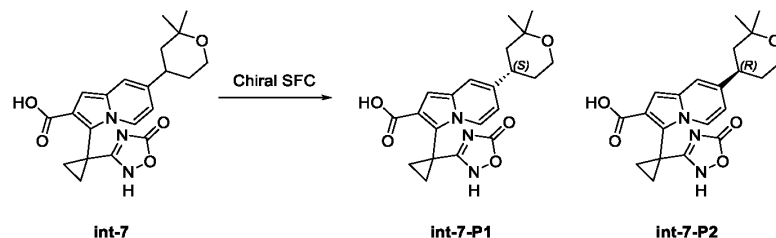
[0221] Step 4: int-6-4

[0222] To a solution of **int-6-3** (120 mg, 0.17 mmol) in NMP (3.6 mL) was added potassium *tert*-butoxide (29 mg, 0.26 mmol). The resulting mixture was stirred at 50 °C for 1 hr. 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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-6-4** (65 mg, 0.1 mmol, 55.8% yield). LCMS: 678.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.76-7.48 (m, 3H), 7.38 (dd, *J* = 20.0, 4.0 Hz, 1H), 7.11-6.67 (m, 3H), 5.18-5.08 (m, 1H), 4.35-4.01 (m, 3H), 3.20 (s, 1H), 2.97-2.86 (m, 1H), 2.74-2.55 (m, 4H), 2.28 (s, 3H), 1.80-1.65 (m, 2H), 1.64-1.49 (m, 2H), 1.45 (d, *J* = 4.0 Hz, 9H), 1.29-1.21 (m, 3H), 1.19-1.12 (m, 2H), 1.12-1.04 (m, 2H).

[0223] Step 5: int-6

[0224] A mixture of **int-6-4** (65 mg, 0.09 mmol) in HCl solution (4 M in dioxane, 2 mL) was stirred at 25 °C for 1 hr. The reaction mixture was concentrated to afford **int-6** (60 mg, 0.09 mmol, 97% yield), which was used directly for the next step. LCMS: 578.4 (M+H)⁺.

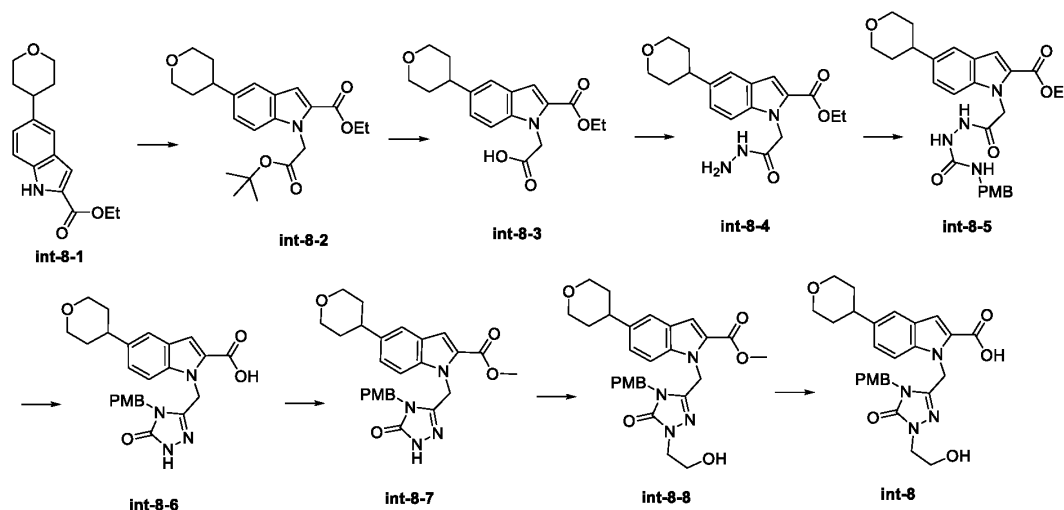
Example g: Int-7, Int-7-P1 and Int-7-P2



[0225] The synthesis of **int-7** was referred to intermediate 31 of WO-2022017338.

[0226] **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-*d*₆) 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 h: Synthesis of int-8



[0227] The synthesis of **int-8-1** was referred to WO-2021155841.

[0228] Step 1: int-8-2

[0229] To a solution of **int-8-1** (10.0 g, 36.60 mmol) in DMF (100 mL) was added NaH (2.20 g, 54.9 mmol, 60% purity) in portions at 0 °C. After being stirred at 20 °C for 0.5 hr, *tert*-butyl 2-bromoacetate (7.85 g, 40.2 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched by H₂O (500 mL) and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-8-2** (12.0 g, 31.0 mmol, 85.0% yield). LCMS: 388.2 [M+H]⁺.

[0230] Step 2: int-8-3

[0231] To a solution of **int-8-2** (12.0 g, 31.0 mmol) in DCM (40 mL) was added TFA (120 mL) at 0 °C. The resulting mixture was stirred at 50 °C for 0.5 hr. The reaction mixture was concentrated and triturated with MTBE (20 mL) at 20 °C for 0.5 hrs to afford **int-8-3** (10.0 g, 30.20 mmol, 97% yield). LCMS: 332.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 12.89 (brs, 1H), 7.58 - 7.51 (m, 2H), 7.30 - 7.21 (m, 2H), 5.27 (s, 2H), 4.28 (q, *J* = 8.0 Hz, 2H), 4.01 - 3.88 (m, 2H), 3.49 - 3.43 (m, 2H), 2.91 - 2.78 (m, 1H), 1.81 - 1.64 (m, 4H), 1.31 (t, *J* = 8.0 Hz, 3H).

[0232] Step 3: int-8-4

[0233] To a solution of **int-8-3** (10.0 g, 30.20 mmol) in THF (100 mL) was added CDI (5.87 g, 36.20 mmol). After being stirred at 20 °C for 2 hrs, hydrazine hydrate (33 mL, 604 mmol, 80% purity) was added. The resulting mixture was stirred at 20 °C for 1 hr. The reaction was filtered and triturated with H₂O (10 mL) at 20 °C for 0.5 hrs. After being filtered, the cake was dried to afford **int-8-4** (9.50 g, 27.50 mmol, 91.0% yield). LCMS: 346.2 [M+H]⁺.

[0234] **Step 4: int-8-5**

[0235] To a solution of **int-8-4** (10.0 g, 29.00 mmol) in DCM (100 mL) was added 1-(isocyanatomethyl)-4-methoxybenzene (5.20 g, 31.80 mmol). The mixture was stirred at 10 °C for 5 hrs. The reaction was concentrated and triturated with MTBE (20 mL) at 10 °C for 0.5 hr to afford **int-8-5** (10.0 g, 19.66 mmol, 67.9% yield). LCMS: 509.2 [M+H]⁺.

[0236] **Step 5: int-8-6**

[0237] A mixture of **int-8-5** (6.0 g, 11.80 mmol) in NaOH (2 M in water, 40.0 mL) and EtOH (40 mL) was stirred at 110 °C for 48 hrs. After cooling to room temperature, the mixture was concentrated, neutralized with diluted HCl, filtered and washed with water (20 mL × 2). The cake was dried to afford **int-8-6** (4.50 g, crude). LCMS: 463.3 [M+H]⁺.

[0238] **Step 6: int-8-7**

[0239] To a solution of **int-8-6** (200 mg, 0.43 mmol, crude) in MeOH (2 mL) was added thionyl chloride (6 mg, 0.04 mmol). The mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the mixture was concentrated and purified by column chromatography to afford **int-8-7** (70 mg, 0.15 mmol, 34.0% yield). LCMS: 477.3 [M+H]⁺.

[0240] **Step 7: int-8-8**

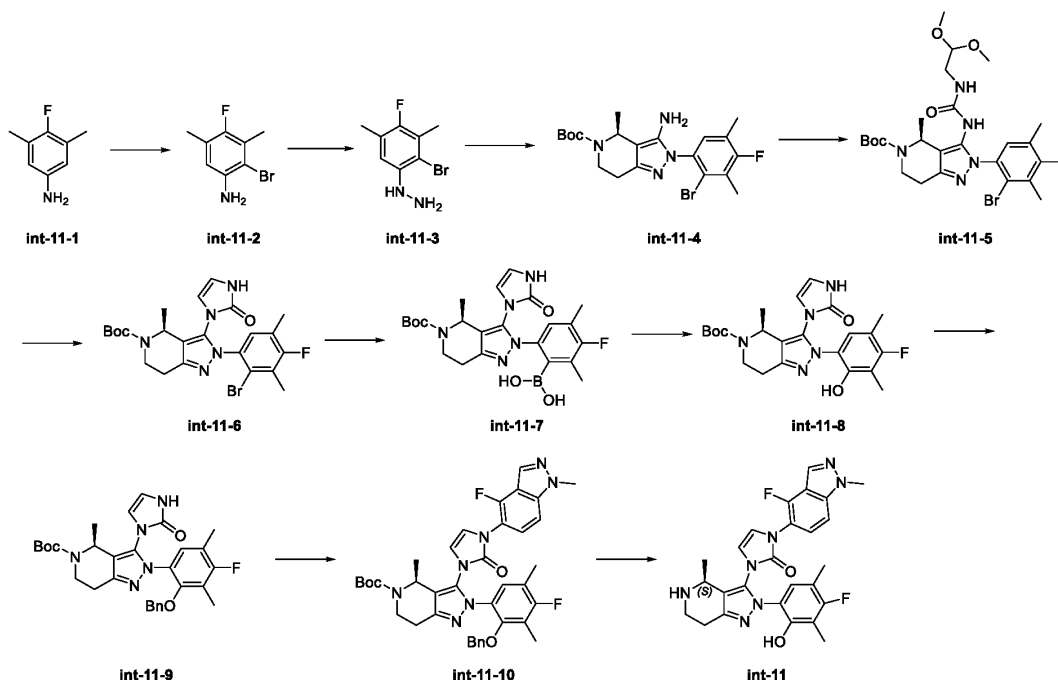
[0241] To a solution of **int-8-7** (500 mg, 1.05 mmol) in DMF (10 mL) was added NaH (126 mg, 3.15 mmol, 60% purity) in portions at 0 °C and stirred for 0.5 hr. Then 2-bromoethan-1-ol (0.22 mL, 3.15 mmol) was added dropwise. The mixture was stirred at 10 °C for 12 hrs. The reaction was quenched by H₂O (30 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (20 mL × 3), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-8-8** (260 mg, 0.50 mmol, 47.6% yield). LCMS: 521.3 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.92 ((d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 5.25 (s, 2H), 4.98 (s, 2H), 4.89 (t, *J* = 8.0 Hz, 1H), 3.98 - 3.93 (m, 2H), 3.87 - 3.81 (m, 2H), 3.76 - 3.71 (m, 5H), 3.64 (s, 3H), 3.48 - 3.41 (m, 2H), 2.86 - 2.78 (m, 1H), 1.74 - 1.69 (m, 4H).

[0242] **Step 8: int-8**

[0243] To a solution of **int-8-8** (250 mg, 0.48 mmol) in MeOH (3 mL) and water (3 mL) was added NaOH (57 mg, 1.44 mmol). The resulting mixture was stirred at 10 °C for 2 hrs. The reaction mixture was diluted with H₂O (20 mL), acidified with 2 M HCl, extracted with DCM (50 mL × 2). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated to afford **int-8** (260 mg, crude). LCMS: 507.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ

7.45 - 7.38 (m, 2H), 7.17 - 7.12 (m, 3H), 6.94 - 6.89 (m, 2H), 6.59 (s, 1H), 5.04 (s, 2H), 4.92 (s, 2H), 3.97 - 3.93 (m, 2H), 3.86 - 3.81 (m, 2H), 3.75 - 3.71 (m, 5H), 3.47 - 3.41 (m, 2H), 2.83 - 2.79 (m, 1H), 1.73 - 1.67 (m, 4H).

Example j: Synthesis of int-11



[0244] Step 1: int-11-2

[0245] To a solution of **int-11-1** (35.0 g, 251.0 mmol) in DMF (400 mL) was added NBS (49.2 g, 277.0 mmol) in portions at 0 °C and the mixture was stirred at 20 °C for 0.5 hrs. The reaction was poured into water (2 L) and extracted with EtOAc (500 mL × 3). The combined organic layers were washed with water (300 mL × 2), followed by brine (300 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-11-2** (40.0 g, 183.0 mmol, 72.9% yield). LCMS: 218.0 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 6.56 (d, *J* = 8.0 Hz, 1H), 5.03 (s, 2H), 2.20 (d, *J* = 4.0 Hz, 3H), 2.09 (d, *J* = 4.0 Hz, 3H).

[0246] Step 2: int-11-3

[0247] To a solution of **int-11-2** (35.0 g, 160.0 mmol) in conc.HCl (6.6 mL) was added a solution of sodium nitrite (12.18 g, 177 mmol) in H₂O (26.5 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 hr. Then a solution of tin(II) chloride dihydrate (145.0 g, 642.0 mmol) in conc.HCl (39.8 mL) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 2 hrs. The reaction was diluted with H₂O (300 mL) and filtered, washed with water (20 mL × 2). After drying, the cake was triturated with MTBE (100 mL) at 20 °C for 30 mins to afford **int-11-3** (30.0 g, 129.00 mmol, 80.0% yield). LCMS: 233.0 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 6.96 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 1H), 4.13 (s, 2H), 2.21 (s, 3H), 2.17 (s, 3H).

[0248] Step 3: int-11-4

[0249] To a solution of **int-11-3** (30.0 g, 195.00 mmol) in EtOH (450 mL) were added *tert*-butyl (2*S*)-3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (37.1 g, 156.0 mmol) and pyridine hydrochloride (2.25 g, 19.46 mmol). The mixture was stirred at 85 °C for 2 hrs. After cooling to room temperature, the reaction was concentrated, dissolved in EtOAc (500 mL), and washed with saturated Na₂CO₃ solution (1 L), followed by brine (500 mL). After being dried over Na₂SO₄ and filtered, the organic layer was concentrated and purified by column chromatography to afford **int-11-4** (45.0 g, 120.0 mmol, 61.8% yield). LCMS: 453.0 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 7.22 (s, 1H), 5.13 - 4.91 (m, 3H), 4.23 - 4.03 (m, 1H), 3.10 - 2.93 (m, 1H), 2.44 (s, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 1.44 (s, 9H), 1.23 (s, 3H).

[0250] Step 4: int-11-5

[0251] To a solution of **int-11-4** (5.0 g, 11.03 mmol) in DMA (60 mL) were added *N*-(2,2-dimethoxyethyl)-1*H*-imidazole-1-carboxamide (2.20 g, 11.0 mmol) and potassium *tert*-butoxide (3.71 g, 33.1 mmol). The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the mixture was poured into water (300 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-11-5** (4.20 g, 7.19 mmol, 65.2% yield). LCMS: 584.1 [M+H]⁺.

[0252] Step 5: int-11-6

[0253] To a solution of **int-11-5** (4.50 g, 7.70 mmol) in THF (225 mL) was added *p*-TsOH·H₂O (4.39 g, 23.10 mmol). The resulting mixture was stirred at 60 °C for 2 hrs. After cooling to room temperature, the mixture was poured into water (500 mL), extracted with EtOAc (150 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-11-6** (2.80 g, 5.38 mmol, 69.8% yield). LCMS: 520.0 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 10.22 (s, 1H), 7.43 (brs, 1H), 6.47 (t, *J* = 4.0 Hz, 1H), 6.33 (s, 1H), 5.17 (brs, 1H), 4.40 - 4.10 (m, 1H), 3.15 - 2.98 (s, 1H), 2.74 - 2.55 (m, 2H), 2.30 (s, 3H), 2.21 (s, 3H), 1.44 (s, 9H), 1.15 - 1.02 (m, 3H).

[0254] Step 6: int-11-7

[0255] To a solution of **int-11-6** (5.00 g, 9.61 mmol) in THF (100 mL) was added *n*BuLi (12.6 mL, 31.70 mmol) dropwise at -65 °C under N₂ atmosphere. The mixture was stirred for 0.5 hrs at -65 °C, trimethyl borate (1.6 mL, 14.41 mmol) was added dropwise below -60 °C. The mixture was stirred at -65 °C for 1 hr. The mixture was quenched by H₂O (300 mL) and extracted with EtOAc (150 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated to afford **int-11-7** (5.10 g, crude). LCMS: 486.3 [M+H]⁺.

[0256] Step 7: int-11-8

[0257] To a solution **int-11-7** (5.00 g, 8.81 mmol, crude) in THF (50 mL) was added acetic acid (0.5 mL, 8.81 mmol) and hydrogen peroxide (1.8 mL, 17.62 mmol, 30% purity). The resulting mixture

was stirred at 30 °C for 9 hrs. The reaction mixture was poured into water (150 mL) and 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-11-8** (3.60 g, 7.87 mmol, 89.0% yield). LCMS: 458.2 [M+H]⁺

[0258] Step 8: int-11-9

[0259] To a solution of **int-11-8** (3.60 g, 7.87 mmol) in DMF (36 mL) were added K₂CO₃ (1.31 g, 9.44 mmol) and (bromomethyl)benzene (808 mg, 4.72 mmol). The resulting mixture was stirred at 20 °C for 1 hr. The reaction mixture was poured into water (300 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by HPLC to afford **int-11-9** (1.00 g, 1.83 mmol, 23.2% yield). LCMS: 548.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 10.20 (s, 1H), 7.35 - 7.27 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.18 - 7.10 (m, 2H), 6.44 (s, 1H), 6.17 (s, 1H), 5.14 (brs, 1H), 4.59 (d, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.39 - 4.11 (m, 1H), 3.21 - 2.91 (m, 1H), 2.75 - 2.56 (m, 2H), 2.20 (s, 3H), 2.08 (s, 3H), 1.45 (s, 9H), 1.09 (d, *J* = 8.0 Hz, 3H).

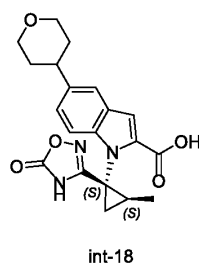
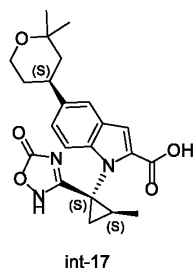
[0260] Step 9: int-11-10

[0261] To a solution of **int-11-9** (850 mg, 1.55 mmol) in NMP (1.5 mL) were added 5-bromo-4-fluoro-1-methyl-1*H*-indazole (711 mg, 3.10 mmol, synthesized according to WO2022017338), copper(I) iodide (296 mg, 1.55 mmol), K₂CO₃ (644 mg, 4.66 mmol) and (1*R*,2*R*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (110 mg, 0.78 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 130 °C for 5 hrs under N₂. After cooling to room temperature, the reaction was poured into water (100 mL) and extracted with EtOAc (60 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-11-10** (800 mg, 1.15 mmol, 74.1% yield). LCMS: 696.3 [M+H]⁺

[0262] Step 10: int-11

[0263] To a solution of **int-11-10** (150 mg, 0.22 mmol) in DCM (3 mL) was added boron tribromide (0.4 mL, 4.3 mmol) dropwise at -65 °C. The resulting mixture was warmed up to 0 °C and stirred for 2 hrs. The reaction was quenched by 5 mL of water, and basified with saturated NaHCO₃ solution. After extraction with DCM (10 mL × 3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-11** (90 mg, 0.18 mmol, 82.6% yield). LCMS: 506.2 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.99 - 6.91 (m, 2H), 6.67 (d, *J* = 4.0 Hz, 1H), 4.16 (s, 3H), 3.99 (q, *J* = 8.0 Hz, 1H), 3.30 - 3.20 (m, 3H), 2.98 - 2.88 (m, 1H), 2.76 - 2.61 (m, 2H), 2.17 (s, 6H), 1.19 (d, *J* = 6.5 Hz, 3H).

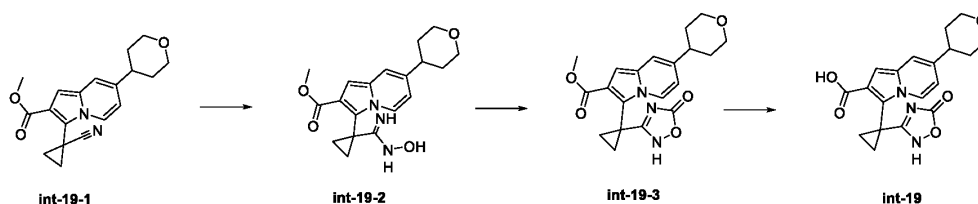
Example p: Synthesis of int-17, int-18



The synthesis of **int-17** was referred to intermediates **31k** of WO-2018056453.

The synthesis of **int-18** was referred to intermediates **8b** of WO-2018056453.

Example q: Synthesis of int-19



Step 1: int-19-2

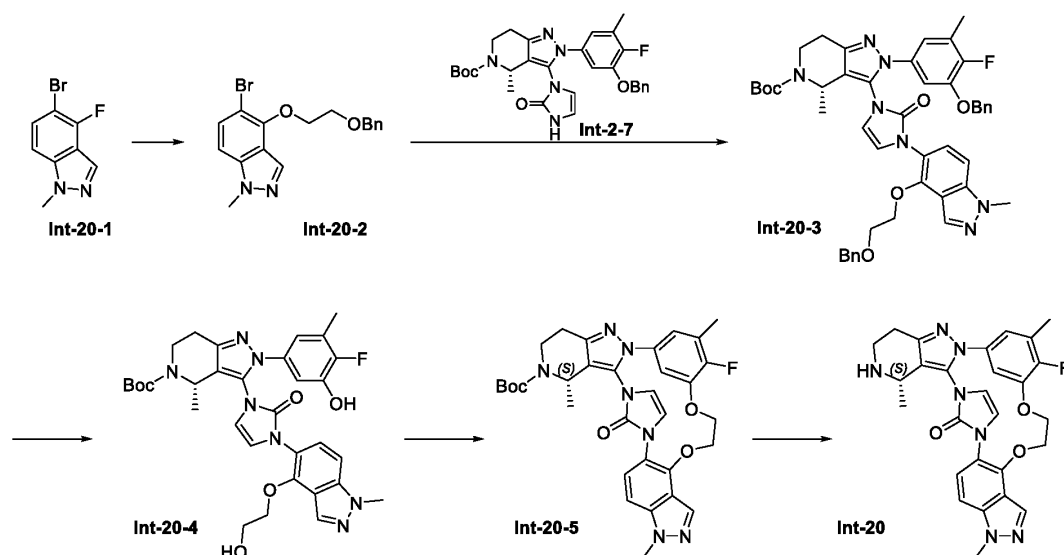
To a solution of **int-19-1** (4.25 g, 13.10 mmol, WO2023169456) in EtOH (50 mL) was added hydroxylamine hydrochloride (2.73 g, 39.3 mmol) and triethylamine (7.95 g, 79.00 mmol). The resulting mixture was stirred at 90 °C for 1 hr. After cooling to room temperature, the reaction mixture was poured into 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-*d*₆) 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

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-*d*₆) 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

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-*d*₆) 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 r: Synthesis of int-20**[0264] Step 1: int-20-2**

To a solution of **int-20-1** (500 mg, 2.18 mmol) and 2-(benzyloxy)ethan-1-ol (399 mg, 2.62 mmol) in DMA (5 mL) was added potassium *tert*-butoxide (367.0 mg, 3.27 mmol) in portions. The resulting mixture was stirred at 25 °C for 1 hr, the reaction mixture was quenched by H₂O (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated, purified by column chromatography to afford **int-20-2** (700 mg, 1.94 mmol, 89.0% yield). LCMS: 361.1 [M+H]⁺.

[0265] Step 2: int-20-3

To a solution of **int-11-8** (300 mg, 0.56 mmol) in NMP (6 mL) were added **int-20-2** (609 mg, 1.69 mmol), copper(I) iodide (107 mg, 0.56 mmol), K₂CO₃ (233 mg, 1.69 mmol) and (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (40 mg, 0.28 mmol). The resulting mixture was degassed and purged with N₂ for 3 times, and then stirred at 130 °C under N₂ for 4 hrs. After cooling to room

temperature, the mixture was diluted with H₂O (50 mL), extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (30 mL × 2), dried over Na₂SO₄, filtered and concentrated, purified by column chromatography to afford **int-20-3** (440 mg, 0.54 mmol, 96.0% yield). LCMS: 814.4 [M+H]⁺.

[0266] Step 3: int-20-4

To a solution of **int-20-3** (440 mg, 0.54 mmol) in THF (20 mL) was added Pd/C (88 mg, 20% w/w, 10% purity). The resulting mixture was degassed and purged with H₂ for 3 times, and then stirred at 40 °C for 12 hrs under H₂ atmosphere. The reaction mixture was filtered. The cake was washed with THF (5 mL × 3) and the filtrate was concentrated and purified by column chromatography to afford **int-20-4** (300 mg, 0.47 mmol, 88.0% yield). LCMS: 634.3 [M+H]⁺.

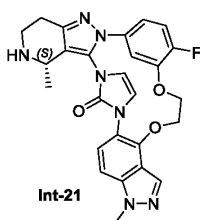
[0267] Step 4: int-20-5

To a solution of **int-20-4** (150 mg, 0.24 mmol) in THF (3 mL) was added PPh₃ (93 mg, 0.355 mmol). The mixture was degassed and purged with N₂ for 3 times, then DIAD (0.069 mL, 0.355 mmol) was added dropwise at 0 °C. After addition, the reaction was stirred at 20 °C under N₂ for 1 hr and quenched by H₂O (20 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-20-5** (100 mg, 0.16 mmol, 68.6% yield). LCMS: 616.3 [M+H]⁺.

[0268] Step 5: int-20

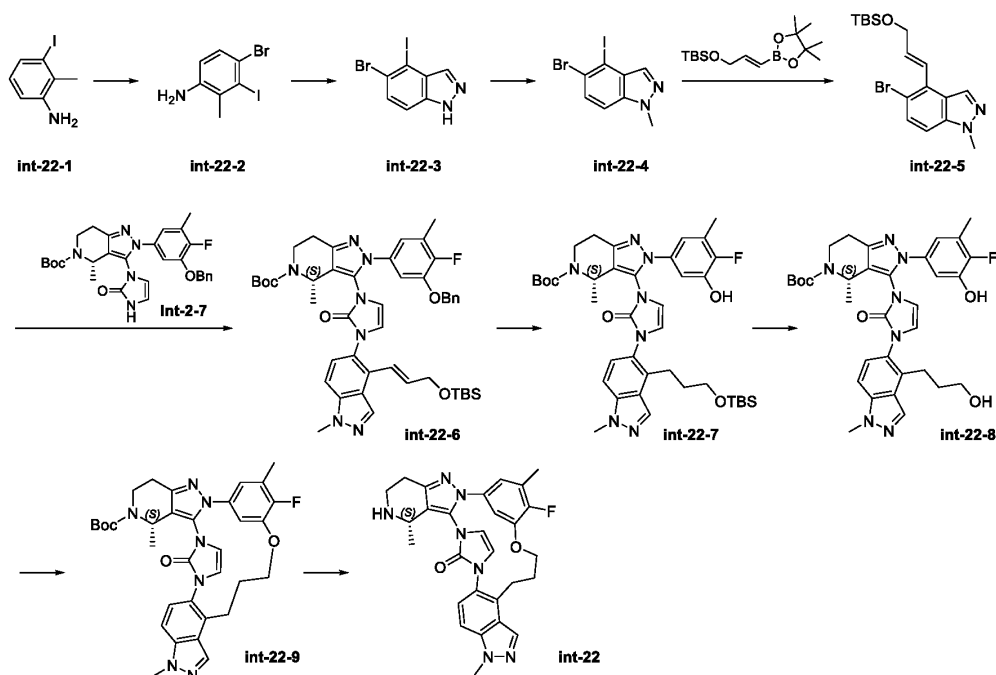
A mixture of **int-20-5** (50.0 mg, 0.081 mmol) in HCl solution (4 M in dioxane, 1 mL) was stirred at 20 °C for 1 hr. After completion, the reaction mixture was concentrated to afford **int-20** (260 mg, 0.41 mmol, 86.0% yield). LCMS: 516.2 [M+H]⁺.

Example o: Synthesis of int-21



The synthesis of **int-21** was referred to **int-20**, the starting material **int-2-1** was replaced by 5-bromo-2-fluorophenol.

Example s: Synthesis of int-22

**[0269] Step 1: int-22-2**

To a solution of **int-22-1** (100.0 g, 429.09 mmol) in DMF (1 L) were added NBS (76.4 g, 429.09 mmol) in portions at 0 °C. The resulting mixture was stirred at 25 °C for 1 h. The mixture was poured into H₂O (3 L) and extracted with EtOAc (2 L × 3). The combined organic layers were washed with brine (1 L), dried over Na₂SO₄, filtered, concentrated, and triturated with H₂O (300 mL) at 20 °C for 1 hr. After filtration, the cake was dried to afford **int-22-2** (118.0 g, 378.0 mmol, 88% yield). LCMS: 312.0 [M+H]⁺.

[0270] Step 2: int-22-3

To a solution of **int-22-2** (85.0 g, 272.0 mmol) in AcOH (850 mL) was added a solution of sodium nitrite (22.56 g, 327 mmol) in water (136 mL) dropwise at 0 °C. The resulting reaction was stirred at 20 °C for 2 hrs. The reaction mixture was concentrated, diluted with water (1.5 L) and adjusted pH to 8 with Na₂CO₃. The mixture was extracted with EtOAc (1 L × 3). The combined organic layers were washed with brine (1 L), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-22-3** (59.0 g, 183.0 mmol, 67.1% yield). LCMS: 323.0 [M+H]⁺.

[0271] Step 3: int-22-4

To a solution of **int-22-3** (60.0 g, 185.80 mmol) in DMF (900 mL) was added NaH (11.15 g, 278.70 mmol, 60% purity) at 0 °C in portions under N₂. The mixture was stirred at 20 °C for 0.5 hr, then MeI (11.6 mL, 185.80 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 1.5 hrs. The reaction mixture was poured into H₂O (3 L), extracted with EtOAc (1 L × 3). The combined organic layers were washed with brine (1 L × 2), dried over Na₂SO₄, filtered, concentrated, purified by column chromatography to afford **int-22-4** (30 g, 89.03 mmol, 47.92% yield). LCMS:

336.9 [M+H]⁺. ¹HNMR (500 MHz, DMSO-*d*₆) δ 7.83 (d, *J* = 0.9 Hz, 1H), 7.67 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 4.04 (s, 3H).

[0272] Step 4: int-22-5

To a solution of **int-22-4** (500 mg, 1.48 mmol) in 1,4-dioxane (5 mL) and water (1 mL) were added (*E*)-tert-butyltrimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (575 mg, 1.93 mmol), PdCl₂(dppf) (109 mg, 0.15 mmol) and K₂CO₃ (410 mg, 2.97 mmol). The resulting mixture was purged with N₂ for 2 mins and then stirred at 100 °C for 2 hrs under N₂. 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 brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-22-5** (250 mg, 0.66 mmol, 44.2% yield). LCMS: 381.0 [M+H]⁺.

[0273] Step 5: int-22-6

To a solution of **int-22-7** (150 mg, 0.28 mmol) in NMP (1.5 mL) were added **int-22-5** (214.0 mg, 0.56 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (20 mg, 0.14 mmol), copper(I) iodide (54 mg, 0.28 mmol) and K₂CO₃ (117 mg, 0.84 mmol). The resulting mixture was purged with N₂ for 2 mins and stirred at 130 °C for 5 hrs under N₂. After cooling to room temperature, the reaction mixture was poured into water (10 mL), extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-22-6** (150 mg, 0.18 mmol, 64.0% yield). LCMS: 834.6 [M+H]⁺.

[0274] Step 6: int-22-7

To a solution of **int-22-6** (130 mg, 0.16 mmol) in THF (3 mL) were added Pd/C (13 mg, 10%w/w, 10% purity) and Pd(OH)₂ (13 mg, 10% w/w, 10% purity). The reaction mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C under H₂ (15 Psi) for 6 hrs. The mixture was filtered. The cake was rinsed with THF (3 mL × 3), the combined filtrate was concentrated to afford **int-22-7** (100 mg, 0.13 mmol, 86.0% yield). LCMS: 746.5 [M+H]⁺.

[0275] Step 7: int-22-8

To a solution of **int-22-7** (90 mg, 0.12 mmol) in THF (0.9 mL) were added a solution of TBAF (0.422 mL, 1 M in THF) dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 30 mins. After completion, the residue was diluted with H₂O (2 mL) and extracted with solvent EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-22-8** (60 mg, 0.095 mmol, 79.0% yield). LCMS: 632.4 [M+H]⁺.

[0276] Step 8: int-22-9

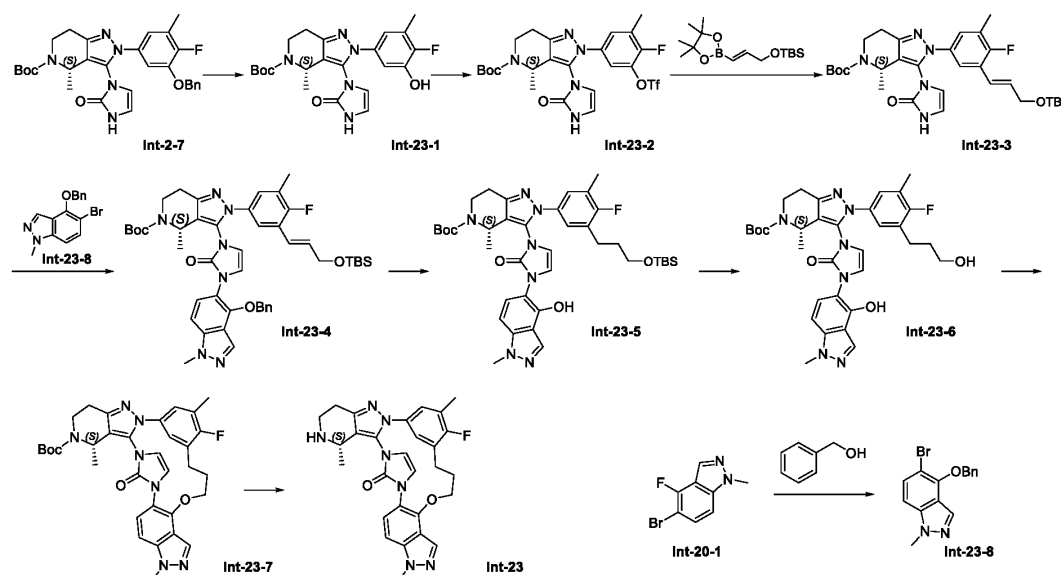
To a solution of **int-22-8** (50 mg, 0.079 mmol) in THF (1 mL) were added triphenylphosphine (42 mg, 0.16 mmol), the mixture was degassed and purged with N₂ for 3 times, and then DIAD (32 mg, 0.158 mmol) was added dropwise at 0 °C under N₂. The resulting mixture was stirred at 25 °C for 1 h

under N₂. After completion, the residue was quenched by H₂O (2 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 pre-TLC to afford **int-22-9** (70 mg, 0.057 mmol, 72.1% yield). LCMS: 614.4 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.39 - 8.33 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.08 - 7.03 (m, 1H), 6.95 - 6.78 (m, 1H), 6.72 - 6.58 (m, 1H), 5.33 - 5.08 (m, 1H), 4.33 (t, *J* = 8.0 Hz, 2H), 4.28 - 4.20 (m, 1H), 4.12 - 4.09 (m, 3H), 3.41 - 3.40 (m, 1H), 3.02 - 2.92 (m, 2H), 2.82 - 2.74 (m, 2H), 2.33 - 2.29 (m, 3H), 1.79 - 1.64 (m, 2H), 1.52 - 1.45 (m, 12H)

[0277] Step 9: int-22

A mixture of **int-22-9** (70 mg, 0.08 mmol) in HCl solution (0.7 mL, 4 M in dioxane) was stirred at 25 °C for 1 h. The reaction mixture was concentrated and diluted with DCM (2 mL). The process was repeated for 3 times to afford **int-22** (50 mg, 0.049 mmol, 61.0% yield), which was used for next step directly without purification. LCMS: 514.4 [M+H]⁺.

Example t: Synthesis of int-23



[0278] Step 1: int-23-8

To a solution of **int-20-1** (3.00 g, 13.10 mmol) in DMA (30 mL) were added phenylmethanol (1.70 g, 15.72 mmol) and *t*BuOK (2.21 g, 19.65 mmol), the mixture was stirred at 25 °C for 1 hr. The reaction mixture was poured into H₂O (150 mL) and extracted with EtOAc (150 mL × 2). The combined organic layers were washed with water (100 mL × 2), followed by brine (150 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-23-8** (3.10 g, 9.77 mmol, 74.6% yield). LCMS: 317.2 [M+H]⁺.

[0279] Step 2: int-23-1

To a solution of **int-2-7** (960.0 mg, 1.80 mmol) in THF (20 mL) and MeOH (20 mL) was added Pd/C (96 mg, 10% w/w, 10% purity). The reaction mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C under H₂ (15 Psi) for 7 hrs. The mixture was filtered through a celite pad and the cake was rinsed with MeOH (10 mL × 3). The combined filtrate was concentrated and purified by column chromatography to afford **int-23-1** (420 mg, 0.95 mmol, 52.6% yield). LCMS: 444.3 [M+H]⁺.

[0280] Step 3: int-23-2

To a solution of **int-23-1** (370.0 mg, 0.83 mmol) in DCM (4 mL) was added TEA (0.35 mL, 2.50 mmol), *N*-phenyl-bis(trifluoromethanesulfonimide) (283 mg, 0.79 mmol). The reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with DCM (20 mL) and washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered and concentrated and purified by column chromatography to afford **int-23-2** (380 mg, 0.66 mmol, 79.0% yield). LCMS: 576.3 [M+H]⁺.

[0281] Step 4: int-23-3

To a solution of **int-23-2** (380 mg, 0.66 mmol), (*E*)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (394 mg, 1.32 mmol) in dioxane (7.6 mL) were added PdCl₂(dppf)*CH₂Cl₂ adduct (108 mg, 0.13 mmol), K₂CO₃ (274 mg, 1.98 mmol) and water (0.76 mL). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 100 °C for 1 hr under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-23-3** (290 mg, 0.49 mmol, 73.5% yield). LCMS: 598.4 [M+H]⁺.

[0282] Step 5: int-23-4

To a solution of **int-23-3** (290 mg, 0.49 mmol), **int-23-8** (308 mg, 0.97 mmol) in NMP (3 mL) were added (1*S*,2*S*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (35 mg, 0.24 mmol), cuprous iodide (92 mg, 0.49 mmol), K₂CO₃ (201 mg, 1.46 mmol). The resulting mixture was purged with N₂ for 2 mins and stirred at 130 °C for 3 hrs under N₂. After cooling to room temperature, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (10 mL × 3), washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered and concentrated, purified by column chromatography to afford **int-23-4** (180 mg, 0.22 mmol, 44.5% yield). LCMS: 834.5 [M+H]⁺.

[0283] Step 6: int-23-5

To a solution of **int-23-4** (180.0 mg, 0.22 mmol) in THF (6 mL) was added Pd/C (36 mg, 20% w/w, 10% purity). The mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C for 12 hrs under H₂ (15 Psi) atmosphere. The mixture was filtered. The cake was washed with THF (3 mL × 3), the combined filtrate was concentrated and purified by column chromatography to afford **int-23-5** (120 mg, 0.16 mmol, 74.5% yield). LCMS: 746.5 [M+H]⁺.

[0284] Step 7: int-23-6

Int-23-5 (120 mg, 0.17 mmol) in THF (1 mL) was added TBAF (228 mg, 0.87 mmol) in portions. The mixture was stirred at 20 °C for 2 hrs under N₂. The reaction mixture was poured into water (10 mL)

and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography to afford **int-23-6** (70 mg, 0.11 mmol, 63.6% yield). LCMS: 632.3 [M+H]⁺.

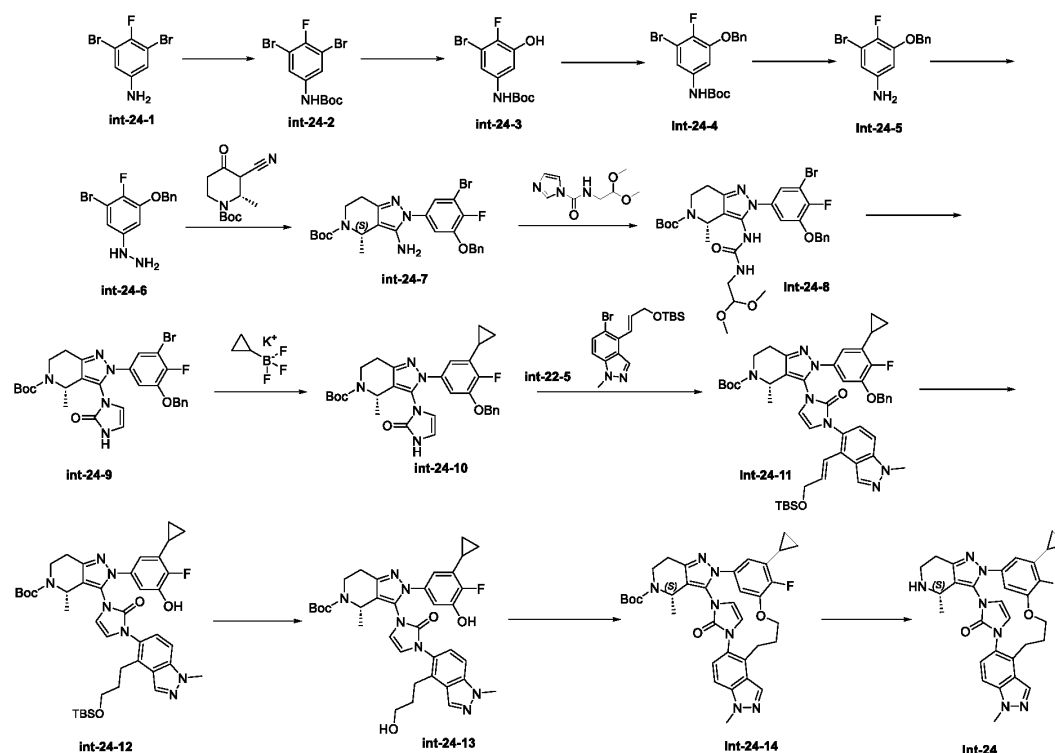
[0285] Step 8: int-23-7

To a solution of **int-23-6** (60 mg, 0.095 mmol) in anhydrous toluene (3 mL) was added CMBP (92 mg, 0.38 mmol). The mixture was purged with N₂ for 2 mins and then stirred at 90 °C for 2 hrs under N₂. After cooling to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-23-7** (30 mg, 0.049 mmol, 51.5% yield). LCMS: 614.4 [M+H]⁺.

[0286] Step 9: int-23

A mixture of **int-23-7** (40 mg, 0.065 mmol) in HCl solution (3 mL, 4 M in dioxane) was stirred at 20 °C for 0.5 hr. The reaction mixture was concentrated and diluted with DCM (10 mL). This process was repeated for three times to afford the title compound (40 mg, 0.062 mmol, 96.0% yield). LCMS: 514.4 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆, 80 °C) δ 9.71 (brs, 1H), 9.07 (brs, 1H), 8.27 (s, 1H), 7.50 - 7.42 (m, 2H), 7.41 - 7.28 (m, 1H), 7.07 - 6.98 (m, 1H), 6.96 - 6.74 (m, 2H), 4.77 - 4.58 (m, 1H), 4.16 - 3.96 (m, 4H), 3.82 - 3.73 (m, 1H), 3.59 (s, 3H), 3.53 - 3.43 (m, 1H), 2.98 - 2.79 (m, 2H), 2.30 (s, 3H), 2.23 - 1.88 (m, 2H), 1.58 - 1.39 (m, 3H).

Example u: Synthesis of int-24



Step 1: int-24-2

To a solution of **int-24-1** (16.60 g, 61.70 mmol) in dioxane (200 mL) was added di-*tert*-butyl dicarbonate (21.5 mL, 93.0 mmol). The mixture resulting was stirred at 80 °C for 6 hrs and then heated to 95 °C for 6 hrs. After cooling to room temperature, the reaction mixture was poured into water (500 mL) and extracted with EtOAc (500 mL × 3). The combined organic layers were washed with water (500 mL × 2), followed by brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography with further purification by trituration with petroleum ether at 0 °C for 30 mins to afford **int-24-2** (18.60 g, 50.40 mmol, 82.0% yield). LC-MS (ESI+): m/z 368.1 (M-H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.71 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 1.47 (s, 9H).

Step 2: int-24-3

A mixture of **int-24-2** (9.00 g, 24.39 mmol), Pd₂(dba)₃ (1.12 g, 1.22 mmol), di-*tert*-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethyl-[1,1'-biphenyl]-2-yl)phosphane (2.34 g, 4.88 mmol), and KOH (4.10 g, 73.2 mmol) in dioxane (90 mL) and water (90 mL) was degassed and purged with N₂ for 3 times, and the resulting mixture was stirred at 105 °C for 3 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (500 mL) and acidified by diluted HCl (2 N) to pH ~ 6, extracted with DCM (500 mL × 3). The combined organic layers were washed with water (400 mL × 2), followed by brine (500 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-24-3** (14.20 g, 23.19 mmol, 95.0% yield). LC-MS (ESI+): m/z 303.9 (M-H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (brs, 1H), 9.39 (s, 1H), 7.22 - 7.10 (m, 2H), 1.45 (s, 9H).

Step 3: int-24-4

To a solution of **int-24-3** (14.20 g, 46.40 mmol) in DMF (200 mL) was added K₂CO₃ (7.69 g, 55.70 mmol) and benzyl bromide (6.6 mL, 55.70 mmol). The resulting mixture was stirred at 20 °C for 2 hrs. After completion, the reaction mixture was poured into water (500 mL) and extracted with EtOAc (500 mL × 3). The combined organic layers were washed with water (500 mL × 2), followed by brine (500 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure to give a residue, which was purified by column chromatography and further purified by trituration with petroleum ether at 20 °C for 1 hr to afford **int-24-4** (9.20 g, 23.22 mmol, 50.1% yield). LC-MS (ESI+): m/z 340.0 (M-56)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.50 (s, 1H), 7.47 - 7.35 (m, 7H), 5.12 (s, 2H), 1.46 (s, 9H).

Step 4: int-24-5

To a solution of **int-24-4** (9.20 g, 23.22 mmol) in dioxane (140 mL) was added HCl (92 mL, 4 M in dioxane). The resulting mixture was stirred at 20 °C for 2 hrs. After completion, the reaction mixture was concentrated under reduced pressure to afford **int-24-5** (7.60 g, crude) as a pale yellow solid,

which was used directly in the next step without purification. LC-MS (ESI+): m/z 296.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49 - 7.35 (m, 5H), 6.98 (dd, J = 16.0, 4.0 Hz, 2H), 5.16 (s, 2H).

Step 5: int-24-6

To a solution of **int-24-5** (5.10 g, 17.22 mmol) in conc. HCl (50 mL) and 1,4-dioxane (50 mL) was added sodium nitrite (1.78 g, 25.80 mmol) in water (20 mL) dropwise at 0 °C. After addition, the mixture was stirred at 0 °C for 1 hr, then a solution of tin(II) chloride (6531 mg, 34.4 mmol) in HCl (50 mL) was added dropwise. The resulting mixture was stirred at 20 °C for 3 hrs. After completion, the reaction mixture was poured into ice-water (50 mL) and the precipitate was collected, rinsed with ice-water (10 mL $\times$ 3) and dried on vacuum to give a residue that was purified by trituration with MTBE (5 mL) at 20 °C for 30 mins to afford **int-24-6** (1.79 g, 5.75 mmol, 33.4% yield). LC-MS (ESI+): m/z 311.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49 - 7.33 (m, 5H), 6.84 (s, 1H), 6.63 (dd, J = 8.0, 4.0 Hz, 1H), 6.60 - 6.53 (m, 1H), 5.10 (s, 2H), 4.05 (s, 2H).

Step 6: int-24-7

A mixture of **int-24-6** (1.46 g, 4.69 mmol) and Na₂CO₃ (497.0 mg, 4.69 mmol) in EtOH (30 mL) was stirred at 20 °C for 0.2 hr, then *tert*-butyl (2*S*)-3-cyano-2-methyl-4-oxopiperidine-1-carboxylate (1.12 g, 4.69 mmol) was added. The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction mixture was filtered and was purified by column chromatography to afford **int-24-7** (2.30 g, 4.33 mmol, 92.0% yield). LC-MS (ESI+): m/z 531.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51 - 7.32 (m, 7H), 5.38 (s, 2H), 5.25 (s, 2H), 5.18 - 4.98 (m, 1H), 4.25 - 4.00 (m, 1H), 3.16 - 2.89 (m, 1H), 2.55 - 2.51 (m, 1H), 2.49 - 2.39 (m, 1H), 1.42 (s, 9H), 1.25 (d, J = 4.0 Hz, 3H).

Step 7: int-24-8

To a solution of **int-24-7** (2.30 g, 4.33 mmol) in DMA (46 mL) was added *N*-(2,2-dimethoxyethyl)-1*H*-imidazole-1-carboxamide (1.72 g, 6.92 mmol) and potassium *tert*-butoxide (1.46 mg, 12.98 mmol). The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction 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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-24-8** (2.00 g, 3.02 mmol, 69.7% yield). LC-MS (ESI+): m/z 662.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 7.49 - 7.34 (m, 7H), 6.60 - 6.49 (m, 1H), 5.20 (s, 2H), 5.18 - 4.93 (m, 1H), 4.31 (t, J = 4.0 Hz, 1H), 4.28 - 4.07 (m, 1H), 3.24 (d, J = 4.0 Hz, 6H), 3.19 - 3.11 (m, 2H), 3.10 - 2.97 (m, 1H), 2.65 - 2.51 (m, 2H), 1.43 (s, 9H), 1.22 (d, J = 8.0 Hz, 3H).

Step 8: int-24-9

To a solution of **int-24-8** (2.00 g, 3.02 mmol) in THF (20 mL) was *p*-toluenesulfonic acid monohydrate (287.0 mg, 1.51 mmol), the resulting mixture was stirred at 60 °C for 2 hrs. After

cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with DCM (100 mL $\times$ 3). The combined organic layers were washed with water (50 mL $\times$ 2), brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-24-9** (1.30 g, 2.17 mmol, 72.0% yield). LC-MS (ESI+): *m/z* 598.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1H), 7.46 - 7.35 (m, 5H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 - 7.15 (m, 1H), 6.68 (t, *J* = 4.0 Hz, 1H), 6.63 (brs, 1H), 5.13 (s, 2H), 5.10 - 4.96 (m, 1H), 4.37 - 4.10 (m, 1H), 3.21 - 2.99 (m, 1H), 2.79 - 2.58 (m, 2H), 1.43 (s, 9H), 1.14 (d, *J* = 4.0 Hz, 3H).

Step 9: int-24-10

To a solution of **int-24-9** (460.0 mg, 0.77 mmol) in 1,4-dioxane (9 mL) and water (2.3 mL) were added potassium cyclopropyltrifluoroborate (227.0 mg, 1.54 mmol), PdCl₂(dppf) (112.0 mg, 0.15 mmol) and K₂CO₃ (212.0 mg, 1.54 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 120 °C for 5 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was concentrated and purified by column chromatography to afford **int-24-10** (290.0 mg, 0.52 mmol, 67.4% yield). LC-MS (ESI+): *m/z* 560.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.45 (s, 1H), 7.47 - 7.37 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.64 - 6.61 (m, 1H), 6.55 (brs, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 2H), 5.08 - 4.95 (m, 1H), 4.35 - 4.10 (m, 1H), 3.21 - 2.99 (m, 1H), 2.76 - 2.56 (m, 2H), 2.12 - 2.02 (m, 1H), 1.42 (s, 9H), 1.14 (d, *J* = 4.0 Hz, 3H), 1.02 - 0.96 (m, 2H), 0.64 - 0.52 (m, 2H).

Step 10: int-24-11

To a solution of **int-24-10** (320.0 mg, 0.57 mmol) in NMP (4.8 mL) were added **int-22-5** (436.0 mg, 1.14 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (81.0 mg, 0.57 mmol), copper(I) iodide (218.0 mg, 1.14 mmol) and K₂CO₃ (237.0 mg, 1.71 mmol). The resulting mixture was degassed and purged with N₂ for 2 mins and then stirred at 140 °C for 5 hrs under N₂ atmosphere. 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 Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-24-11** (120.0 mg, 0.14 mmol, 24.4% yield). LC-MS (ESI+): *m/z* 860.4 (M+H)⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 7.34 - 7.27 (m, 6H), 7.25 - 7.22 (m, 1H), 7.16 - 7.09 (m, 1H), 6.70 - 6.56 (m, 2H), 6.49 - 6.40 (m, 2H), 6.27 - 6.19 (m, 1H), 5.45 - 5.15 (m, 1H), 5.01 (s, 2H), 4.40 - 4.26 (m, 3H), 4.09 (s, 3H), 3.23 - 3.06 (m, 1H), 2.84 - 2.75 (m, 2H), 2.19 - 2.09 (m, 1H), 1.50 (s, 9H), 1.36 (d, *J* = 8.0 Hz, 3H), 0.96 (dd, *J* = 8.0, 4.0 Hz, 2H), 0.89 (s, 9H), 0.75 - 0.66 (m, 2H), 0.07 (s, 6H).

Step 11: int-24-12

To a solution of **int-24-11** (120.0 mg, 0.14 mmol) in MeOH (4 mL) was added Pd/C (24.0 mg, 20%w/w) and Pd(OH)₂ (24.0 mg, 20%w/w). The resulting reaction mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C for 2 hrs. The reaction mixture was filtered through a pad of

Celite and the cake was rinsed with MeOH (10 mL $\times$ 3). The filtrate was concentrated under reduced pressure to afford **int-24-12** (115.0 mg, crude, which was used for next step directly without purification. LC-MS (ESI+): m/z 772.2 (M+H)⁺.

Step 12: int-24-13

To a solution of **int-24-12** (115.0 mg, 0.15 mmol) in THF (0.6 mL) was added TBAF (0.8 mL, 0.80 mmol). The resulting mixture was stirred at 20 °C for 2 hrs. After completion, the reaction mixture was quenched by water (20 mL) and extracted with DCM (20 mL $\times$ 3). The combined organic layers were washed with water (20 mL $\times$ 2), followed by brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-24-13** (70.0 mg, 0.11 mmol, 71.4% yield). LC-MS (ESI+): m/z 658.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.23 (brs, 1H), 8.21 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.00 - 6.81 (m, 3H), 6.32 (d, J = 4.0 Hz, 1H), 5.23 - 5.04 (m, 1H), 4.55 - 4.44 (m, 1H), 4.35 - 4.14 (m, 1H), 4.06 (s, 3H), 3.21 - 3.03 (m, 1H), 2.85 - 2.73 (m, 2H), 2.72 - 2.69 (m, 1H), 2.65 - 2.59 (m, 1H), 2.13 - 2.03 (m, 1H), 1.71 - 1.60 (m, 2H), 1.43 (s, 9H), 1.23 (s, 3H), 1.21 (d, J = 8.0 Hz, 2H), 0.99 (d, J = 8.0 Hz, 2H), 0.65 - 0.55 (m, 2H).

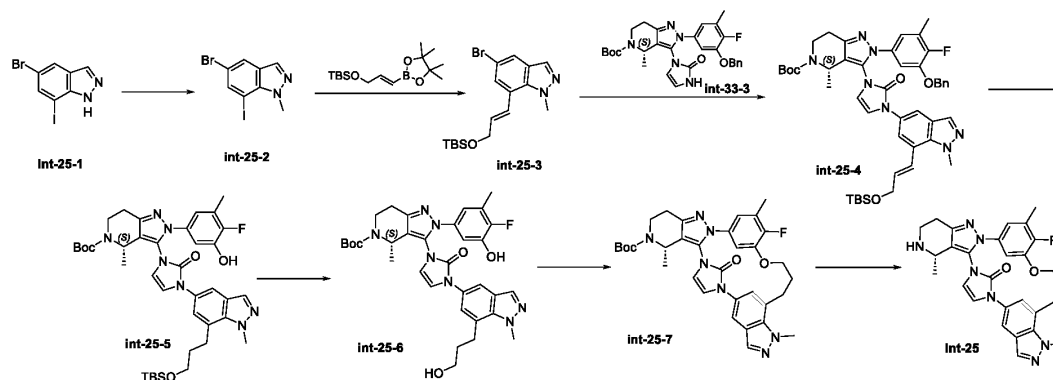
Step 13: int-24-14

To a solution of **int-24-13** (80.0 mg, 0.12 mmol) in anhydrous toluene (2.4 mL) was added 2-(tributylphosphoranylidene)acetonitrile (117.0 mg, 0.49 mmol). The resulting mixture was degassed and purged with N₂ for 2 mins and then stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with water (20 mL $\times$ 2), brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-24-14** (50.0 mg, 0.08 mmol, 64.3% yield). LC-MS (ESI+): m/z 640.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (s, 1H), 7.62 - 7.54 (m, 1H), 7.40 - 7.26 (m, 1H), 7.12 - 6.85 (m, 2H), 6.84 - 6.74 (m, 1H), 6.67 - 6.57 (m, 1H), 5.24 - 5.08 (m, 1H), 4.33 - 4.14 (m, 3H), 4.06 (s, 3H), 3.15 - 3.07 (m, 1H), 2.97 - 2.88 (m, 1H), 2.83 - 2.69 (m, 2H), 2.65 - 2.59 (m, 1H), 2.13 - 2.03 (m, 1H), 1.77 - 1.56 (m, 2H), 1.43 (s, 9H), 1.27 - 1.22 (m, 3H), 1.05 - 0.99 (m, 2H), 0.78 - 0.67 (m, 2H).

Step 14: int-24

A mixture of **int-24-14** (50.0 mg, 0.08 mmol) in HCl solution (4 M in dioxane, 2 mL) was stirred at 20 °C for 1 hr. After completion, the reaction mixture was concentrated to give a residue that was basified by NaHCO₃ (aq) to pH~7 and extracted with DCM (20 mL $\times$ 3). The combined organic layers were washed with water (20 mL $\times$ 2), brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-24** (30.0 mg, 0.06 mmol, 71.1% yield). LC-MS (ESI+): m/z 540.3 (M+H)⁺.

Example v: Synthesis of int-25



Step 1: int-25-2

To a solution of **int-25-1** (2.0 g, 6.19 mmol) in DMF (30 mL) was added NaH (372 mg, 9.29 mmol, 60% purity) at 0 °C. The reaction mixture was stirred at 20 °C for 0.5 hr and then MeI (0.46 mL, 7.43 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 20 °C for 1.5 hr. After completion, the reaction mixture was quenched by cold water (150 mL), and extracted with EtOAc (150 mL × 3). The combined organic layers were washed with water (150 mL × 2), followed by brine (150 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-25-2** (1.00 g, 2.97 mmol, 47.9 % yield). LCMS: 336.7 [M+H]⁺.

Step 2: int-25-3

A mixture of **int-25-2** (870 mg, 2.29 mmol), *(E)*-tert-butyl(dimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) allyl) oxy) silane (886 mg, 2.97 mmol), Pd₂(dba)₃ (210 mg, 0.23 mmol) and potassium carbonate (632 mg, 4.57 mmol) in dioxane (14 mL) and water (2.8 mL) was degassed and purged with N₂ for 3 times and then the mixture was stirred at 100 °C for 2 hrs under N₂ atmosphere. After cooling, the reaction mixture was poured into H₂O (50 mL), and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (90 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-25-3** (810 mg, 1.10 mmol, 99.0% yield). LCMS: 381.1 [M+H]⁺.

Step 3: int-25-4

To a solution of **int-25-3** (1.33 g, 2.09 mmol) in NMP (16 mL) was added **int-33-3** (560.0 mg, 1.05 mmol), copper(I) iodide (200.0 mg, 1.05 mmol), K₂CO₃ (290.0 mg, 2.10 mmol) and (1*R*,2*R*)-*N'*,*N'*-dimethylcyclohexane-1,2-diamine (75.0 mg, 0.52 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 130 °C under N₂ atmosphere for 2 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 (50 mL × 3), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-25-4** (540.0 mg, 0.39 mmol, 74.0% yield). LC-MS(ESI⁺): m/z 834.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ

8.26 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.01 (dt, $J = 16.0, 4.0$ Hz, 1H), 6.64 (dt, $J = 16.0, 4.0$ Hz, 1H), 4.47 – 4.42 (m, 2H), 4.05 (s, 3H), 0.94 (s, 9H), 0.12 (s, 6H).

Step 4: int-25-5

To a solution int-25-4 (510.0 mg, 0.61 mmol) in MeOH (15.0 mL) was added Pd/C (102.0 mg, 20% w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C under H₂ atmosphere (15 psi) for 4 hrs. After completion, the reaction mixture was filtered, concentrated and purified by column chromatography to afford int-25-5 (440.0 mg, 0.41 mmol, 67.5% yield). LC-MS(ESI+): m/z 746.5 [M+H]⁺

Step 5: int-25-6

To a solution of int-25-5 (440.0 mg, 0.59 mmol) in THF (4.5 mL) was added TBAF (3.0 mL, 3.00 mmol). The resulting mixture was stirred at 20 °C for 1 hr. After completion, the reaction mixture was diluted with H₂O (10 mL), and extracted with EtOAc (10 mL × 4). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography to afford int-25-6 (300.0 mg, 0.46 mmol, 78.0% yield). LC-MS(ESI+): m/z 632.3 [M+H]⁺

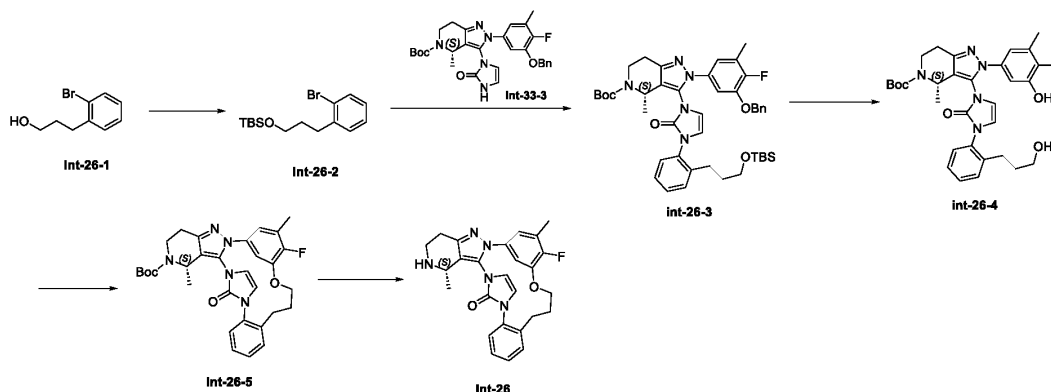
Step 6: int-25-7

To a solution of int-25-6 (300 mg, 0.475 mmol) in Toluene (12.4 mL) was added 2-(tributylphosphoranylidene)acetonitrile (573.0 mg, 2.37 mmol). The resulting mixture was stirred at 90 °C under N₂ for 1 hr. After cooling to room temperature, the reaction mixture was poured into H₂O (30 mL), and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford int-25-7 (50.0 mg, 81.5 μmol, 17.7 % yield). LC-MS(ESI+): m/z 614.4 [M+H]⁺

Step 7: int-25

A mixture of int-25-7 (45 mg, 0.073 mmol) in HCl solution (4 M in dioxane, 2 mL) was stirred at 20 °C for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure to afford int-25 (41.0 mg, crude), which was used directly in the next step without purification. LC-MS(ESI+): m/z 514.2 [M+H]⁺

Example w: Synthesis of int-26



Step 1: int-26-2

To a solution of **int-26-1** (3.00 g, 13.95 mmol) in DCM (30 mL) was added imidazole (1.42 g, 20.92 mmol) and TBS-Cl (2.52 g, 16.74 mmol). The resulting mixture was stirred at 25 °C for 1 hr. After completion, the reaction mixture was diluted with DCM (30 mL) and washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-26-2** (3.20 g, 9.72 mmol, 69.7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53 (dt, *J* = 7.9, 0.8 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.10 (dt, *J* = 8.0, 4.5 Hz, 1H), 3.59 (t, *J* = 6.2 Hz, 2H), 2.75 – 2.65 (m, 2H), 1.77 – 1.64 (m, 2H), 0.84 (s, 10H), -0.00 (s, 6H).

Step 2: int-26-3

To a solution of **int-33-3** (500.0 mg, 0.94 mmol) in NMP (5 mL) was added **int-26-2** (926.0 mg, 2.81 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (67.0 mg, 0.47 mmol), copper(I) iodide (178.0 mg, 0.94 mmol) and K₂CO₃ (259.0 mg, 1.87 mmol). The resulting mixture was degassed and purged with N₂ for three times, and stirred at 150 °C under N₂ atmosphere for 3 hrs. After cooling to room temperature, the residue was poured into H₂O (25 mL) and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with water (25 mL × 3), followed by brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-26-3** (300.0 mg, 0.38 mmol, 40.9% yield). LC-MS(ESI+): *m/z* 782.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 – 7.41 (m, 4H), 7.40 – 7.37 (m, 2H), 7.367 – 7.30 (m, 2H), 7.19 – 7.13 (m, 2H), 7.00 – 6.93 (m, 2H), 6.92 – 6.88 (m, 1H), 5.22 – 5.11 (m, 1H), 5.09 (s, 2H), 4.39 – 4.10 (m, 1H), 3.46 (t, *J* = 8.0 Hz, 2H), 3.38 – 3.36 (m, 1H), 3.22 – 3.08 (m, 1H), 2.80 – 2.60 (m, 2H), 2.27 (s, 3H), 1.67 – 1.54 (m, 2H), 1.46 (s, 9H), 1.26 – 1.21 (m, 3H), 0.85 (s, 9H), 0.00 (s, 6H).

Step 3: int-26-4

To a solution of **int-26-3** (280.0 mg, 0.36 mmol) in MeOH (10 mL) was added Pd/C (60 mg, 20% w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 40 °C under H₂ atmosphere (15 psi) for 2 hrs. After completion, the reaction mixture was filtered through a celite pad and rinsed with MeOH (5 mL × 2). The filtrate was concentrated and purified by prep-TLC to

afford **int-26-4** (100.0 mg, 0.17 mmol, 48.4% yield). LC-MS(ESI+): m/z 578.4 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.18 (brs, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 6.92 – 6.82 (m, 2H), 6.73 – 6.67 (m, 1H), 5.23 – 5.06 (m, 1H), 4.62 – 4.15 (m, 2H), 3.48 – 3.42 (m, 1H), 3.41 – 3.39 (m, 1H), 3.17 – 3.03 (m, 1H), 2.77 – 2.63 (m, 2H), 2.23 (s, 3H), 1.66 – 1.54 (m, 3H), 1.46 (s, 9H), 1.21 (d, J = 8.0 Hz, 3H).

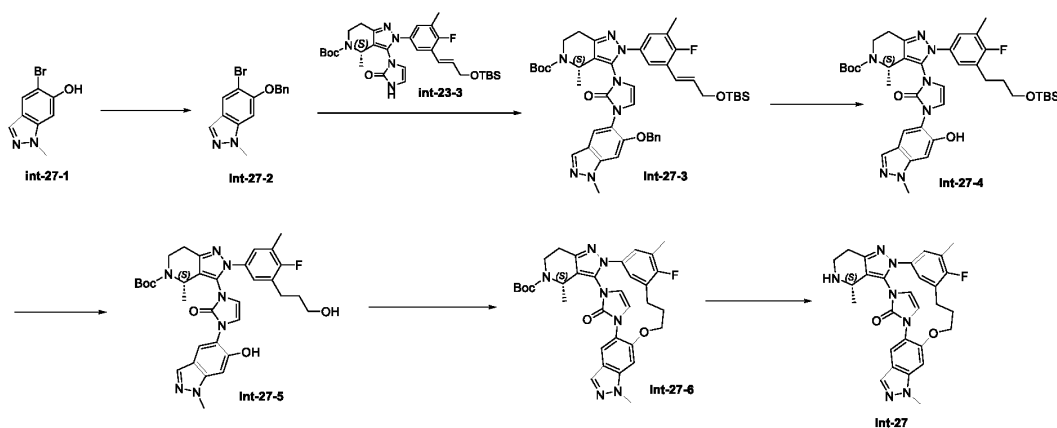
Step 4: int-26-5

To a solution of **int-26-4** (90.0 mg, 0.16 mmol) in anhydrous toluene (3.6 mL) were added 2-(tributylphosphoranylidene)acetonitrile (0.12 mL, 0.47 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 1 hr. After cooling to room temperature, the reaction mixture was poured into 10 mL of water and extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered, concentrated and purified by prep-TLC (SiO_2 , DCM: MeOH=20:1, v/v) to afford **int-26-5** (50.0 mg, 0.089 mmol, 57.3% yield). LC-MS(ESI+): m/z 560.4 $[M+H]^+$. 1H NMR (400 MHz,) δ 7.50 – 7.37 (m, 3H), 7.36 – 7.10 (m, 3H), 7.05 – 6.94 (m, 1H), 6.70 – 6.51 (m, 1H), 5.36 – 4.99 (m, 1H), 4.45 – 4.04 (m, 3H), 3.49 – 3.44 (m, 1H), 3.21 – 2.84 (m, 2H), 2.77 – 2.63 (m, 2H), 2.31 – 2.26 (m, 3H), 1.67 – 1.54 (m, 2H), 1.46 (s, 9H), 1.26 (d, J = 8.0 Hz, 3H).

Step 5: int-26

A mixture of **int-26-5** (50 mg, 0.089 mmol) in HCl solution (4M in dioxane, 0.5 mL) was stirred at 25 °C for 1 hr. After completion, the reaction mixture was concentrated to give a residue, which was diluted with DCM (10 mL) and washed with saturated $NaHCO_3$ solution (10 mL), followed by brine (10 mL), dried over Na_2SO_4 , filtered, concentrated and purified by prep-TLC to afford **int-26** (30.0 mg, 0.065 mmol, 73.1% yield). LC-MS(ESI+): m/z 460.4 $[M+H]^+$

Example x: Synthesis of int-27



Step 1: int-27-2

To a solution of **int-27-1** (1.08 g, 4.76 mmol) in DMF (10 mL) was added benzyl bromide (0.60 mL, 5.00 mmol) and K₂CO₃ (0.99 g, 7.13 mmol). The resulting mixture was stirred at 25 °C for 2 hrs. After completion, the reaction mixture was poured into water (50 mL), 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-27-2** (1.50 g, 4.73 mmol, 99.0% yield). LC-MS(ESI+): m/z 317.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (s, 1H), 7.92 (s, 1H), 7.59 – 7.53 (m, 2H), 7.48 – 7.40 (m, 3H), 7.39 – 7.34 (m, 1H), 5.29 (s, 2H), 4.01 (s, 3H).

Step 2: int-27-3

To a solution of **int-23-3** (450.0 mg, 0.75 mmol) in NMP (5 mL) were added **int-27-2** (478.0 mg, 1.51 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (54.0 mg, 0.38 mmol), copper(I) iodide (143.0 mg, 0.75 mmol) and potassium carbonate (208.0 mg, 1.51 mmol). The resulting mixture was degassed and purged with N₂ for 3 times, and stirred at 140 °C for 3 hrs under N₂ atmosphere. After cooling to room temperature, the reaction was filtered through a Celite pad and rinsed with EtOAc (10 mL × 3). The filtrate was washed with water (50 mL × 3), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-27-3** (1.10 g, 1.32 mmol, 73.0% yield). LC-MS(ESI+): m/z 834.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (s, 1H), 7.61 – 7.48 (m, 4H), 7.39 (s, 1H), 7.38 – 7.35 (m, 1H), 7.34 – 7.32 (m, 1H), 7.27 – 7.24 (m, 2H), 7.20 – 7.13 (m, 1H), 6.86 – 6.83 (m, 1H), 6.65 (dt, *J* = 16.0, 4.0 Hz, 1H), 6.31 (dt, *J* = 16.0, 4.0 Hz, 1H), 5.18 (s, 2H), 5.15 – 4.99 (m, 1H), 4.32 – 4.11 (m, 3H), 3.99 (s, 3H), 3.15 – 2.98 (m, 1H), 2.74 – 2.67 (m, 1H), 2.65 – 2.56 (m, 1H), 2.14 (s, 3H), 1.40 (s, 9H), 1.08 (d, *J* = 4.0 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

Step 3: int-27-4

To a solution of **int-27-3** (700.0 mg, 0.84 mmol) in MeOH (14 mL) was added Pd/C (140.0 mg, 20% w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 50 °C for 4 hrs under H₂ atmosphere. After completion, the reaction was filtered through a Celite pad and rinsed with MeOH (10 mL × 3). The filtrate was concentrated to afford **int-27-4** (720.0 mg, crude), which was used directly for the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (brs, 1H), 7.92 (s, 1H), 7.65 – 7.63 (m, 1H), 7.21 – 7.12 (m, 2H), 6.98 (s, 1H), 6.83 (d, *J* = 4.0 Hz, 1H), 6.80 – 6.68 (m, 1H), 5.23 – 5.06 (m, 1H), 4.41 – 4.15 (m, 1H), 3.94 (s, 3H), 3.60 (t, *J* = 8.0 Hz, 2H), 3.21 – 3.08 (m, 1H), 2.74 – 2.64 (m, 4H), 2.26 (s, 3H), 1.79 – 1.65 (m, 2H), 1.45 (s, 9H), 1.24 (d, *J* = 8.0 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H).

Step 4: int-27-5

To a solution of **int-27-4** (700.0 mg, 0.94 mmol) in THF (5 mL) was added TBAF (4.7 ml, 4.70 mmol). The resulting mixture was stirred at 25 °C for 2 hrs. After completion, the reaction was poured

into water (10 mL), extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-27-5** (350.0 mg, 0.55 mmol, 59.0% yield). LC-MS(ESI⁺): m/z 632.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.34 (s, 1H), 7.95 (s, 1H), 7.65 (s, 1H), 7.26 – 7.12 (m, 2H), 6.98 (s, 1H), 6.85 (d, $J = 4.0$ Hz, 1H), 6.78 (brs, 1H), 5.24 – 5.03 (m, 1H), 4.69 – 4.53 (m, 1H), 4.25 (s, 1H), 3.95 (s, 3H), 3.46 – 3.42 (m, 2H), 3.25 – 3.02 (m, 1H), 2.76 – 2.64 (m, 4H), 2.27 (s, 3H), 1.76 – 1.65 (m, 2H), 1.46 (s, 9H), 1.24 (d, $J = 8.0$ Hz, 3H).

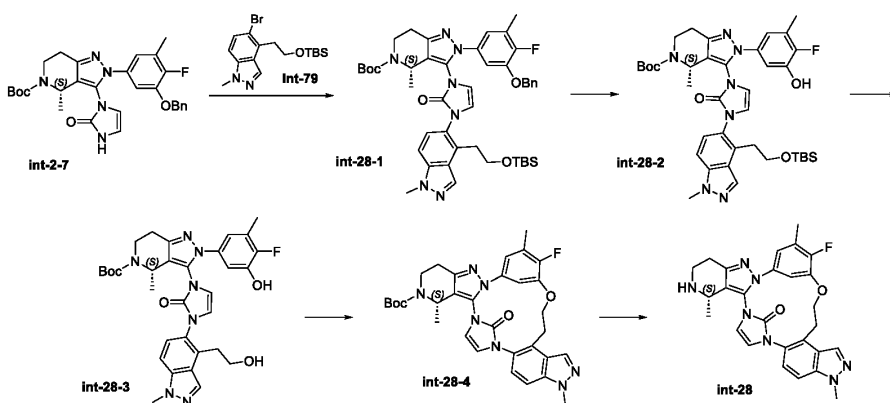
Step 5: int-27-6

To a solution of **int-27-5** (330.0 mg, 0.52 mmol) in anhydrous toluene (3.5 mL) was added 2-(tributylphosphoranylidene)acetonitrile (504.0 mg, 2.09 mmol). The resulting mixture was stirred at 90 °C for 2 hrs. After cooling to room temperature, the reaction was diluted with EtOAc (10 mL), washed with brine (10 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-27-6** (170.0 mg, 0.28 mmol, 53.0% yield). LC-MS(ESI⁺): m/z 614.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.99 (s, 1H), 7.83 (s, 1H), 7.43 – 7.30 (m, 2H), 7.17 – 6.91 (m, 1H), 6.81 – 6.51 (m, 2H), 5.28 – 5.01 (m, 1H), 4.34 – 4.00 (m, 6H), 3.24 – 3.03 (m, 1H), 2.94 – 2.82 (m, 1H), 2.77 – 2.62 (m, 3H), 2.28 (s, 3H), 2.26 – 2.18 (m, 1H), 2.05 – 1.84 (m, 1H), 1.45 (s, 9H), 1.30 – 1.21 (m, 3H).

Step 6: int-27

A mixture of **int-27-6** (150.0 mg, 0.24 mmol) in HCl solution (4 mL, 4 M in dioxane) 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 NaHCO_3 solution (10 mL), followed by brine (10 mL), dried over Na_2SO_4 , filtered, concentrated and purified by prep-TLC to afford **int-27** (80.0 mg, 0.16 mmol, 63.7% yield). LC-MS(ESI⁺): m/z 514.4 $[\text{M}+\text{H}]^+$.

Example y: Synthesis of int-28, int-79



Step 1: int-28-1

To a solution of **int-2-7** (200.0 mg, 0.38 mmol) in NMP (3.0 mL) was added **int-79** (277.0 mg, 0.75 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (48.0 mg, 0.37 mmol), copper(I) iodide (143.0 mg, 0.75 mmol) and K₂CO₃ (155.0 mg, 1.12 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 140 °C for 4 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into cold water (20 mL), extracted by 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-28-1** (370.0 mg, 0.45 mmol, 80.0 % yield). LC-MS(ESI⁺): m/z 822.4 [M+H]⁺

Step 2: int-28-2

To a solution of **int-28-1** (360.0 mg, 0.44 mmol) in MeOH (5.0 mL) and THF (5.0 mL) was added Pd/C (72.0 mg, 20% w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 40 °C for 2 hrs under H₂ (15 psi) atmosphere. After completion, the reaction was filtered through a pad of Celite and rinsed with MeOH (10 mL × 3). The filtrate was concentrated to afford **int-28-2** (240.0 mg, crude). LC-MS(ESI⁺): m/z 732.4 [M+H]⁺

Step 3: int-28-3

To a solution of **int-28-2** (220.0 mg, 0.30 mmol) in THF (2.0 mL) was added tetrabutylammonium fluoride (1.5 mL, 1.50 mmol). The resulting mixture was stirred at 25 °C for 2 hrs. After completion, the reaction mixture was poured into water (10 mL), extracted with DCM (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-28-3** (100.0 mg, 0.16 mmol, 53.9% yield). LC-MS(ESI⁺): m/z 618.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.20 (s, 1H), 8.20 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 4.0 Hz, 1H), 6.89 – 6.77 (m, 2H), 6.74 – 6.67 (m, 1H), 5.15 (brs, 1H), 4.70 (brs, 1H), 4.34 – 4.17 (m, 1H), 4.06 (s, 3H), 3.80 – 3.57 (m, 3H), 3.21 – 3.06 (m, 1H), 2.96 – 2.87 (m, 2H), 2.72 – 2.66 (m, 1H), 2.23 (s, 3H), 1.44 (s, 9H), 1.23 – 1.19 (m, 3H).

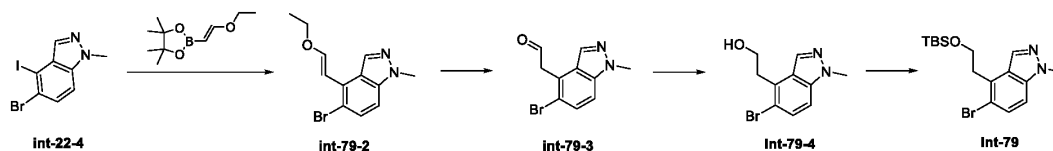
Step 4: int-28-4

To a solution of **int-28-3** (40.0 mg, 0.065 mmol) in anhydrous toluene (2.0 mL) was added 2-(tributylphosphoranylidene)acetonitrile (24.0 mg, 0.10 mmol). The resulting mixture was purged with N₂ for 3 mins and stirred at 120 °C for 2 hrs. After cooling to room temperature, the reaction mixture was poured into water (10 mL), extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by Prep-TLC to afford **int-28-4** (20.0 mg, 0.03 mmol, 51.5% yield). LC-MS(ESI⁺): m/z 600.4 [M+H]⁺

Step 5: int-28

A mixture of **int-28-4** (20.0 mg, 0.03 mmol) in HCl solution (1 mL, 4 M in dioxane) was stirred at 25 °C for 2 hrs. After completion, the reaction mixture was concentrated and diluted with DCM (10

mL). The organic layer was washed with saturated NaHCO_3 solution (10 mL), followed by brine (10 mL), dried over Na_2SO_4 , filtered and concentrated to afford **int-28** (20.0 mg, crude), which was used directly for the next step without purification. LC-MS(ESI^+): m/z 500.4 $[\text{M}+\text{H}]^+$



Step 1: int-79-2

To a solution of **int-22-4** (4.00 g, 11.87 mmol) in 1,4-dioxane (67 mL) and water (13 mL) were added (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.00 g, 20.18 mmol), $\text{Pd}_2(\text{dba})_3$ (1.09 g, 1.19 mmol) and potassium carbonate (3.28 g, 23.74 mmol). The resulting mixture was degassed and purged with N_2 for 2 mins and then stirred at 100 °C under N_2 for 2 hrs. After cooling to room temperature, the reaction mixture was concentrated and purified by column chromatography to afford **int-79-2** (2.30 g, 8.18 mmol, 68.9% yield). LC-MS (ESI^+): m/z 281.0 $(\text{M}+\text{H})^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.25 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 12.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 6.15 (d, $J = 12.0$ Hz, 1H), 4.05 (q, $J = 8.0$ Hz, 2H), 4.02 (s, 3H), 1.31 (t, $J = 8.0$ Hz, 3H).

Step 2: int-79-3

To a solution of **int-79-2** (2.30 g, 8.18 mmol) in DCM (50 mL) was added TFA (10 mL, 130.00 mmol) at 0 °C. The reaction was stirred at 20 °C for 2 hrs. After completion, the reaction mixture was quenched by H_2O (100 mL), basified with NaHCO_3 (aq) to pH~7, and extracted with DCM (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-79-3** (1.50 g, 5.93 mmol, 72.4% yield). LC-MS (ESI^+): m/z 253.0 $(\text{M}+\text{H})^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.74 (s, 1H), 8.16 (s, 1H), 7.57 (s, 2H), 4.26 (s, 2H), 4.05 (s, 3H).

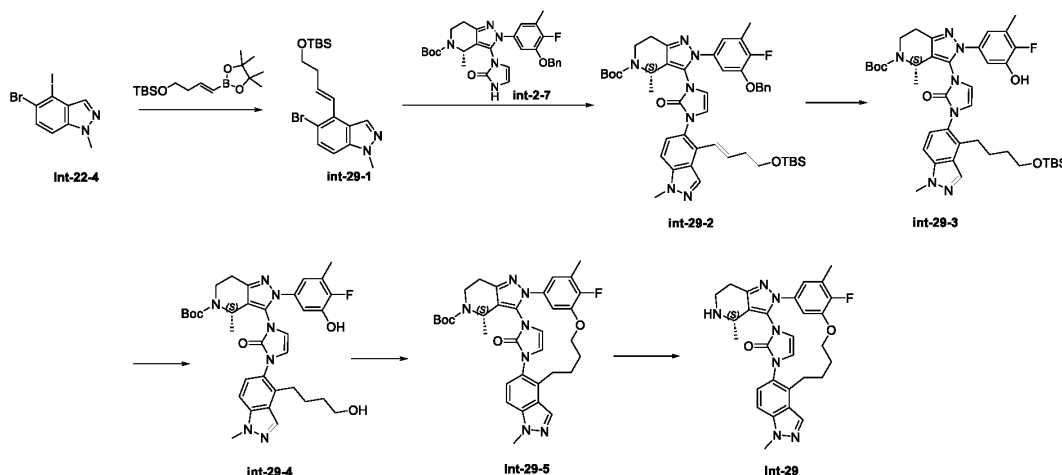
Step 3: int-79-4

To a solution of **int-79-3** (1.50 g, 5.93 mmol) in MeOH (45 mL) was added NaBH_4 (448.0 mg, 11.85 mmol) in portions at 0 °C. The resulting mixture was stirred at 20 °C for 0.5 hr. After completion, the reaction mixture was poured into water (100 mL), extracted with DCM (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-79-4** (1.20 g, 4.70 mmol, 79.0% yield). LC-MS (ESI^+): m/z 255.0 $(\text{M}+\text{H})^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.12 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 4.79 (t, $J = 8.0$ Hz, 1H), 4.02 (s, 3H), 3.69 – 3.61 (m, 2H), 3.17 (t, $J = 8.0$ Hz, 2H).

Step 4: int-79

To a solution of **int-79-4** (1.20 g, 4.70 mmol) in DCM (24 mL) were added 1*H*-imidazole (640.0 mg, 9.41 mmol) and *tert*-butylchlorodimethylsilane (1.42 g, 9.41 mmol). The resulting mixture was stirred at 20 °C for 1 hr. After completion, the reaction mixture was poured into water (100 mL) and extracted with DCM (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-79** (1.60 g, 4.33 mmol, 92.0% yield). LC-MS (ESI⁺): *m/z* 369.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 4.01 (s, 3H), 3.85 (t, *J* = 8.0 Hz, 2H), 3.20 (t, *J* = 8.0 Hz, 2H), 0.74 (s, 9H), 0.15 (s, 6H).

Example z: Synthesis of int-29



Step 1: int-29-1

A mixture of **int-22-4** (500 mg, 1.48 mmol), (*E*)-*tert*-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)silane (695 mg, 2.23 mmol), Pd(Ph₃P)₄ (171 mg, 0.15 mmol) and K₂CO₃ (410 mg, 2.97 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was degassed and purged with N₂ for 3 times, the mixture was stirred at 100 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the reaction mixture was poured into 10 mL of water and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-29-1** (450 mg, 1.14 mmol, 77.0% yield). LC-MS(ESI⁺): *m/z* 395.3 [M+H]⁺.

Step 2: int-29-2

To a solution of **int-2-7** (200 mg, 0.38 mmol) in NMP (1 mL) were added **int-29-1** (267 mg, 0.68 mmol), (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (22 mg, 0.19 mmol), copper(I) iodide (36 mg, 0.19 mmol) and K₂CO₃ (155 mg, 1.12 mmol). The resulting mixture was stirred at 130 °C for 3 hrs. After cooling to room temperature, the reaction mixture was poured into H₂O (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 2), followed by brine (10 mL),

dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-29-2** (300 mg, 0.35 mmol, 94.0% yield). LC-MS(ESI⁺): m/z 848.5 [M+H]⁺.

Step 3: int-29-3

To a solution of **int-29-2** (250 mg, 0.30 mmol) in MeOH (10 mL) was added Pd/C (25 mg, 50% purity, 10% w/w). The reaction mixture was degassed and purged with H₂ for 3 times, and then stirred at 40 °C for 8 hrs. The reaction mixture was filtered, after rinsing the cake with MeOH (5 mL × 3), the filtrate was concentrated to afford **int-29-3** (210 mg, 0.276 mmol, 94 % yield). LC-MS(ESI⁺): m/z 760.5 [M+H]⁺.

Step 4: int-29-4

To a solution of **int-29-3** (210 mg, 0.28 mmol) in THF (2.0 mL) was added TBAF (1.4 mL, 1 M in THF) at 0 °C. The resulting mixture was stirred at 25 °C for 1 h. The residue was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-29-4** (43 mg, 0.067 mmol, 24.1% yield). LC-MS (ESI⁺): m/z 646.4 [M+H]⁺.

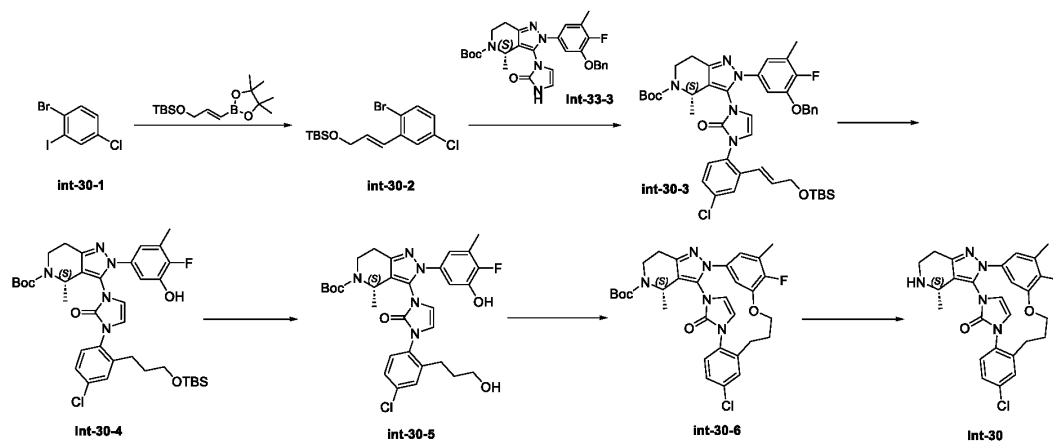
Step 5: int-29-5

To a solution of **int-29-4** (43 mg, 0.067 mmol) in anhydrous toluene (1.72 mL) was added CMBP (0.06 mL, 0.24 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 90 °C for 2 h under N₂. After cooling to room temperature, the reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-29-5** (30 mg, 0.048 mmol, 71.8% yield). LC-MS(ESI⁺): m/z 628.3 [M+H]⁺. ¹H NMR (400 MHz,) δ 8.31 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 5.16 (s, 1H), 4.12 (s, 2H), 4.10 (d, *J* = 4.0 Hz, 3H), 2.75 (s, 2H), 2.69 (s, 2H), 2.31 (s, 3H), 2.02 (q, *J* = 8.0 Hz, 2H), 1.64 (s, 2H), 1.57 (s, 3H), 1.46 (s, 9H).

Step 6: int-29

A mixture of **int-29-5** (30.0 mg, 0.048 mmol) in HCl solution (0.5 mL, 4 M in dioxane) was stirred at 20 °C for 1 h. The mixture was concentrated and diluted with DCM (10 mL). The process was repeated for 3 times to afford **int-29** (20 mg, 0.038 mmol, 79.0% yield). LC-MS(ESI⁺): m/z 528.4 [M+H]⁺.

Example aa: Synthesis of int-30



Step 1: int-30-2

To a solution of **int-30-1** (2.00 g, 6.30 mmol) and $(E)\text{-tert-butyl(dimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane)}$ (2.44 g, 8.19 mmol) in dioxane (20.0 mL) and water (4.0 mL) were added tris(dibenzylideneacetone)dipalladium(0) (0.58 g, 0.63 mmol) and K_2CO_3 (1.74 g, 12.60 mmol). The resulting mixture degassed and purged with nitrogen three times and stirred at 100 °C for 2 hrs under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was poured into water (50 mL), extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with water (100 mL), followed by brine (100 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-30-2** (1.69 g, 4.44 mmol, 70.4% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.75 (d, J = 4.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.27 (dd, J = 8.0, 4.0 Hz, 1H), 6.85 (dt, J = 16.0, 4.0 Hz, 1H), 6.57 (dt, J = 16.0, 4.0 Hz, 1H), 4.40 – 4.35 (m, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

Step 2: int-30-3

To a solution of **int-30-2** (1.26 g, 3.49 mmol) and **int-33-3** (930.0 mg, 1.74 mmol) in NMP (10 mL) were added $(1R,2R)\text{-}N^1,N^2\text{-dimethylcyclohexane-1,2-diamine}$ (248.0 mg, 1.74 mmol) and copper(I) iodide (664.0 mg, 3.49 mmol) and K_2CO_3 (723.0 mg, 5.23 mmol). The resulting mixture was degassed and purged with N_2 for three times and stirred at 140 °C for 6 hr under N_2 atmosphere. After cooling to room temperature, the mixture was poured into water (50 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 Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-30-3** (700.0 mg, 0.82 mmol, 46.8% yield). LC-MS (ESI+): m/z 814.4 ($\text{M}+\text{H}$) $^+$.

Step 3: int-30-4

To a solution of **int-30-3** (1.02 g, 1.25 mmol) in THF (50.0 mL) and MeOH (50.0 mL) was added platinum(IV) oxide (102.0 mg, 10% w/w.). The resulting mixture was degassed and purged with H_2 for 3 times stirred under H_2 (15 Psi) at 25 °C for 16 hrs. After completion, the reaction mixture was filtered

through a Celite pad and rinsed with MeOH (5 mL $\times$ 3). The filtrate was concentrated and purified by column to afford **int-30-4** (800.0 mg, 1.05 mmol, 84.0% yield). LC-MS (ESI+): m/z 726.4 (M+H)⁺.

Step 4: int-30-5

To a solution of **int-30-4** (807.0 mg, 1.11 mmol) in THF (8 mL) was added TBAF (2.91 g, 11.11 mmol) in portions. The resulting mixture was stirred at 25 °C for 4 hrs. After completion, the reaction mixture was poured into water (50 mL), 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 Na₂SO₄, filtered and concentrated under reduced pressure to afford **int-30-5** (430.0 mg, crude), which was used directly in the next step without purification. LC-MS (ESI+): m/z 612.3 (M+H)⁺.

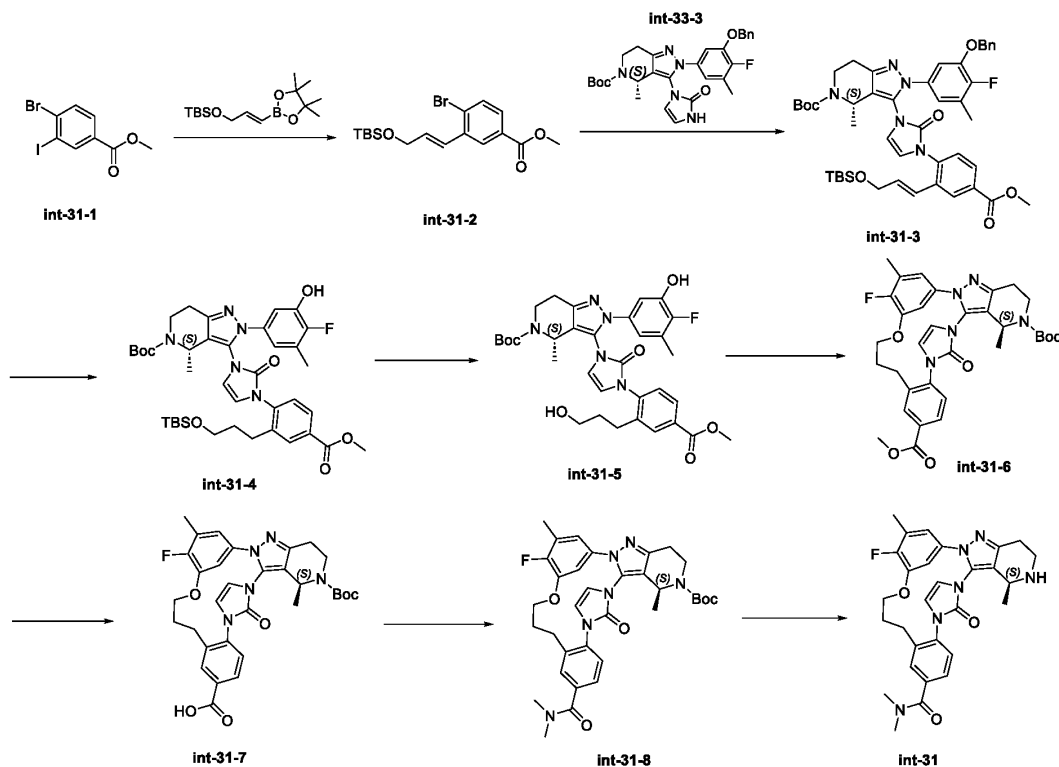
Step 5: int-30-6

To a solution of **int-30-5** (400.0 mg, 0.65 mmol) in anhydrous toluene (1.2 mL) was added 2-(tributylphosphoranylidene)acetonitrile (945.0 mg, 3.92 mmol). The mixture was purged with N₂ for 3 mins and stirred at 90 °C for 1 hr under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL), followed by brine (10 mL), dried over Na₂SO₄, filtered and concentrated and purified by column chromatography to afford **int-30-6** (170.0 mg, 0.26 mmol, 39.4% yield). LC-MS (ESI+): m/z 594.2 (M+H)⁺.

Step 6: int-30

A mixture of **int-30-6** (170.0 mg, 0.29 mmol) in HCl solution (4 M in Dioxane, 3 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 (20 mL), washed with saturated NaHCO₃ (20 mL), followed by brine (20 mL). The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-30** (70.0 mg, 0.14 mmol, 47.0% yield). LC-MS (ESI+): m/z 494.1 (M+H)⁺.

Example ab: Synthesis of int-31



Step 1: int-31-2

To a solution of **int-31-1** (3.10 g, 9.09 mmol) and (*E*)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (2.85 g, 9.55 mmol) in THF (75 mL) and water (7.5 mL) were added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.74 g, 0.91 mmol) and K_2CO_3 (2.51 g, 18.18 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 60 °C under N_2 for 16 hrs. After cooling to room temperature, the mixture was concentrated and purified by column chromatography to afford **int-31-2** (1.98 g, 5.14 mmol, 56.5% yield). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.01 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 8.0, 4.0 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 6.39 (dt, J = 16.0, 4.0 Hz, 1H), 4.37 – 4.21 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

Step 2: int-31-3

To a solution of **int-33-3** (2.00 g, 3.75 mmol) and **int-31-2** (1.98 g, 5.14 mmol) in NMP (20 mL) were added copper(I) iodide (0.71 g, 3.75 mmol), K_2CO_3 (1.04 g, 7.50 mmol) and (1*R*,2*R*)- N^1,N^2 -dimethylcyclohexane-1,2-diamine (0.27 g, 1.87 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 140 °C under N_2 for 3 hrs. After cooling to room temperature, the reaction mixture was poured into 100 mL of water 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-31-3** (1.80 g, 2.15 mmol, 57.3% yield). LC-MS (ESI⁺): m/z 838.4 (M+H)⁺.

Step 3: int-31-4

To a solution of **int-31-3** (1.30 g, 1.55 mmol) in MeOH (30 mL) was added Pd/C (300.0 mg, 20%w/w.). The resulting mixture was degassed and purged with H₂ for three times and stirred at 25 °C for 16 hrs under H₂ (15 psi). After completion, the reaction mixture was filtered through a celite pad and resined with MeOH (5 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-31-4** (1.60 g, crude), which was used directly in the next step without purification. LC-MS (ESI⁺): m/z 750.4 (M+H)⁺.

Step 4: int-31-5

To a solution of **int-31-4** (1.60 g, 2.13 mmol) in THF (10 mL) were added TBAF (5 mL, 1 M in THF). The resulting mixture was stirred at 25 °C for 3 hrs. After completion, the reaction mixture was poured into water (150 mL). and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-31-5** (950.0 mg, 1.49 mmol, 70.0% yield). LC-MS (ESI⁺): m/z 636.4 (M+H)⁺.

Step 5: int-31-6

To a solution of **int-31-5** (140.0 mg, 0.22 mmol) in anhydrous toluene (5 mL) was added 2-(tributyl-15-phosphaneylidene)acetonitrile (159.0 mg, 0.66 mmol). The resulting mixture was stirred at 90 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-31-6** (30.0 mg, 0.05 mmol, 22.1% yield). LC-MS (ESI⁺): m/z 618.2 (M+H)⁺.

Step 6: int-31-7

To a solution of **int-31-6** (30.0 mg, 0.05 mmol) in THF (0.3 mL) and water (0.3 mL) was added LiOH (6.0 mg, 0.25 mmol). The resulting mixture was stirred at 25 °C for 2 hrs. After completion, the reaction mixture was acidified by HCl (aq., 1 M) to pH~1 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 and concentrated under reduced pressure to afford **int-31-7** (29.0 mg, crude). LC-MS (ESI⁺): m/z 604.2 (M+H)⁺.

Step 6: int-31-8

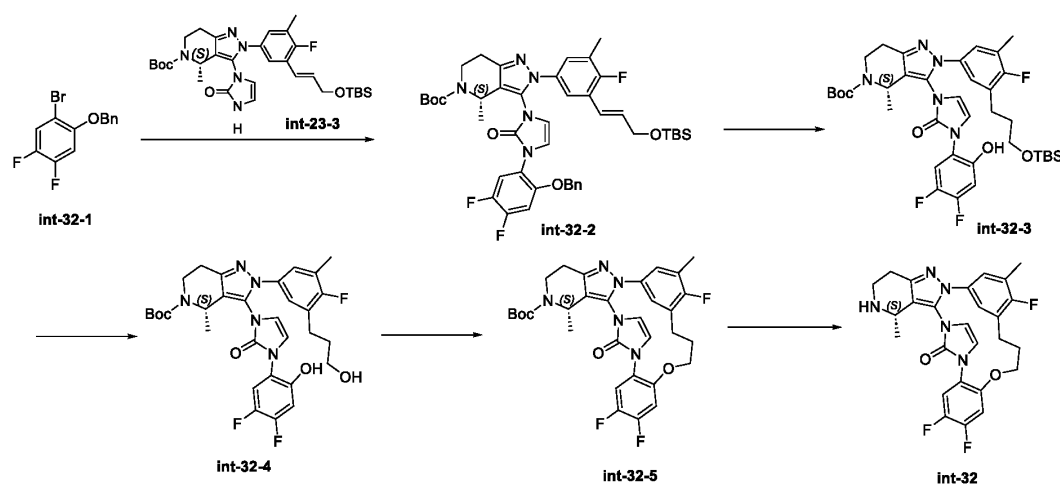
To a solution of **int-31-7** (400.0 mg, 0.66 mmol) in DMF (4 mL) were added dimethylamine hydrogen chloride (107.0 mg, 1.33 mmol), DIEA (0.4 mL, 2.00 mmol) and HATU (378.0 mg, 1.00 mmol). The resulting mixture was stirred at 25 °C for 16 hrs. After completion, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with

water (30 mL $\times$ 2), followed by brine (30 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-31-8** (311.0 mg, 0.49 mmol, 74.0% yield). LC-MS (ESI+): m/z 631.2 ($\text{M}+\text{H}$)⁺. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.47 (s, 1H), 7.43 – 7.33 (m, 2H), 7.23 – 7.16 (m, 1H), 7.09 – 7.02 (m, 1H), 6.99 – 6.70 (m, 1H), 6.69 – 52 (m, 1H), 5.54 – 5.04 (m, 1H), 4.33 – 4.17 (m, 3H), 3.20 – 3.08 (m, 1H), 3.06 – 2.92 (m, 6H), 2.77 – 2.63 (m, 4H), 2.32 – 2.26 (m, 3H), 1.68 – 1.57 (m, 2H), 1.49 – 1.44 (m, 9H), 1.29 – 1.24 (m, 3H).

Step 7: int-31

A solution of **int-31-8** (320.0 mg, 0.51 mmol) in HCl solution (2mL, 4 M in dioxane) was stirred at 25 °C for 0.5 hr. After completion, the reaction was concentrated under reduced pressure to give a residue, which was diluted with DCM (30 mL) and washed with saturated NaHCO_3 (aq., 50 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-31** (140.0 mg, 0.26 mmol, 52.0% yield). LC-MS (ESI+): m/z 531.5 ($\text{M}+\text{H}$)⁺.

Example ac: Synthesis of int-32



Step 1: int-32-2

To a solution of **int-23-3** (450.0 mg, 0.75 mmol) in NMP (4.5 mL) were added **int-32-1** (450.0 mg, 1.51 mmol), copper(I) iodide (143.0 mg, 0.75 mmol), (1*R*,2*R*)- N^1,N^2 -dimethylcyclohexane-1,2-diamine (107.0 mg, 0.75 mmol) and K_2CO_3 (312.0 mg, 2.26 mmol). After addition, the resulting mixture was degassed and purged with N_2 for 2 mins and then stirred at 130 °C for 1 hr under N_2 . After cooling to room temperature, the mixture was poured into water (50 mL) and 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 Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-32-2** (500.0 mg, 0.61 mmol, 81.0% yield). LC-MS(ESI+): m/z 816.4 [$\text{M}+\text{H}$]⁺

Step 2: int-32-3

To a solution of **int-32-2** (450.0 mg, 0.55 mmol) in MeOH (15 mL) was added Pd/C (50.0 mg, 10% w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 20 °C for 4 hrs under H₂ (15 psi). After completion, the mixture was filtered through a celite pad and rinsed with MeOH (5 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-32-3** (220.0 mg, 0.30 mmol, 54.8% yield). LC-MS(ESI+): m/z 728.4 [M+H]⁺

Step 3: int-32-4

To a solution of **int-32-3** (200.0 mg, 0.28 mmol) in THF (2 mL) was added TBAF (1.4 mL, 1 M in THF). The resulting mixture was stirred at 30 °C for 0.5 hr. After completion, the mixture was poured into 10 mL of water and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-32-4** (120.0 mg, 0.20 mmol, 71.2% yield). LC-MS(ESI+): m/z 614.3 [M+H]⁺

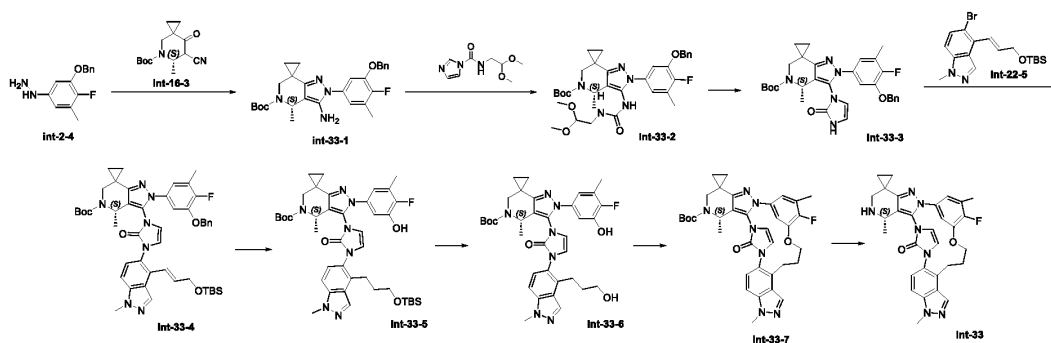
Step 4: int-32-5

To a solution of **int-32-4** (100.0 mg, 0.16 mmol) in anhydrous toluene (2.0 mL) was added 2-(tributylphosphoranylidene)acetonitrile (236.0 mg, 0.98 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 90 °C for 2 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 brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC (SiO₂, DCM: MeOH=15:1, v/v) to afford **int-32-5** (80.0 mg, 0.13 mmol, 82.0% yield). LC-MS(ESI+): m/z 596.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 – 7.70 (m, 1H), 7.49 – 7.42 (m, 1H), 7.37 – 7.32 (m, 1H), 7.05 – 6.98 (m, 1H), 6.80 – 6.76 (m, 1H), 6.75 – 6.61 (m, 1H), 6.78 (d, *J* = 4.0 Hz, 1H), 5.17 – 5.07 (m, 1H), 4.38 – 4.23 (m, 1H), 4.02 – 3.92 (m, 2H), 3.16 – 3.08 (m, 1H), 2.78 – 2.65 (m, 4H), 2.26 (s, 3H), 2.18 – 2.10 (m, 2H), 1.95 – 1.87 (m, 1H), 1.44 (s, 9H), 1.25 – 1.23 (m, 3H).

Step 5: int-32

A mixture of **int-32-5** (60.0 mg, 0.10 mmol) in HCl (1 mL, 4 M in dioxane) was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure to afford **int-32** (50.0 mg, crude), which was used directly in the next step without purification. LC-MS(ESI+): m/z 496.2 [M+H]⁺

Example ad: Synthesis of int-33



Step 1: int-33-1

To a solution of **int-16-3** (5.00 g, 18.92 mmol) and **int-2-4** (5.59 g, 22.70 mmol) in EtOH (50 mL) was added pyridine (3.06 mL, 37.8 mmol). The resulting mixture was stirred at 90 °C for 2 hrs. After cooling to room temperature, the mixture was concentrated and purified by column chromatography to afford **int-33-1** (10.00 g, 20.30 mmol, 89.4% yield). LC-MS(ESI⁺): m/z 493.4 [M+H]⁺

Step 2: int-33-2

To a solution of **int-33-1** (10.00 g, 20.30 mmol) in DMAc (200 mL) was added NaH (3.25 g, 81.00 mmol) at 0 °C. After being stirred at 0 °C for 30 mins, *N*-(2,2-dimethoxyethyl)-1*H*-imidazole-1-carboxamide (8.08 g, 40.6 mmol) was added portion-wise at 0 °C. The resulting mixture was stirred at 20 °C for 1 hr. After completion, the reaction mixture was added poured into water (500 mL) and extracted with EtOAc (500 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-33-2** (9.00 g, 14.43 mmol, 71.1% yield). LC-MS(ESI⁺): m/z 624.4 [M+H]⁺

Step 3: int-33-3

To a solution of **int-33-2** (9.00 g, 14.43 mmol) in THF (90 mL) was added TsOH·H₂O (1.37 g, 7.21 mmol). The resulting mixture was stirred at 60 °C for 1 hr. After cooling to room temperature, the mixture was poured into water (200 mL) and extracted with EtOAc (200 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-33-3** (6.70 g, 11.97 mmol, 83.0% yield). LC-MS(ESI⁺): m/z 560.4 [M+H]⁺

Step 4: int-33-4

To a solution of **int-33-3** (1.00 g, 1.79 mmol) in NMP (13 mL) was added **int-22-5** (1.36 g, 3.57 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (254.0 mg, 1.79 mmol), copper(I) iodide (681.0 mg, 3.57 mmol) and potassium carbonate (741.0 mg, 5.36 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 140 °C for 4 hrs under N₂ atmosphere. After cooling to room

temperature, the reaction mixture was poured into water (50 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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-33-4** (830.0 mg, 0.96 mmol, 54.0% yield). LC-MS (ESI+): *m/z* 860.5 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.43 - 7.29 (m, 5H), 7.18 - 7.04 (m, 2H), 7.01 - 6.9 (m, 1H), 6.91 - 6.84 (m, 2H), 6.65 - 6.49 (m, 2H), 5.40 - 5.17 (m, 1H), 5.01 (s, 2H), 4.33 - 4.25 (m, 2H), 4.07 (s, 3H), 3.62 - 3.48 (m, 2H), 2.25 (s, 3H), 1.43 (s, 9H), 1.37 - 1.32 (m, 1H), 1.29 (d, *J* = 8.0 Hz, 3H), 1.26 - 1.20 (m, 1H), 1.01 - 0.95 (m, 2H), 0.85 (s, 9H), 0.03 (s, 6H).

Step 5: int-33-5

To a solution of **int-33-4** (830.0 mg, 0.96 mmol) in MeOH (25 mL) was added Pd/C (166.0 mg, 20% w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C for 2 hrs under H₂ atmosphere (15 psi). After completion, the reaction mixture was filtered through a celite pad and rinsed with MeOH (20 mL $\times$ 3). The filtrate was concentrated under reduced pressure to afford **int-33-5** (720.0 mg, crude), which was used for next step directly without purification. LC-MS (ESI+): *m/z* 772.4 (M+H)⁺.

Step 6: int-33-6

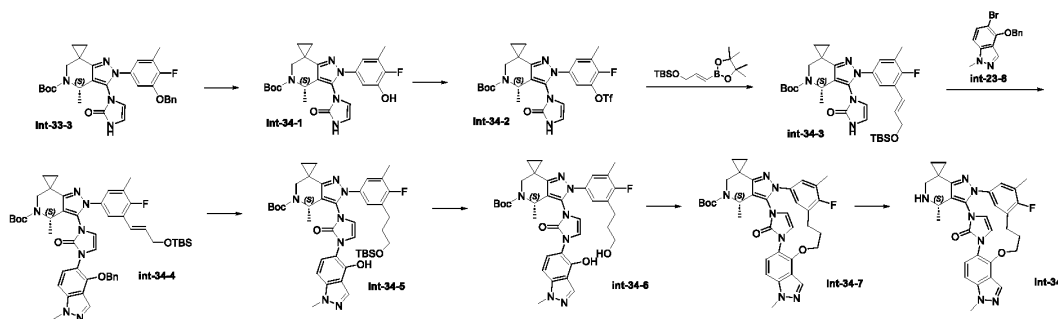
To a solution of **int-33-5** (720.0 mg, 0.93 mmol) in THF (3.6 mL) was added TBAF (4.66 mL, 1 M in THF). The resulting mixture was stirred at 20 °C for 2 hrs. After completion, the mixture was poured into water (50 mL) and extracted with DCM (50 mL $\times$ 3). The combined organic layers were washed with water (50 mL $\times$ 2), brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-33-6** (520.0 mg, 0.79 mmol, 85.0% yield). LC-MS (ESI+): *m/z* 658.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (brs, 1H), 8.21 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.96 - 6.86 (m, 2H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.71 - 6.64 (m, 1H), 5.42 - 5.13 (m, 1H), 4.47 (brs, 1H), 4.06 (s, 3H), 3.67 - 3.41 (m, 2H), 3.37 - 3.31 (m, 2H), 2.86 - 2.73 (m, 2H), 2.21 (s, 3H), 1.67 (p, *J* = 8.0 Hz, 2H), 1.43 (s, 9H), 1.37 - 1.31 (m, 1H), 1.27 (d, *J* = 8.0 Hz, 3H), 1.02 - 0.94 (m, 2H), 0.87 - 0.77 (m, 1H).

Step 7: int-33-7

To a solution of **int-33-6** (520.0 mg, 0.79 mmol) in anhydrous toluene (13 mL) was added 2-(tributylphosphoranylidene)acetonitrile (1.15 g, 4.74 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 90 °C for 4 hrs under N₂ atmosphere. After cooling to room temperature, the reaction 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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-33-7** (430.0 mg, 0.67 mmol, 85.0% yield). LC-MS (ESI+): *m/z* 640.3 (M+H)⁺.

Step 8: int-33

A mixture of **int-33-7** (430.0 mg, 0.67 mmol) in HCl solution (3 mL, 4 M in dioxane) was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated to give a residue that was diluted with DCM (50 mL). The organic layer was washed with saturated NaHCO₃ (aq., 100 mL), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-33** (230.0 mg, 0.43 mmol, 63.4% yield). LC-MS (ESI⁺): *m/z* 540.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 – 8.29 (m, 1H), 7.61 – 7.54 (m, 1H), 7.34 – 7.20 (m, 1H), 7.16 – 7.07 (m, 1H), 7.02 – 6.68 (m, 2H), 6.67 – 6.54 (m, 1H), 4.41 – 4.09 (m, 3H), 4.08 – 4.04 (m, 3H), 3.23 – 2.85 (m, 4H), 2.82 – 2.70 (m, 1H), 2.29 – 2.21 (m, 3H), 1.78 – 1.54 (m, 2H), 1.30 – 1.22 (m, 3H), 1.21 – 1.15 (m, 1H), 1.07 – 0.98 (m, 1H), 0.96–0.89 (m, 1H), 0.88 – 0.79 (m, 1H).

Example ae: Synthesis of int-34**Step 1: int-34-1**

To a solution of **int-33-3** (4.00 g, 7.15 mmol) in MeOH (60 mL) and THF (60 mL) was added Pd/C (800 mg, 20% w/w). The resulting reaction mixture was degassed and purged with H₂ for 3 times and stirred at 20 °C for 1 hr. After completion, the mixture was filtered through a celite pad and rinsed with MeOH (10 mL × 2). The filtrate was concentrated under reduced pressure to afford **int-34-1** (3.20 g, crude), which was used for next step directly without purification. LC-MS(ESI⁺): *m/z* 470.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (s, 1H), 10.09 (s, 1H), 6.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.62 – 6.59 (m, 1H), 6.58 – 6.56 (m, 1H), 6.55 – 6.51 (m, 1H), 5.25 – 5.08 (m, 1H), 3.61 – 3.41 (m, 2H), 2.16 (s, 3H), 1.42 (s, 9H), 1.34 – 1.29 (m, 1H), 1.19 – 1.14 (m, 3H), 0.98 – 0.90 (m, 2H), 0.84 – 0.74 (m, 1H).

Step 2: int-34-2

To a solution of **int-34-1** (3.20 g, 6.82 mmol) in DCM (60 mL) was added 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (1.83 g, 6.13 mmol) and TEA (2.85 mL, 20.45 mmol). The resulting mixture was stirred at 20 °C for 1 hr. After completion, the mixture was poured into water (500 mL) and extracted with DCM (200 mL × 3). The combined organic layers were washed with water (200 mL × 2), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-34-2** (2.40 g, 3.99 mmol, 58.5 % yield). LC-MS(ESI⁺): *m/z* 602.2

$[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.44 (s, 1H), 7.51 – 7.44 (m, 1H), 7.36 – 7.31 (m, 1H), 6.69 – 6.62 (m, 2H), 5.27 – 5.07 (m, 1H), 3.62 – 3.44 (m, 2H), 2.34 (s, 3H), 1.42 (s, 9H), 1.39 – 1.33 (m, 1H), 1.17 (d, J = 8.0 Hz, 3H), 1.01 – 0.95 (m, 2H), 0.89 – 0.82 (m, 1H).

Step 3: int-34-3

To a mixture of **int-34-2** (1.00 g, 1.66 mmol) in dioxane (10 mL) and water (1 mL) was added (*E*)-*tert*-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (744.0 mg, 2.49 mmol), $NaHCO_3$ (279.0 mg, 3.32 mmol) and $Pd(Ph_3P)_4$ (192.0 mg, 0.166 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 100 °C for 2 hrs. After cooling to room temperature, the mixture was poured into water (250 mL) and extracted with EtOAc (200 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-34-3** (650.0 mg, 1.04 mmol, 62.7% yield). LC-MS(ESI $^+$): m/z 624.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.36 (s, 1H), 7.31 – 7.24 (m, 1H), 7.17 – 7.11 (m, 1H), 6.72 – 6.60 (m, 2H), 6.60 – 6.55 (m, 1H), 6.32 (dt, J = 16.0, 8.0 Hz, 1H), 5.27 – 5.08 (m, 1H), 4.38 – 4.30 (m, 2H), 3.61 – 3.44 (m, 2H), 2.21 (s, 3H), 1.42 (s, 9H), 1.37 – 1.31 (m, 1H), 1.18 (d, J = 8.0 Hz, 3H), 0.98 – 0.92 (m, 2H), 0.90 (s, 9H), 0.85 – 0.83 (m, 1H), 0.08 (s, 6H).

Step 4: int-34-4

To a solution of **int-34-3** (650.0 mg, 1.04 mmol) in NMP (6 mL) were added **int-23-8** (661.0 mg, 2.08 mmol), copper(I) iodide (198.0 mg, 1.04 mmol), K_2CO_3 (432.0 mg, 3.13 mmol) and (1*R*, 2*R*)- N^1,N^2 -dimethylcyclohexane-1,2-diamine (148.0 mg, 1.04 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 140 °C for 2 hrs under N_2 . After cooling to room temperature, the reaction mixture was poured into water (300 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layers were washed with water (200 mL $\times$ 2), followed by brine (100 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-34-4** (500 mg, 0.581 mmol, 55.8 % yield). LC-MS(ESI $^+$): m/z 860.4 $[M+H]^+$

Step 5: int-34-5

To a solution of **int-34-4** (1.25 g, 1.45 mmol) in MeOH (40 mL) was added Pd/C (250 mg, 20% w/w). The resulting mixture was degassed and purged with H_2 for 3 times and then stirred at 30 °C for 2 hrs under H_2 (15 psi). After completion, the reaction mixture was filtered and resined with MeOH (10 mL $\times$ 2). The filtrate was concentrated under reduced pressure to afford **int-34-5** (1.00 g, crude), which was used for next step directly. LC-MS(ESI $^+$): m/z 772.4 $[M+H]^+$

Step 6: int-34-6

To a solution of **int-34-5** (1.00 g, 1.29 mmol) in THF (10 mL) was added TBAF (1.69 mg, 6.48 mmol). The resulting mixture was stirred at 30 °C for 1 hr. After completion, the reaction mixture was poured

into water (200 mL) and extracted with EtOAc (200 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-34-6** (570.0 mg, 0.87 mmol, 66.9% yield). LC-MS(ESI⁺): m/z 658.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.60 (brs, 1H), 8.21 (s, 1H), 7.16 – 7.06 (m, 4H), 6.87 – 6.77 (m, 2H), 5.38 – 5.19 (m, 1H), 4.64 – 4.48 (m, 1H), 4.01 (s, 3H), 3.62 – 3.48 (m, 2H), 3.43 – 3.40 (m, 2H), 2.66 – 2.59 (m, 2H), 2.24 (s, 3H), 1.70 – 1.62 (m, 2H), 1.43 (s, 9H), 1.39 – 1.34 (m, 1H), 1.28 (d, *J* = 8.0 Hz, 3H), 1.01 – 0.92 (m, 2H), 0.89 – 0.82 (m, 1H).

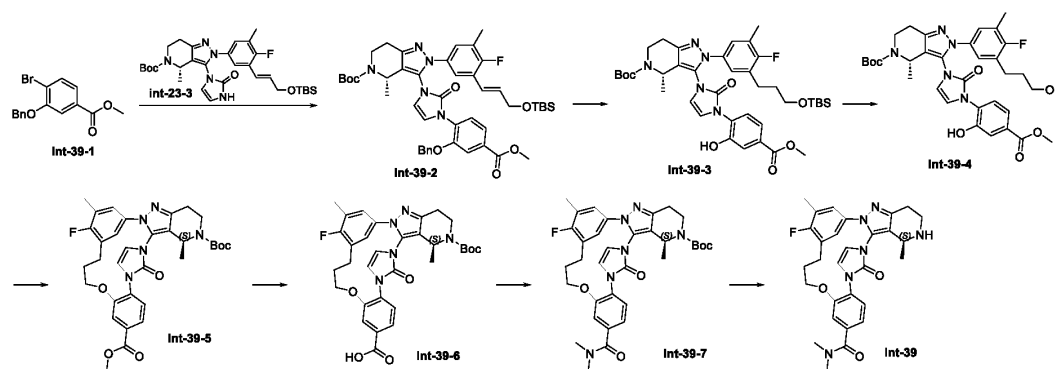
Step 7: int-34-7

To a solution of **int-34-6** (470.0 mg, 0.72 mmol) in anhydrous toluene (15 mL) was added 2-(tributylphosphoranylidene)acetonitrile (689.0 mg, 2.86 mmol). The resulting mixture was degassed and purged with N₂ for 2 mins and stirred at 90 °C for 1 hr. After cooling to room temperature, the reaction mixture was diluted with EtOAc (200 mL) and washed with water (100 mL $\times$ 2), followed by brine (100 mL). The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-34-7** (450.0 mg, 0.70 mmol, 98.0% yield). LC-MS(ESI⁺): m/z 640.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 – 8.22 (m, 1H), 7.45 – 7.31 (m, 3H), 7.06 – 6.73 (m, 3H), 5.38 – 5.17 (m, 1H), 4.06 (s, 3H), 4.02 – 3.98 (m, 1H), 3.81 – 3.70 (m, 1H), 3.67 – 3.50 (m, 2H), 2.91 – 2.75 (m, 2H), 2.26 (s, 3H), 2.23 – 2.14 (m, 1H), 2.10 – 1.99 (m, 1H), 1.44 (s, 9H), 1.38 – 1.27 (m, 4H), 1.02 – 0.95 (m, 2H), 0.89 – 0.81 (m, 1H).

Step 8: int-34

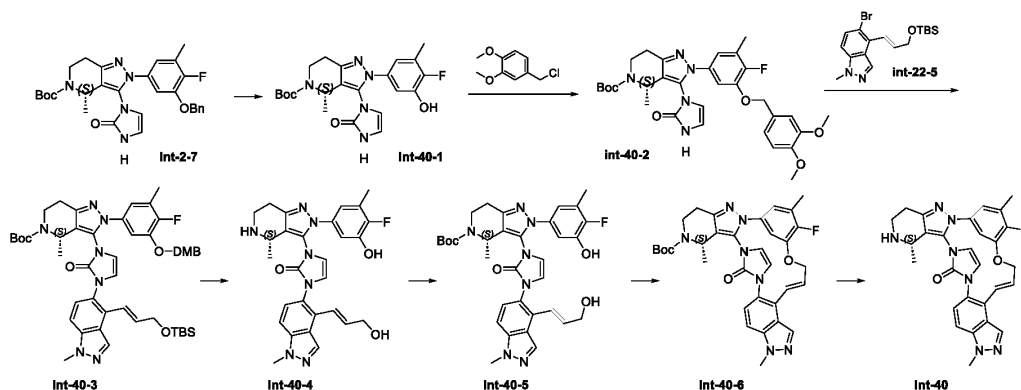
A mixture of **int-34-7** (450.0 mg, 0.70 mmol) in HCl solution (4 mL, 4 M in dioxane) was stirred at 30 °C for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure to afford **int-34** (350.0 mg, 0.65 mmol, 92.0% yield). LC-MS(ESI⁺): m/z 540.3 [M+H]⁺

Example ah: Synthesis of int-39, int-40, int-41, int-42, int-43



Int-39-5 was synthesized following the procedure for **int-27-6** and **int-23-7** using **int-39-1** instead of **int-23-8** and **int-27-2**. The conversion of **int-39-5** to **int-39** was carried out following the procedure for the synthesis of **int-31** from **int-31-6**. **Int-39**: (280.0 mg, 0.53 mmol, 83.0% yield). LC-MS

(ESI+): m/z 531.3 ($M+H$)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.50 – 7.40 (m, 1H), 7.38 – 7.32 (m, 1H), 7.28 – 7.21 (m, 1H), 7.15 – 6.98 (m, 2H), 6.84 – 6.74 (m, 1H), 6.74 – 6.57 (m, 1H), 4.06 – 3.97 (m, 2H), 3.94 – 3.86 (m, 1H), 3.31 – 3.17 (m, 2H), 3.05 – 2.92 (m, 6H), 2.91 – 2.76 (m, 2H), 2.70 – 2.63 (m, 2H), 2.28 (s, 3H), 2.24 – 2.11 (m, 1H), 2.04 – 1.85 (m, 1H), 1.28 – 1.16 (m, 3H).



Step 1: int-40-1

To a solution of **int-2-7** (960.0 mg, 1.80 mmol) in THF (20 ml) and MeOH (20 mL) was added Pd/C (96.0 mg, 10% w/w, 10% purity). The reaction mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C under H₂ (15 Psi) for 7 hrs. After completion, the mixture was filtered through a celite pad and the cake was rinsed with MeOH (10 mL × 3). The combined filtrate was concentrated and purified by column chromatography to afford **int-40-1** (420.0 mg, 0.95 mmol, 52.6% yield). LC-MS(ESI+): m/z 444.3 [$M+H$]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 10.16 (brs, 1H), 6.77 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 4.0 Hz, 1H), 6.58 (s, 1H), 6.50 (s, 1H), 5.11 – 4.97 (m, 1H), 4.35 – 4.14 (m, 1H), 3.12 – 2.97 (m, 1H), 2.69 – 2.60 (m, 2H), 2.17 (s, 3H), 1.42 (s, 9H), 1.11 (d, J = 8.0 Hz, 3H).

Step 2: int-40-2

To a solution of **int-40-1** (1.00 g, 2.26 mmol) in DMF (10 mL) were added K₂CO₃ (374.0 mg, 2.71 mmol), followed by 4-(chloromethyl)-1,2-dimethoxybenzene (461.0 mg, 2.48 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 16 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 (50 mL × 2), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-40-2** (700.0 mg, 1.18 mmol, 52.3% yield). LC-MS (ESI+): m/z 594.4 ($M+H$)⁺.

Step 3: int-40-3

A mixture of **int-22-5** (549.0 mg, 1.44 mmol), K₂CO₃ (298.0 mg, 2.16 mmol), **int-40-2** (427.0 mg, 0.72 mmol), CuI (137.0 mg, 0.72 mmol) and (1*R*,2*R*)-*N,N'*-Dimethyl-1,2-cyclohexanediamine (51.0

mg, 0.36 mmol) in NMP (5 mL) was degassed and purged with N₂ for 3 mins and stirred at 140°C for 3 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was diluted with ethyl acetate (50 mL) and washed with H₂O (50 mL × 3), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-40-3** (370.0 mg, 0.36 mmol, 50.1% yield). LC-MS (ESI+): m/z 894.3 (M+H)⁺

Step 4: int-40-4

To a solution of **int-40-3** (300.0 mg, 0.34 mmol) in DCM (6 mL) was added TFA (1.2 mL) dropwise and the mixture was stirred at 25 °C for 1 hr. After completion, the reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated NaHCO₃ (aq., 20 mL). The organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford **int-40-4** (250.0 mg, crude), which was used directly in the next step without purification. LC-MS (ESI+): m/z 530.2 (M+H)⁺.

Step 5: int-40-5

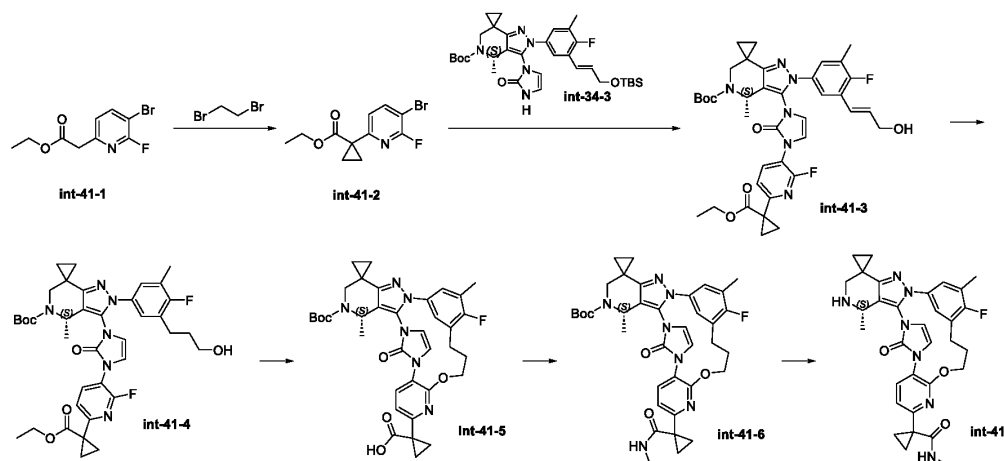
To a solution **int-40-4** (250.0 mg, 0.47 mmol) in DCM (5 mL) were added TEA (0.13 mL, 0.94 mmol) and (Boc)₂O (0.16 mL, 0.70 mmol). The mixture was stirred at 25 °C for 1 hr. After completion, the mixture was diluted with DCM (20 mL) and washed with water (20 mL × 2). The organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was dissolved in MeOH (6 mL) and K₂CO₃ (284.0 mg, 2.06 mmol) was added. After being stirred at 25 °C for 2 hrs, the mixture was filtered and rinsed with dichloromethane (5 mL × 3). The combined organic layers were concentrated and purified by prep-TLC to afford **int-40-5** (70.0 mg, 0.11 mmol, 27.0% yield). LC-MS (ESI+): m/z 630.2(M+H)⁺.

Step 6: int-40-6

To a solution of **int-40-5** (60 mg, 0.095 mmol) in anhydrous toluene (1.8 mL) was added 2-(tributylphosphoranylidene)acetonitrile (92.0 mg, 0.38 mmol). The resulting mixture was stirred at 100 °C for 2 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL × 2), dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC to afford **int-40-6** (40.0 mg, 0.07 mmol, 68.6% yield). LC-MS (ESI+): m/z 612.2 (M+H)⁺.

Step 7: int-40

A mixture of **int-40-6** (40.0 mg, 0.07 mmol) in HCl solution (4 M in dioxane, 0.6 mL) was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated to afford **int-40** (20.0 mg, 0.04 mmol, 59.8% yield). LC-MS (ESI+): m/z 512.1 (M+H)⁺.



Step 1: int-41-2

To a solution of **int-41-1** (1.60 g, 6.45 mmol) in DMF (9.0 mL) was added NaH (0.568 g, 14.19 mmol) in portions under N₂ atmosphere at 0 °C. After being stirred at 0 °C for 0.5 hr, 1,2-dibromoethane (2.67 g, 14.19 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 hrs. After completion, the mixture was poured into cold 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-41-2** (1.50 g, 4.93 mmol, 76.0% yield). LC-MS (ESI+): m/z 288.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 – 8.19 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 4.10 (q, *J* = 8.0 Hz, 2H), 1.59 – 1.51 (m, 2H), 1.51 – 1.39 (m, 2H), 1.15 (t, *J* = 8.0 Hz, 3H).

Step 2: int-41-3

To a mixture of **int-34-3** (1.00 g, 1.60 mmol) and **int-41-2** (924.0 mg, 3.21 mmol) in NMP (10.0 mL) was added K₂CO₃ (665.0 mg, 4.81 mmol), CuI (305 mg, 1.60 mmol) and (1*R*,2*R*)-*N,N'*-Dimethyl-1,2-cyclohexanediamine (114.0 mg, 0.80 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 130 °C for 3 hrs under N₂ atmosphere. After cooling to room temperature, the mixture was poured into water (100 mL) and extracted with ethyl acetate (50 mL × 4). 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-41-3** (900.0 mg, 1.13 mmol, 70.5% yield). LC-MS (ESI+): m/z 717.1 (M+H)⁺.

Step 3: int-41-4

To a solution of **int-41-3** (800.0 mg, 1.12 mmol) in MeOH (24.0 mL) was added Pd/C (160 mg, 20%w/w.). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 2 hrs under H₂ (15 psi). After completion, the reaction mixture was filtered through a Celite pad and resined with MeOH (30 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-**

41-4 (600.0 mg, 0.75 mmol, 67.3% yield). LC-MS (ESI+): m/z 719.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.15 – 7.06 (m, 2 H), 7.05 - 6.94 (m, 2H), 5.34 – 5.13 (m, 1H), 4.55 – 4.45 (m, 1H), 4.13 – 4.08 (m, 2H), 3.66 – 3.48 (m, 2H), 3.44 – 3.38 (m, 2H), 2.65 – 2.56 (m, 2H), 2.22 (s, 3H), 1.65 – 1.59 (m, 2H), 1.58 – 1.54 (m, 2H), 1.46 – 1.44 (m, 1H), 1.43 (s, 9H), 1.37 – 1.34 (m, 1H), 1.25 (d, J = 8.0 Hz, 3H), 1.18 – 1.10 (m, 4H), 1.03 - 0.96 (m, 2H), 0.89 – 0.82 (m, 1H).

Step 4: int-41-5

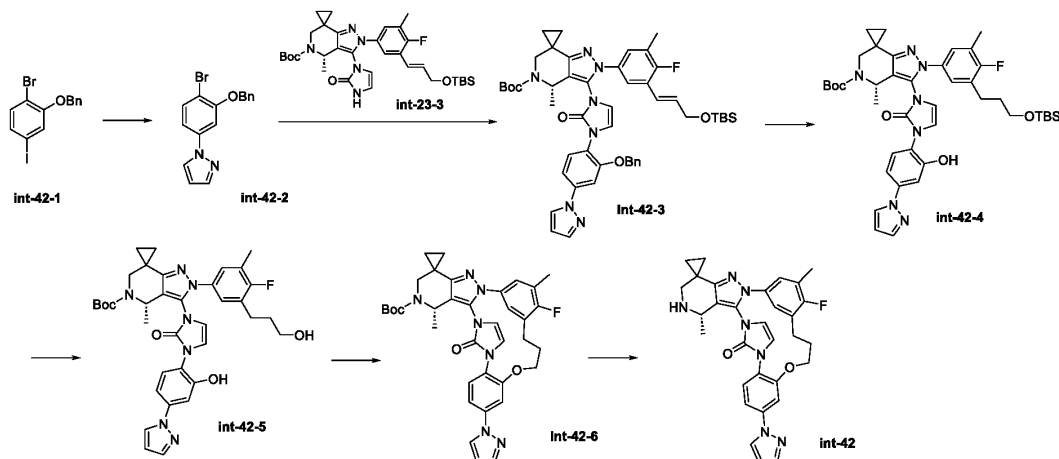
To a solution of **int-41-4** (640.0 mg, 0.89 mmol) in DMA (25.0 mL) was added NaH (43.0 mg, 1.781 mmol, 60% purity) in portions at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was poured into cold water (100 mL) and extracted with EtOAc (100 mL $\times$ 3). The combined aqueous layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-41-5** (200.0 mg, 0.15 mmol, 16.7% yield). LC-MS (ESI+): m/z 671.1(M+H)⁺.

Step 5: int-41-6

To a mixture of **int-41-5** (100.0 mg, 0.15 mmol) and methylamine hydrochloride (10.0 mg, 0.15 mmol) in DMF (1.5 mL) were added HATU (85.0 mg, 0.22 mmol) and DIEA (0.08 mL, 0.45 mmol). The resulting mixture was stirred at 25 °C for 16 hrs. After completion, the mixture was diluted with EtOAc (20 mL) and washed with water (15 mL $\times$ 2). The organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography on silica gel to afford **int-41-6** (25.0 mg, 0.029 mmol, 19.6% yield). LC-MS (ESI+): m/z 684.3 (M+H)⁺.

Step 6: int-41

A mixture of **int-41-6** (50 mg, 0.073 mmol) in HCl solution (4 M in dioxane, 1 mL) was stirred at 25 °C for 1 hr. After completion, the reaction mixture was concentrated under reduced pressure to afford **int-41** (40.0 mg, 0.06 mmol, 84.0% yield), which was used directly in the next step without purification. LC-MS (ESI+): m/z 584.2 (M+H)⁺.



Step 1: int-42-2

To a solution of **int-42-1** (3.00 g, 7.71 mmol) in DMF (60 mL) were added 1*H*-pyrazole (0.709 g, 10.41 mmol), copper(I) iodide (0.147 g, 0.771 mmol), Cs₂CO₃ (7.54 g, 23.13 mmol) and 2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole (151.0 mg, 0.77 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 100 °C for 12 hrs under N₂. After cooling to room temperature, the mixture was poured into water (300 mL) and extracted with EtOAc (200 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-42-2** (1.10 g, 3.34 mmol, 43.3% yield). LC-MS(ESI⁺): *m/z* 329.0 [M+H]⁺

Step 2: int-42-3

To a solution of **int-23-3** (500.0 mg, 0.80 mmol) in NMP (5 mL) was added **int-42-2** (528.0 mg, 1.60 mmol), (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (57.0 mg, 0.40 mmol), K₂CO₃ (332.0 mg, 2.40 mmol) and copper(I) iodide (153.0 mg, 0.80 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 130 °C for 3 hrs under N₂. After cooling to room temperature, the mixture was poured into water (200 mL) and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with water (100 mL × 2), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-42-3** (420.0 mg, 0.48 mmol, 60.1% yield). LC-MS(ESI⁺): *m/z* 872.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 4.0 Hz, 1H), 7.74 (d, *J* = 4.0 Hz, 1H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.36 – 7.23 (m, 7H), 7.14 – 7.10 (m, 1H), 6.89 (s, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.57 – 6.53 (m, 1H), 6.29 (dt, *J* = 16.0, 4.0 Hz, 1H), 5.32 – 5.13 (m, 3H), 4.28 – 4.21 (m, 2H), 3.60 – 3.42 (m, 2H), 2.12 (s, 3H), 1.39 (s, 9H), 1.36 – 1.31 (m, 1H), 1.18 – 1.14 (m, 3H), 0.98 – 0.90 (m, 2H), 0.86 – 0.81 (m, 10H), 0.00 (s, 6H).

Step 3: int-42-4

To a solution of **int-42-3** (320.0 mg, 0.37 mmol) in MeOH (9 mL) was added Pd/C (60 mg, 20% w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C for 5 hrs under H₂ (15 psi). After completion, the reaction mixture was filtered and resined with MeOH (3 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-42-4** (360.0 mg, crude), which was used directly in the next step. LC-MS (ESI⁺): m/z 784.4 [M+H]⁺

Step 4: int-42-5

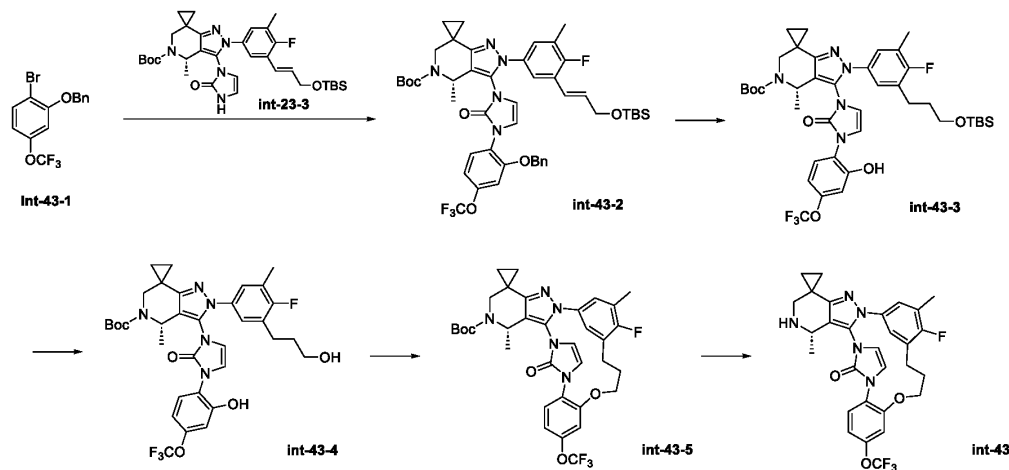
To a solution of **int-42-4** (360.0 mg, 0.46 mmol) in THF (4 mL) was added TBAF (2.3 mL, 2.30 mmol). The resulting mixture was stirred at 30 °C for 1 hr. After completion, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (50 mL), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-42-5** (220.0 mg, 0.33 mmol, 71.4% yield). LC-MS(ESI⁺): m/z 670.2 [M+H]⁺

Step 5: int-42-6

To a solution of **int-42-5** (210.0 mg, 0.31 mmol) in anhydrous toluene (6 mL) was added 2-(tributylphosphoranylidene)acetonitrile (303.0 mg, 1.25 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 90 °C for 1 hr under N₂. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (100 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-42-6** (170.0 mg, 0.26 mmol, 83.0% yield). LC-MS(ESI⁺): m/z 652.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 – 8.59 (m, 1H), 7.81 – 7.74 (m, 1H), 7.69 – 7.65 (m, 1H), 7.60 – 7.53 (m, 2H), 7.28 – 7.18 (m, 1H), 7.09 – 6.95 (m, 1H), 6.90 – 6.80 (m, 1H), 6.79 – 6.61 (m, 1H), 6.60 – 6.56 (m, 1H), 5.37 – 5.14 (m, 1H), 4.10 – 3.98 (m, 2H), 3.66 – 3.48 (m, 2H), 2.88 – 2.79 (m, 1H), 2.74 – 2.66 (m, 1H), 2.26 (s, 3H), 2.22 – 2.16 (m, 1H), 1.97 – 1.88 (m, 1H), 1.45 – 1.41 (m, 10H), 1.33 – 1.30 (m, 3H), 0.99 – 0.95 (m, 2H), 0.88 – 0.86 (m, 1H).

Step 6: int-42

A mixture of **int-42-6** (170.0 mg, 0.26 mmol) in HCl solution (4 M in dioxane, 2 mL) was stirred at 30 °C for 1 hr. After completion, the mixture was filtered and concentrated under reduced pressure to afford **int-42** (150.0 mg, crude). LC-MS(ESI⁺): m/z 552.3 [M+H]⁺



Step 1: int-43-2

To a mixture of **int-23-3** (300.0 mg, 0.48 mmol) and **int-43-1** (334.0 mg, 0.96 mmol) in NMP (4.5 mL) was added (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (68.0 mg, 0.48 mmol), copper(I) iodide (183.0 mg, 0.96 mmol) and K₂CO₃ (199.0 mg, 1.44 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and then stirred at 130 °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 H₂O (50 mL × 2), followed by brine (50 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-43-2** (300.0 mg, 0.34 mmol, 70.1% yield). LC-MS (ESI⁺): *m/z* 890.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43 - 7.24 (m, 8H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 - 6.89 (m, 2H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 16.0, 4.0 Hz, 1H), 5.39 - 5.20 (m, 1H), 5.19 (s, 2H), 4.33 - 4.19 (m, 2H), 3.65 - 3.43 (m, 2H), 2.15 (s, 3H), 1.42 (s, 9H), 1.38 - 1.34 (m, 1H), 1.26 - 1.22 (m, 1H), 1.17 (d, *J* = 8.0 Hz, 3H), 1.00 - 0.92 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Step 2: int-43-3

To a solution of **int-43-2** (300.0 mg, 0.34 mmol) in MeOH (9 mL) was added Pd/C (60 mg, 20% w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 30 °C for 2 hrs under H₂ atmosphere (15 psi). After completion, the reaction mixture was filtered through a celite pad and rinsed with MeOH (30 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-43-3** (260.0 mg, crude), which was used directly for the next step. LC-MS (ESI⁺): *m/z* 802.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.33 - 7.23 (m, 1H), 7.14 - 7.09 (m, 1H), 7.08 - 7.03 (m, 1H), 6.91 (d, *J* = 4.0 Hz, 1H), 6.87 - 6.75 (m, 2H), 6.74 - 6.63 (m, 1H), 5.43 - 5.07 (m, 1H), 3.62 - 3.53 (m, 4H), 2.67 - 2.59 (m, 2H), 2.23 (s, 3H), 1.76 - 1.64 (m, 2H), 1.44 (s, 9H), 1.40 - 1.34 (m, 1H), 1.32 - 1.20 (m, 4H), 1.03 - 0.96 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H).

Step 3: int-43-4

To a solution of **int-43-3** (260.0 mg, 0.32 mmol) in THF (1.5 mL) was added TBAF (1.6 mL, 1.60 mmol). The resulting mixture was stirred at 30 °C for 2 hrs. After completion, the mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water (30 mL), followed by brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue that was purified by pre-TLC to afford **int-43-4** (190.0 mg, 0.28 mmol, 85.0% yield). LC-MS (ESI+): m/z 688.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.70 (brs, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.13 - 7.02 (m, 2H), 6.96 - 6.92 (m, 1H), 6.92 - 6.86 (m, 2H), 6.85 - 6.77 (m, 1H), 5.35 - 5.06 (m, 1H), 4.51 (brs, 1H), 3.64 - 3.44 (m, 2H), 3.40 - 3.37 (m, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.22 (s, 3H), 1.68 - 1.60 (m, 2H), 1.43 (s, 9H), 1.38 - 1.32 (m, 1H), 1.26 - 1.23 (m, 3H), 1.01 - 0.94 (m, 2H), 0.88 - 0.81 (m, 1H).

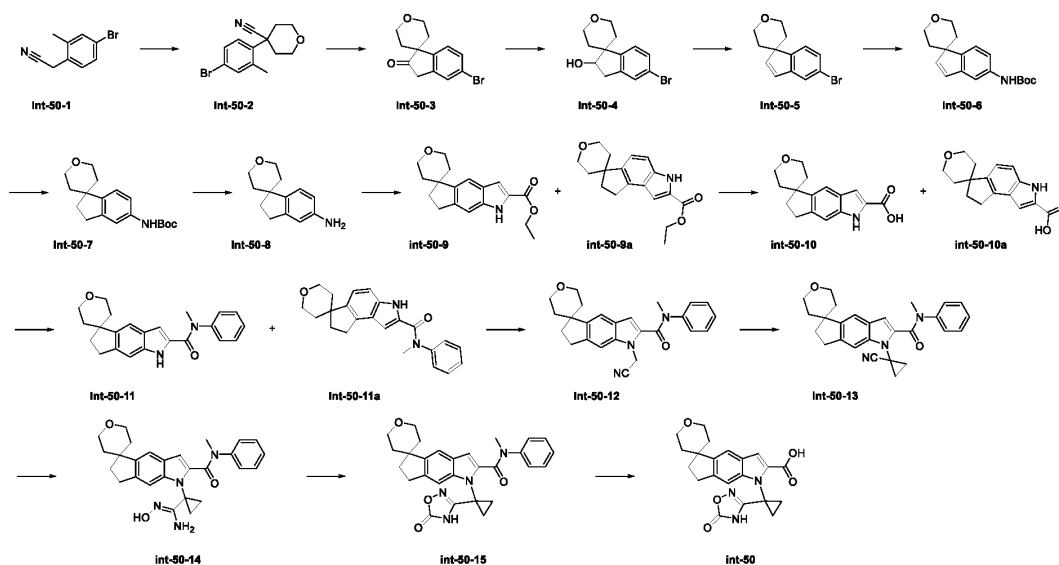
Step 4: int-43-5

To a solution of **int-43-4** (190.0 mg, 0.28 mmol) in anhydrous toluene (5.8 mL) was added 2-(tributylphosphoranylidene)acetonitrile (267.0 mg, 1.11 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 mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3), the combined organic layers were washed with water (30 mL × 2), followed by brine (30 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-43-5** (135.0 mg, 0.20 mmol, 73.0% yield). LC-MS (ESI+): m/z 670.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 - 7.56 (m, 1H), 7.29 - 7.21 (m, 2H), 7.15 - 6.97 (m, 2H), 6.96 - 6.80 (m, 1H), 6.80 - 6.58 (m, 1H), 5.55 - 5.00 (m, 1H), 4.10 - 3.93 (m, 2H), 3.70 - 3.44 (m, 2H), 2.84 - 2.62 (m, 2H), 2.25 (s, 3H), 2.23 - 2.14 (m, 1H), 1.96 - 1.84 (m, 1H), 1.43 (s, 9H), 1.36 - 1.28 (m, 4H), 1.01 - 0.95 (m, 2H), 0.89 - 0.82 (m, 1H).

Step 5: int-43

A mixture of **int-43-5** (135.0 mg, 0.20 mmol) in HCl solution (1 mL, 4 M in dioxane) was stirred at 30 °C for 1 hr. After completion, the reaction mixture was concentrated to give a residue, which was diluted with DCM (10 mL) and washed with saturated NaHCO₃ (aq., 10 mL). The organic layer was washed with water (30 mL), followed by brine (30 mL), dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC to afford **int-43** (110.0 mg, 0.19 mmol, 96.0% yield). LC-MS (ESI+): m/z 570.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 - 7.44 (m, 1H), 7.32 - 7.17 (m, 2H), 7.13 - 6.92 (m, 2H), 6.83 - 6.53 (m, 2H), 4.14 - 3.92 (m, 3H), 3.08 - 3.02 (m, 1H), 2.86 - 2.68 (m, 3H), 2.25 (s, 3H), 2.20 - 2.13 (m, 1H), 1.95 - 1.84 (m, 1H), 1.25 - 1.21 (m, 3H), 1.20 - 1.14 (m, 1H), 1.02 - 0.96 (m, 1H), 0.93 - 0.79 (m, 2H).

Example aj: Synthesis of int-50



Step 1: int-50-2

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, $\text{DMSO}-d_6$) 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

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

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 × 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 [M+ H]⁺.

Step 4: int-50-5

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

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

[0331] 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

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

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

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 Na₂SO₄, filtered and concentrated to give **int-50-10** and **int-50-10a** (6.00 g, 66% yield). LCMS: 272.2 [M+ 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 × 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 [M+ H]⁺.

Step 11: **int-50-12** & **int-50-12a**

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 × 3). The combined organic layers were wash with H₂O (50 mL × 2), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by SFC to give **int-50-12**. (2.80 g, 39% yield). LCMS: 400.2 [M+ H]⁺, t_R = 1.81 min. ¹HNMR (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**

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 N₂ for 2 hrs. The mixture reaction was quenched with NH₄Cl (100 mL) and extracted with EA (200 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered, concentrated to give **int-50-13** (1.90 g, 80% yield). LCMS: 425.7 [M+ H]⁺.

Step 13: **int-50-14**

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 $[\text{M} + \text{H}]^+$.

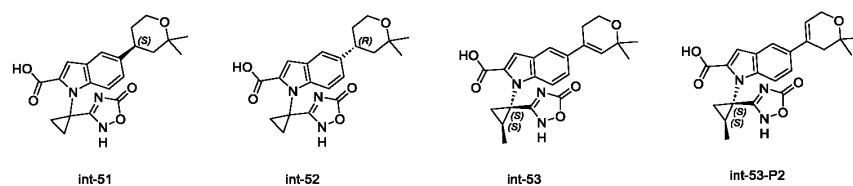
Step 14: int-50-15

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 H_2O (100 mL) and extracted with EA (100 mL $\times$ 3). The combined organic layers were washed with brine (25 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated to give **int-50-15** (1.00 g, 63% yield). LCMS: 485.2 $[\text{M} + \text{H}]^+$.

[0348] Step 15: int-50

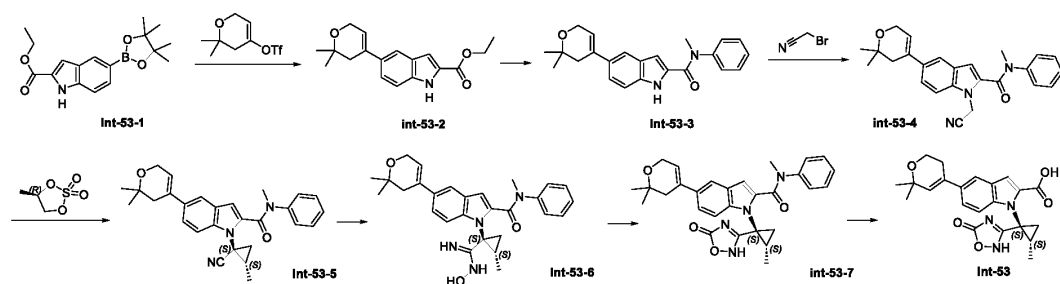
[0349] To a solution of **int-50-15** (500 mg, 1.03 mmol) in n-PrOH was added KOH (579 mg, 10.32 mmol). The mixture was stirred at 90 °C for 5 hrs. The reaction was adjusted pH = 2 with 2 N HCl aq. The mixture extracted with EA (50 mL $\times$ 3). The combined organic layers were washed with brine (25 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated to afford **int-50** (186.9 mg, 42% yield). LCMS: 394.1 $[\text{M} + \text{H}]^+$.

Example ak: Synthesis of int-51, int-52, int-53 and int-53-P2



The synthesis of **int-51** was referred to intermediate **46-P1** of WO2022017338.

The synthesis of **int-52** was referred to intermediate **46-P2** of WO2022017338.



Step 1: int-53-2

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), $\text{Pd}(\text{dppf})\text{Cl}_2$ (2.32 g, 3.17 mmol) and potassium carbonate (17.54 g, 127.00 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 100 °C for 2 hrs under N_2 . After

cooling to room temperature, the mixture was poured into 500 mL of water and extracted with ethyl acetate (300 mL $\times$ 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

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 $\times$ 3). The combined organic layers were washed with H₂O (100 mL $\times$ 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-*d*₆) 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

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 $\times$ 3). The organic phase was separated, washed with H₂O (50 mL $\times$ 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-*d*₆) 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

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 $\times$ 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

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 Na₂SO₄, 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).

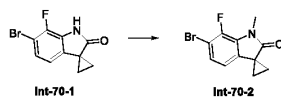
Step 6: int-53-7

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 × 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-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

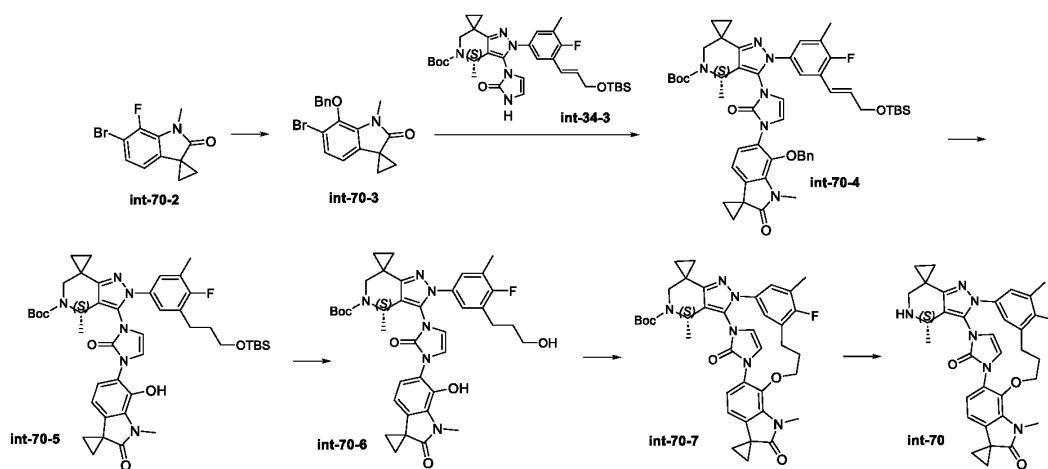
To a solution of **int-53-7** (1.00 g, 2.01 mmol) in *t*-BuOK in THF (20.06 mL, 1 M in THF) was added H₂O (0.04 mL, 2.01 mmol). The resulting mixture was stirred at 25 °C for 12 hrs. After completion, the reaction mixture was poured into water (50 mL), acidified by HCl (2 N) to adjusted pH ~1 and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered, concentrated and purified by SFC (ChiralCel OJ, 250*30 mm I.D., 10 μm; Mobile Phase [A%: CO₂; 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 am: Synthesis of int-70-2



To a solution of **int-70-1** (1.07 g, 4.18 mmol) in DMF (5 mL) were added Cs_2CO_3 (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 $\times$ 3). The combined organic layers were washed with water (20 mL $\times$ 2), followed by brine (20 mL), dried over Na_2SO_4 , 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, $\text{DMSO}-d_6$) 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).

Example an: Synthesis of int-70



Step 1: int-70-3

To a solution of **int-70-2** (5.00 g, 18.51 mmol) and phenylmethanol (2.40 g, 22.21 mmol) in DMAc (50 mL) was added $t\text{BuOK}$ (3.12 g, 27.80 mmol) at 0 °C in portions. The resulting mixture was stirred at 25 °C for 3.5 hrs. After completion, the reaction mixture was poured into water (200 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layers were washed with water (200 mL $\times$ 2), followed by brine (100 mL), dried over Na_2SO_4 , filtered, concentrated and purified by column chromatography to afford **int-70-3** (3.80 g, 10.61 mmol, 57.3% yield). LC-MS (ESI⁺): m/z 358.1 ($\text{M}+\text{H}$)⁺. ^1H NMR (500 MHz, $\text{DMSO}-d_6$)

Step 2: int-70-4

To a solution of **int-34-3** (450.0 mg, 0.72 mmol) in NMP (5 mL) were added **int-70-3** (517 mg, 1.443 mmol), CuI (137.0 mg, 0.72 mmol), (1*R*,2*R*)- N^1,N^2 -dimethylcyclohexane-1,2-diamine (51.0 mg, 0.36 mmol) and K_2CO_3 (299.0 mg, 2.16 mmol). The resulting mixture was degassed and purged with N_2 for 3 times and stirred at 130 °C for 6 hrs under N_2 . 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 Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-70-4** (170.0 mg, 0.19 mmol, 26.2% yield). LC-MS (ESI⁺): m/z 923.4 (M+Na)⁺

Step 3: int-70-5

To a solution of **int-70-4** (170.0 mg, 0.19 mmol) in MeOH (3 mL) was added Pd/C (34.0 mg, 20% w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 40 °C for 2 hrs under H₂ atmosphere (15 psi). After completion, the reaction mixture was filtered through a Celite pad and resined with MeOH (5 mL $\times$ 4). The filtrate was concentrated under reduced pressure to afford **int-70-5** (110.0 mg, 0.14 mmol, 71.7% yield). LC-MS (ESI⁺): m/z 813.4 (M+H)⁺

Step 4: int-70-6

To a solution of **int-70-5** (110.0 mg, 0.14 mmol) in THF (1 mL) was added TBAF (177.0 mg, 0.68 mmol). The resulting mixture was stirred at 30 °C for 1 hr. After completion, the mixture was poured into water (20 mL) and extracted with EtOAc (20 $\times$ 3 mL). The combined organic layers were washed with water (20 mL $\times$ 2), followed by brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-70-6** (50.0 mg, 0.07 mmol, 52.9% yield). LC-MS (ESI⁺): m/z 699.4 (M+H)⁺

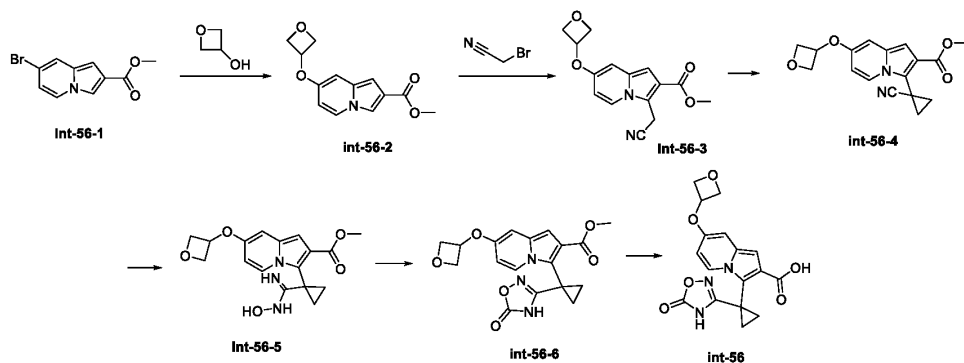
Step 5: int-70-7

To a solution of **int-70-6** (40.0 mg, 0.06 mmol) in anhydrous toluene (1.5 mL) was added 2-(tributylphosphoranylidene)acetonitrile (55.0 mg, 0.23 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 90 °C for 2 hrs. After cooling to room temperature, the mixture was poured into water (20 mL) and extracted with EtOAc (20 mL $\times$ 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 **int-70-7** (30.0 mg, 0.044 mmol, 77.0% yield). LC-MS (ESI⁺): m/z 681.2 (M+H)⁺

Step 6: int-70

To a solution of **int-70-7** (30 mg, 0.04 mmol) in DCM (1 mL) was added TFA (0.2 mL). The resulting mixture was stirred at 25 °C for 1 hr. After completion, the mixture was concentrated under reduced pressure to afford **int-70** (30.0 mg, crude), which was used directly for the next step without purification. LC-MS (ESI⁺): m/z 581.3 (M+H)⁺

Example aq: Synthesis of int-56



Step 1: int-56-2

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), Cs_2CO_3 (3.85 g, 11.81 mmol), CuI (0.15 g, 0.79 mmol) and (1*R*,2*R*)- N^1,N^2 -dimethylcyclohexane-1,2-diamine (0.22 g, 1.57 mmol). The resulting mixture was degassed and purged with N_2 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 Na_2SO_4 , 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

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 $\times$ 3) and dissolved in 20 mL DCM. The organic layer was dried over Na_2SO_4 , 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

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 $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , 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-*d*₆) 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-56-5

To 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 $\times$ 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-*d*₆) 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).

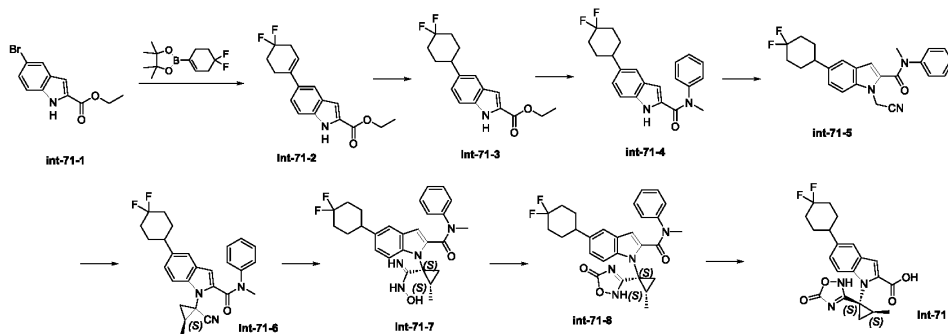
Step 5: int-56-6

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 Na₂SO₄, 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

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~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 Na₂SO₄, 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 as: Synthesis of int-71



Step 1: int-71-2

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-*d*₆) 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

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

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) dropwised at 0 °C under N₂ atomsphere 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 chromatography 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-*d*₆) 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

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

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

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-*d*₆) 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

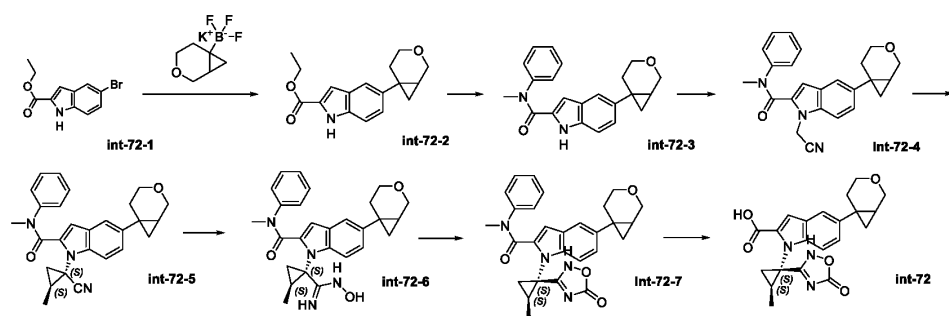
To a solution of **int-71-7** (930.0 mg, 1.94 mmol) and DBU (0.88 mL, 5.81 mmol) in dioxane (9.3 mL) were added CDI (941.0 mg, 5.81 mmol). The resulting mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction mixture was poured into water (50 mL), acidified by diluted 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 $\times$ 2), followed by brine (50 mL), dried over Na_2SO_4 , 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 ($\text{M}+\text{H}$)⁺.

Step 8: int-71

To a solution in **int-71-8** (730mg, 1.44 mmol) in $t\text{BuOK}$ 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 $\times$ 2). The aqueous layer was acidified by diluted HCl (3 M aqueous) to pH=2 and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , 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 ($\text{M}-\text{H}$)⁻. ¹H NMR (400 MHz, $\text{DMSO}-d_6$) 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

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), Cs_2CO_3 (9.48 g, 29.1 mmol) and water (2.60 mL). The resulting mixture was degassed and purged with N_2 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 $\times$ 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-72-2** (1.38 g, 4.35 mmol, 44.9% yield). LC-MS (ESI+): m/z 284.0 ($\text{M}-\text{H}$)⁻. ¹H NMR (400 MHz, $\text{DMSO}-d_6$) 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

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

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

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

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-*d*₆) 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).

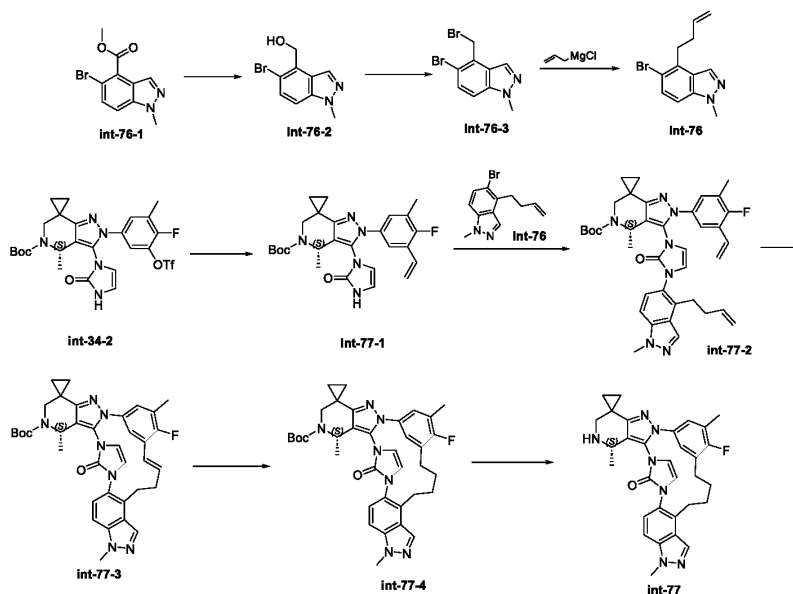
Step 6: int-72-7

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

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-*d*₆) 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 av: Synthesis of int-76 & int-77

**Step 1: int-76-2**

To a solution of **int-76-1** (1.00 g, 3.72 mmol) in EtOH (10 mL) was added NaBH₄ (422.0 mg, 11.15 mmol). The resulting mixture was stirred at 60 °C for 4 hrs. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (50 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-76-2** (550.0 mg, 2.28 mmol, 61.4% yield). LC-MS (ESI⁺): m/z 241.2 (M+H)⁺.

Step 2: int-76-3

To a solution of **int-76-2** (500.0 mg, 2.07 mmol) in DCM (10 mL) was added carbon tetrabromide (894.0 mg, 2.70 mmol) and triphenylphosphane (707.0 mg, 2.70 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 25 °C for 2 hrs. After completion, the reaction mixture concentrated and purified by column to afford **int-76-3** (400.0 mg, 2.07 mmol, 63.4% yield). LC-MS (ESI⁺): m/z 303.0 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.70 – 7.56 (m, 2H), 5.07 (s, 2H), 4.08 (s, 3H).

Step 3: int-76

To a solution of **int-76-3** (400.0 mg, 1.32 mmol) in THF (8 mL) was added allylmagnesium bromide (1.97 mL, 1 M in THF) dropwise at -60 °C under N₂. The resulting mixture was stirred at -60 °C for 1 hr. 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 (100 mL), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-76** (200.0 mg, 0.75 mmol, 57.3% yield). LC-MS (ESI⁺): m/z 265.0 (M+H)⁺. ¹H NMR (400 MHz,

DMSO-*d*₆) δ 8.17 (s, 1H), 7.56 – 7.40 (m, 2H), 5.98 – 5.83 (m, 1H), 5.08 – 4.99 (m, 1H), 4.99 – 4.91 (m, 1H), 4.03 (s, 3H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.42 – 2.30 (m, 2H).

Step 1: int-77-1

To a solution of **int-34-2** (2.00 g, 3.32 mmol) in dioxane (30 mL) and water (6 mL) were added potassium trifluoro(vinyl)borate (1.34 g, 9.97 mmol), Cs₂CO₃ (3.25 g, 9.97 mmol) and 1,1'-Bis (di-*t*-butylphosphino)ferrocene palladium dichloride (227.0 mg, 0.33 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 100 °C for 2 hrs. 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), followed by brine (100 mL), dried over Na₂SO₄, filtered, concentrated and purified by column chromatography to afford **int-77-1** (1.2.0 g, 1.25 mmol, 37.6% yield). LC-MS (ESI+): *m/z* 480.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 7.37 – 7.29 (m, 1H), 7.24 – 7.17 (m, 1H), 6.87 – 6.74 (m, 1H), 6.68 – 6.54 (m, 2H), 5.81 – 5.71 (m, 1H), 5.44 (d, *J* = 12.0 Hz, 1H), 5.28 – 5.05 (m, 1H), 3.63 – 3.42 (m, 2H), 2.23 (s, 3H), 1.42 (s, 9H), 1.37 – 1.30 (m, 1H), 1.23 – 1.15 (m, 3H), 1.04 – 0.91 (m, 2H), 0.90 – 0.76 (m, 1H).

Step 2: int-77-2

To a mixture of **int-77-1** (300.0 mg, 0.63 mmol) and **int-76** (199.0 mg, 0.75 mmol) in NMP (3 mL) was added (1*R*,2*R*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (89.0 mg, 0.63 mmol), copper(I) iodide (119.0 mg, 0.63 mmol) and K₂CO₃ (259.0 mg, 1.88 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 130 °C for 4 hrs. After cooling to room temperature, the reaction mixture was poured into water (30 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-77-2** (90.0 mg, 0.14 mmol, 21.7% yield). LC-MS (ESI+): *m/z* 664.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.22 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.38 (m, 1H), 7.30 – 7.20 (m, 1H), 7.14 – 6.96 (m, 2H), 6.95 – 6.89 (m, 1H), 6.88 – 6.77 (m, 1H), 5.83 (d, *J* = 16.0 Hz, 1H), 5.75 – 5.55 (m, 1H), 5.47 (d, *J* = 12.0 Hz, 1H), 5.40 – 5.10 (m, 1H), 5.00 - 4.72 (t, *J* = 13.1 Hz, 2H), 4.05 (s, 3H), 3.70 – 3.46 (m, 2H), 2.87 – 2.72 (m, 2H), 2.29 – 2.13 (m, 5H), 1.43 (s, 9H), 1.38 – 1.33 (m, 1H), 1.28 (d, *J* = 8.0 Hz, 3H), 1.09 - 0.91 (m, 2H), 0.90 - 0.80 (m, 1H).

Step 3: int-77-3

To a solution of **int-77-2** (140.0 mg, 0.211 mmol) in DCE (280 mL) was added Hoveyda-Grubbs 2nd reagent (52.0 mg, 0.084 mmol). The resulting mixture was degassed and purged with N₂ for 3 times and stirred at 80 °C for 12 hrs. After cooling to room temperature, the reaction was concentrated and purified by pre-TLC to afford **int-77-3** (120.0 mg, 0.19 mmol, 89.0% yield). LC-MS (ESI+): *m/z* 636.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 – 8.37 (m, 1H), 7.67 – 7.57 (m, 1H), 7.50 – 7.31 (m, 2H), 7.01 – 6.69 (m, 3H), 6.49 (d, *J* = 12.0 Hz, 1H), 6.18 – 6.02 (m, 1H), 5.38 – 5.13 (m, 1H), 4.12 – 4.03 (m,

3H), 3.69 – 3.45 (m, 2H), 3.21 – 3.13 (m, 1H), 3.11 – 2.90 (m, 1H), 2.60 – 2.56 (m, 1H), 2.32 – 2.21 (m, 3H), 2.10 – 1.91 (m, 1H), 1.46 – 1.41 (m, 9H), 1.32 – 1.28 (m, 3H), 1.01 – 0.95 (m, 2H), 0.91 – 0.85 (m, 2H).

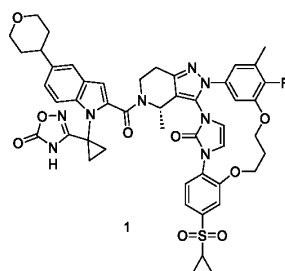
Step 4: int-77-4

To a solution of **int-77-3** (120.0 mg, 0.19 mmol) in MeOH (5 mL) was added Pd/C (12.0 mg, 10% w/w). The resulting mixture was degassed and purged with H₂ for 3 times and stirred at 20 °C for 2 hrs under H₂ atmosphere (15 psi). After completion, the reaction mixture was filtered through a Celite pad and rinsed with MeOH (10 mL × 3). The filtrate was concentrated under reduced pressure to afford **int-77-4** (120 mg, crude), which was used directly for the next step without purification. LC-MS (ESI+): m/z 638.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 – 8.32 (m, 1H), 7.64 – 7.58 (m, 1H), 7.45 – 7.30 (m, 2H), 7.17 – 6.96 (m, 1H), 6.95 – 6.79 (m, 2H), 5.55 – 5.19 (m, 1H), 4.14 – 4.10 (m, 3H), 3.74 – 3.55 (m, 2H), 3.10 – 2.94 (m, 2H), 2.93 – 2.81 (m, 2H), 2.33 – 2.29 (m, 3H), 1.95 – 1.80 (m, 2H), 1.53 – 1.49 (m, 9H), 1.46 – 1.42 (m, 2H), 1.39 – 1.32 (m, 3H), 1.11 – 1.02 (m, 2H), 1.00 – 0.83 (m, 2H).

Step 5: int-77

A mixture of **int-77-4** (100.0 mg, 0.157 mmol) in HCl solution (2 mL, 4 M in dioxane) was stirred at 20 °C for 1 hr. After completion, the reaction solution was concentrated to give a residue, which was diluted with DCM (20 mL) and washed with saturated NaHCO₃ (aq., 20 mL). The organic layer was washed with brine 10 mL, dried over Na₂SO₄, filtered, concentrated and purified by pre-TLC (SiO₂, DCM/MeOH=10/1, v/v) to afford **int-77** (80.0 mg, 0.15 mmol, 95.0% yield). LC-MS (ESI+): m/z 538.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 – 8.24 (m, 1H), 7.59 – 7.49 (m, 1H), 7.34 – 7.15 (m, 2H), 6.93 (s, 1H), 6.85 – 6.69 (m, 2H), 4.12 – 4.00 (m, 4H), 3.13 – 2.91 (m, 2H), 2.89 – 2.74 (m, 2H), 2.74 – 2.67 (m, 2H), 2.28 – 2.20 (m, 3H), 1.89 – 1.68 (m, 2H), 1.30 – 1.19 (m, 6H), 0.89 – 0.79 (m, 3H).

Example 1.1: Synthesis of Compound 1



[0287] 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 μ mol, 21.5% yield). LCMS: 931.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) 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).

[0288] The Compounds in Table a below were prepared in accordance with the synthetic sequence in **Compound 1** using the corresponding starting materials.

TABLE a

Compound No.	Starting material	MW $[M+H]^+$ & ^1H NMR
2	int-1 & int-3	LCMS: 917.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.61 (s, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.31 - 7.13 (m, 2H), 7.08 (dd, J = 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, J = 12.0, 8.4, 4.1 Hz, 2H), 3.49 (td, J = 12.0, 4.7 Hz, 2H), 2.99 - 2.79 (m, 5H), 2.28 (d, J = 4.0 Hz, 3H), 1.84 - 1.68 (m, 6H), 1.45 (d, J = 8.0 Hz, 3H), 1.19 (dh, J = 12.0, 4.8 Hz, 2H), 1.13 - 1.05 (m, 2H).
3	int-1 & int-4	LCMS: 915.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) 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, J = 16.9 Hz, 2H), 1.84 - 1.66 (m, 5H), 1.63 - 1.54 (m, 2H), 1.38 (d, J = 8.0 Hz, 3H), 1.22 - 1.66 (s, 2H), 1.12 - 1.08 (m, 2H).
4	int-1 & int-6	LCMS: 929.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) 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, J = 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).
19-1 & 21	int-7-P2 & int-20	Prep-HPLC(Column: YMC Triart C18, 20 *250mm, 5 μ m; Mobile Phase A: 0.1% FA, B: ACN; 15mL/min; gradient: 55-75%) was used to separate the two isomers. 19-1 : retention time: 17 min. LCMS: 895.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) δ 8.42 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.29 - 7.10 (m, 4H), 6.69 (d, J = 8.0 Hz, 2H), 6.40 (s, 2H), 5.70 (s, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 8.0 Hz, 1H), 4.59 (t, J = 16.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.04 (s, 4H), 3.79 - 3.66 (m, 2H), 3.41 (s, 1H), 2.96 - 2.89 (m, 1H), 2.71 (s, 2H), 2.27 (s, 3H), 1.77 - 1.68 (m, 2H), 1.63 (s, 2H), 1.58 - 1.52 (m, 1H), 1.51 - 1.48 (m, 1H), 1.40 (s, 2H), 1.28 - 1.24 (m, 6H), 1.20 (s, 3H). 21 : retention time: 20 min. LCMS: 895.4 $(M+H)^+$. ^1H NMR (400 MHz, DMSO- d_6 , 80 $^\circ\text{C}$) δ 8.43 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.50 - 7.37 (m, 1H), 7.35 - 7.21 (m, 2H), 7.12 ((d, J = 4.0 Hz, 1H), 7.06 (d, J = 4.0 Hz, 1H), 6.77 - 6.57 (m, 2H), 6.56 - 6.46 (m, 1H), 6.39 (s, 1H), 5.87 - 5.52 (m, 1H), 4.95 - 4.89 (m, 1H), 4.77 (t, J = 8.0 Hz, 1H), 4.62 - 4.55 (m, 1H), 4.46 - 4.40 (m, 1H), 4.17 - 3.97 (m, 4H), 3.70 (d, J = 8.0 Hz, 2H), 3.39 - 3.32 (m, 1H), 2.93 - 2.87 (m,

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		1H), 2.75 - 2.61 (m, 2H), 2.28 (s, 3H), 1.75 - 1.66 (m, 1H), 1.65 - 1.56 (m, 4H), 1.47 - 1.37 (m, 4H), 1.30 - 1.22 (m, 6H), 1.19 (s, 3H).
20 - 1&22	int-7-P2 & int-21	Prep-HPLC(Column: YMC Triart C18, 20 *250mm, 5μm; Mobile Phase A: 0.1% FA, B: ACN; 15mL/min; gradient: 50-70%) was used to separate the two isomers. 20-1: retention time: 15 min. LCMS: 881.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.88 (brs, 1H), 8.42 (s, 1H), 8.12 (d, <i>J</i> = 4.0 Hz, 1H), 7.49 - 7.12 (m, 6H), 6.70 (d, <i>J</i> = 4.0 Hz, 2H), 6.62 - 6.20 (m, 2H), 5.82 - 4.96 (m, 1H), 4.93 - 4.73 (m, 2H), 4.69 - 4.57 (m, 1H), 4.52 - 4.38 (m, 1H), 4.25 - 3.92 (m, 4H), 3.79 - 3.62 (m, 2H), 3.50 - 3.35 (m, 1H), 2.97 - 2.88 (m, 1H), 2.87 - 2.64 (m, 2H), 1.79 - 1.59 (m, 4H), 1.58 - 1.51 (m, 1H), 1.50 - 1.44 (m, 1H), 1.43 - 1.34 (m, 3H), 1.33 - 1.21 (m, 5H), 1.20 (s, 3H). 22: retention time: 18 min. LCMS: 881.3 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.82 (brs, 1H), 8.43 (s, 1H), 8.08 (d, <i>J</i> = 8.0 Hz, 1H), 7.53 - 7.08 (m, 7H), 6.67 (d, <i>J</i> = 8.0 Hz, 1H), 6.64 - 6.50 (m, 1H), 6.40 (s, 1H), 5.81 - 5.57 (m, 1H), 4.99 - 4.89 (m, 1H), 4.80 (t, <i>J</i> = 8.0 Hz, 1H), 4.67 - 4.58 (m, 1H), 4.50 - 4.41 (m, 1H), 4.15 - 3.98 (m, 4H), 3.78 - 3.64 (m, 2H), 3.40 - 3.32 (m, 1H), 2.97 - 2.67 (m, 3H), 1.77 - 1.56 (m, 4H), 1.56 - 0.99 (m, 13H).
23	int-18 & int-24	LCMS: 905.0 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.65 (brs, 1H), 8.29 (s, 1H), 7.63 - 7.48 (m, 2H), 7.45 - 7.36 (m, 1H), 7.34 - 7.19 (m, 2H), 6.98 - 6.80 (m, 3H), 6.76 - 6.54 (m, 2H), 5.77 - 5.56 (m, 1H), 4.48 - 4.17 (m, 3H), 4.06 (s, 3H), 4.02 - 3.91 (m, 2H), 3.68 - 3.58 (m, 1H), 3.51 - 3.45 (m, 2H), 2.99 - 2.82 (m, 3H), 2.55 - 2.51 (m, 2H), 2.16 - 2.06 (m, 1H), 1.87 - 1.59 (m, 9H), 1.57 - 1.38 (m, 3H), 1.25 - 1.12 (m, 3H), 1.08 - 0.99 (m, 2H), 0.82 - 0.70 (m, 2H).
24 & 25	int-7-P2 & int-22	Prep-HPLC (Column: Welch Triart C18 250 *21.2 mm *10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 65%-85%) was used to separate the two isomers. 24: retention time: 18 min. LCMS: 893.4 (M+H)⁺. ¹HNMR (500 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.87 (brs, 1H), 8.27 (s, 1H), 8.09 (d, <i>J</i> = 4.0 Hz, 1H), 7.60 - 7.43 (m, 1H), 7.36 - 7.12 (m, 3H), 7.05 - 6.57 (m, 4H), 6.39 (s, 1H), 5.82 - 4.75 (m, 1H), 4.28 (s, 2H), 4.20 - 4.32 (m, 4H), 3.77 - 3.66 (m, 2H), 3.50 - 3.28 (s, 1H), 2.92 (t, <i>J</i> = 8.0 Hz, 2H), 2.75 - 2.68 (m, 1H), 2.26 (s, 3H), 2.07 - 1.94 (m, 1H), 1.80 - 1.66 (m, 4H), 1.65 - 1.59 (m, 2H), 1.58 - 1.52 (m, 1H), 1.51 - 1.43 (m, 2H), 1.41 - 1.36 (m, 2H), 1.28 - 1.22 (m, 6H), 1.19 (s, 3H). 25: retention time: 21 min. LCMS: 893.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 8.30 (s, 1H), 8.10 (d, <i>J</i> = 8.0 Hz, 1H), 7.65 - 7.50 (m, 1H), 7.46 - 7.09 (m, 3H), 6.94 - 6.53 (m, 4H), 6.41 (s, 1H), 5.80 - 5.60 (m, 1H), 4.44 - 4.31 (m, 1H), 4.30 - 4.20 (m, 1H), 4.17 - 4.00 (m, 4H), 3.79 - 3.60 (m, 3H), 3.42 - 3.37 (m, 1H), 3.02 - 2.91 (m, 2H), 2.81 - 2.65 (m, 2H), 2.30 (s, 3H), 1.83 - 1.58 (m, 6H), 1.57 - 1.49 (m, 1H), 1.48 - 1.41 (m, 3H), 1.40 - 1.33 (m, 1H), 1.32 - 1.23 (m, 5H), 1.20 (s, 3H).
26 & 27	int-7-P2 & int-23	Prep-HPLC (column: Welch Triart C18 250*2.12 mm *10μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-80%) was used to separate the two isomers. 26: retention time: 17 min. LCMS: 893.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.86 (brs, 1H), 8.18 (s, 1H), 8.12 (d, <i>J</i> = 8.0 Hz, 1H), 7.55 - 7.19 (m, 4H), 7.11 - 6.80 (m, 2H), 6.79 - 6.46 (m, 2H), 6.41 (s, 1H), 5.79 - 4.93 (m, 1H), 4.16 - 3.95 (m, 4H), 3.86 - 3.77 (m, 1H), 3.76 - 3.66 (m, 2H), 3.51 - 3.27 (m, 1H), 2.98 - 2.89 (m, 1H), 2.87 - 2.67 (m, 4H), 2.27 (s, 3H), 2.24 - 2.14 (m, 1H), 2.12 - 1.98 (m, 1H), 1.78 - 1.61 (m, 4H), 1.60 - 1.53 (m, 1H), 1.52 - 1.43 (m, 2H), 1.41 - 1.32 (m, 3H), 1.30 - 1.22 (m, 5H), 1.19 (s, 3H).

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		27 : retention time: 19 min. LCMS: 893.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.92 (brs, 1H), 8.20 (s, 1H), 8.07 (d, <i>J</i> = 8.0 Hz, 1H), 7.51 - 7.14 (m, 4H), 6.98 (dd, <i>J</i> = 8.0, 4.0 Hz, 1H), 6.85 - 6.56 (m, 3H), 6.38 (s, 1H), 5.67 (brs, 1H), 4.11 - 4.01 (m, 4H), 3.91 - 3.80 (m, 1H), 3.76 - 3.63 (m, 2H), 3.41 - 3.29 (m, 1H), 2.97 - 2.61 (m, 5H), 2.30 - 2.17 (m, 4H), 2.07 - 1.94 (m, 1H), 1.77 - 1.66 (m, 2H), 1.65 - 1.57 (m, 2H), 1.56 - 1.51 (m, 1H), 1.49 - 1.41 (m, 4H), 1.27 - 1.24 (m, 6H), 1.18 (s, 3H).
28	Int-17 & int-77	LCMS: 931.3 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.79 (brs, 1H), 8.23 (s, 1H), 7.67 - 7.45 (m, 2H), 7.44 - 7.19 (m, 4H), 7.06 - 6.54 (m, 4H), 6.26 - 5.09 (m, 1H), 4.17 - 3.92 (m, 4H), 3.85 - 3.58 (m, 3H), 3.08 - 2.93 (m, 2H), 2.92 - 2.65 (m, 3H), 2.29 - 2.23 (m, 3H), 1.94 - 1.84 (m, 1H), 1.82 - 1.67 (m, 5H), 1.66 - 1.46 (m, 6H), 1.45 - 1.33 (m, 3H), 1.30 - 1.22 (m, 6H), 1.21 - 1.14 (m, 5H), 0.99 - 0.88 (m, 1H).
29 & 30	int-7-P2 & int-25	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 65%-85%) was used to separate the two isomers. 29 : retention time: 17 min. LCMS: 893.4 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.94 (brs, 1H), 8.17 - 8.01 (m, 2H), 7.88 - 7.63 (m, 1H), 7.33 - 7.25 (m, 1H), 7.12 - 6.87 (m, 2H), 6.87 - 6.50 (m, 3H), 6.47 - 6.29 (m, 2H), 5.83 - 4.74 (m, 1H), 4.29 (s, 3H), 4.21 - 3.87 (m, 2H), 3.85 - 3.76 (m, 1H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.61 - 3.50 (m, 1H), 3.45 - 3.34 (m, 1H), 3.02 - 2.93 (m, 2H), 2.80 - 2.66 (m, 2H), 2.35 - 2.25 (m, 4H), 1.88 - 1.77 (m, 1H), 1.76 - 1.70 (m, 2H), 1.64 (d, <i>J</i> = 9.2 Hz, 2H), 1.60 - 1.53 (m, 1H), 1.52 - 1.48 (m, 1H), 1.47 - 1.42 (m, 2H), 1.30 - 1.24 (m, 6H), 1.21 (s, 3H). 30 : retention time: 20 min. LCMS: 893.4 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.92 (brs, 1H), 8.17 - 8.02 (m, 2H), 7.88 - 7.62 (m, 1H), 7.32 - 7.24 (m, 1H), 7.10 - 6.87 (m, 2H), 6.87 - 6.50 (m, 3H), 6.48 - 6.29 (m, 2H), 5.79 - 4.76 (m, 1H), 4.29 (s, 3H), 4.21 - 3.90 (m, 2H), 3.84 - 3.76 (m, 1H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.62 - 3.48 (m, 1H), 3.45 - 3.32 (m, 1H), 3.03 - 2.92 (m, 2H), 2.80 - 2.65 (m, 2H), 2.35 - 2.22 (m, 4H), 1.88 - 1.78 (m, 1H), 1.77 - 1.61 (m, 4H), 1.60 - 1.54 (m, 1H), 1.52 - 1.48 (m, 1H), 1.47 - 1.42 (m, 2H), 1.31 - 1.23 (m, 6H), 1.21 (s, 3H).
31	int-18 & int-22	LCMS: 879.3 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.64 (brs, 1H), 8.29 (s, 1H), 7.63 - 7.47 (m, 2H), 7.46 - 7.36 (m, 1H), 7.35 - 7.18 (m, 3H), 7.06 - 6.59 (m, 4H), 5.80 - 5.46 (m, 1H), 4.53 - 4.19 (m, 3H), 4.06 (s, 3H), 4.01 - 3.92 (m, 2H), 3.77 - 3.55 (m, 1H), 3.51 - 3.43 (m, 2H), 3.01 - 2.80 (m, 3H), 2.31 - 2.25 (m, 3H), 1.87 - 1.40 (m, 13H), 1.31 - 1.10 (m, 4H).
33	int-17 & int-22	LCMS: 907.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.65 (brs, 1H), 8.29 (s, 1H), 7.66 - 7.48 (m, 2H), 7.45 - 7.37 (m, 1H), 7.35 - 7.18 (m, 3H), 7.05 - 6.60 (m, 4H), 5.80 - 5.45 (m, 1H), 4.57 - 4.15 (m, 3H), 4.06 (s, 3H), 3.80 - 3.37 (m, 3H), 3.11 - 2.97 (m, 3H), 2.96 - 2.85 (m, 2H), 2.32 - 2.27 (m, 3H), 1.80 - 1.65 (m, 6H), 1.64 - 1.59 (m, 1H), 1.58 - 1.46 (m, 4H), 1.33 - 1.23 (m, 6H), 1.20 (s, 3H), 1.19 - 1.18 (m, 1H).
34	int-1 & int-22	LCMS: 865.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 12.09 (brs, 1H), 8.33 (s, 1H), 7.65 - 7.44 (m, 3H), 7.38 - 7.17 (m, 3H), 7.02 (s, 1H), 6.92 - 6.48 (m, 3H), 5.68 - 4.71 (m, 1H), 4.39 - 4.24 (m, 2H), 4.07 (s, 3H), 3.98 (d, <i>J</i> = 8.0 Hz, 2H), 3.67 - 3.53 (m, 1H), 3.52 - 3.44 (m, 3H), 3.21 - 3.07 (m, 2H), 2.94 - 2.78 (m, 3H), 2.28 (s, 3H), 1.91 - 1.54 (m, 10H), 1.41 (s, 3H).
37	int-17 & int-26	LCMS: 853.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (s, 1H), 7.56 - 7.47 (m, 1H), 7.46 - 7.28 (m, 5H), 7.27 - 7.18 (m, 2H), 6.99 - 6.55 (m, 4H), 5.77 - 5.49 (m, 1H), 4.51 - 4.29 (m, 1H), 4.29 - 4.07 (m, 2H), 3.77 - 3.68 (m, 2H), 3.67 - 3.47 (m, 1H), 3.08 - 2.96 (m, 2H), 2.96 - 2.82 (m, 2H), 2.65 -

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		2.54 (m, 1H), 2.30 – 2.26 (m, 3H), 1.89 – 1.75 (m, 1H), 1.73 – 1.64 (m, 4H), 1.63 – 1.58 (m, 2H), 1.57 – 1.54 (m, 1H), 1.53 – 1.44 (m, 3H), 1.33 – 1.22 (m, 5H), 1.20 – 1.10 (m, 5H).
42	Int-1 & int-40	LCMS: 863.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.86 (brs, 1H), 8.17 (s, 1H), 7.69 – 7.59 (m, 1H), 7.51 – 7.44 (m, 2H), 7.39 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (d, <i>J</i> = 8.0 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.93 – 6.67 (m, 4H), 6.57 – 6.45 (m, 1H), 6.21 – 6.05 (m, 1H), 5.83 – 5.18 (m, 1H), 5.02 (d, <i>J</i> = 16.0 Hz, 1H), 4.86 (d, <i>J</i> = 16.0 Hz, 1H), 4.52 – 4.21 (m, 1H), 4.07 (s, 3H), 3.97 (d, <i>J</i> = 8.0 Hz, 2H), 3.52 – 3.44 (m, 3H), 2.88 – 2.79 (m, 3H), 2.27 (s, 3H), 1.78 – 1.72 (m, 6H), 1.51 – 1.45 (m, 1H), 1.41 – 1.35 (m, 3H), 1.20 – 1.17 (m, 1H).
43	int-18 & int-27	LCMS: 879.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.52 (brs, 1H), 7.84 (brs, 1H), 7.66 (brs, 1H), 7.41 (s, 1H), 7.34 – 7.23 (m, 2H), 7.20 – 7.10 (m, 2H), 7.05 – 6.86 (m, 1H), 6.85 – 6.71 (s, 1H), 6.66 – 6.24 (m, 2H), 5.65 – 5.28 (m, 1H), 4.40 – 4.12 (m, 1H), 3.98 – 3.91 (m, 2H), 3.89 (s, 3H), 3.84 (d, <i>J</i> = 8.0 Hz, 2H), 3.61 – 3.43 (m, 1H), 3.38 – 3.31 (m, 2H), 2.77 – 2.71 (m, 2H), 2.64 – 2.53 (m, 1H), 2.16 (s, 3H), 2.14 – 2.06 (m, 1H), 1.88 – 1.80 (m, 1H), 1.67 – 1.55 (m, 6H), 1.54 – 1.25 (m, 5H), 1.22 – 1.14 (m, 1H), 1.10 – 0.90 (m, 3H).
44	int-18 & int-23	LCMS: 879.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.50 (brs, 1H), 8.22 – 8.16 (m, 1H), 7.53 (brs, 1H), 7.47 – 7.36 (m, 3H), 7.35 – 7.29 (m, 1H), 7.28 – 7.20 (m, 1H), 7.08 – 6.97 (m, 1H), 6.94 – 6.62 (m, 3H), 5.73 – 5.56 (m, 1H), 4.47 – 4.23 (m, 1H), 4.10 – 4.03 (m, 4H), 3.97 (d, <i>J</i> = 8.0 Hz, 2H), 3.86 – 3.79 (m, 1H), 3.64 – 3.59 (m, 1H), 3.51 – 3.44 (m, 2H), 2.90 – 2.78 (m, 4H), 2.53 – 2.51 (m, 1H), 2.28 (s, 3H), 2.24 – 2.15 (m, 1H), 2.08 – 1.95 (m, 1H), 1.81 – 1.58 (m, 7H), 1.55 – 1.39 (m, 3H), 1.23 – 1.08 (m, 3H).
45	int-17 & int-23	LCMS: 907.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.20 (d, <i>J</i> = 4.0 Hz, 1H), 7.52 (brs, 1H), 7.47 – 7.37 (m, 3H), 7.36 – 7.28 (m, 1H), 7.27 – 7.21 (m, 1H), 7.08 – 6.96 (m, 1H), 6.96 – 6.64 (m, 3H), 5.72 – 5.57 (m, 1H), 4.43 – 4.30 (m, 1H), 4.10 – 4.02 (m, 4H), 3.87 – 3.82 (m, 1H), 3.74 – 3.71 (m, 2H), 3.06 – 3.02 (m, 1H), 2.93 – 2.78 (m, 4H), 2.54 – 2.52 (m, 1H), 2.29 (s, 3H), 2.26 – 2.17 (m, 1H), 2.10 – 1.97 (m, 1H), 1.88 – 1.77 (m, 1H), 1.76 – 1.60 (m, 5H), 1.58 – 1.43 (m, 4H), 1.29 – 1.16 (m, 9H).
46	int-1 & int-23	LCMS: 865.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.19 (s, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 7.25 – 7.20 (m, 1H), 7.08 – 6.98 (m, 1H), 6.92 – 6.57 (m, 3H), 5.75 – 5.40 (m, 1H), 4.59 – 4.28 (m, 1H), 4.10 – 4.01 (m, 4H), 4.01 – 3.95 (m, 2H), 3.86 – 3.77 (m, 1H), 3.52 – 3.45 (m, 3H), 2.92 – 2.79 (m, 5H), 2.28 (s, 3H), 2.25 – 2.17 (m, 1H), 2.08 – 1.99 (m, 1H), 1.81 – 1.71 (m, 6H), 1.69 – 1.45 (m, 2H), 1.44 – 1.36 (m, 3H).
48&49	int-19 & int-23	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 50%-70%) was used to separate the two isomers. 48: retention time: 17 min. LCMS: 865.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.95 (brs, 1H), 8.23 – 8.11 (m, 2H), 7.48 – 7.26 (m, 4H), 7.10 – 6.48 (m, 4H), 6.47 – 6.41 (m, 1H), 5.94 – 5.47 (m, 1H), 5.18 – 4.69 (m, 1H), 4.23 – 4.01 (m, 5H), 4.00 – 3.94 (m, 2H), 3.82 (brs, 1H), 3.48 (t, <i>J</i> = 12.0 Hz, 2H), 2.88 – 2.71 (m, 5H), 2.27 (s, 3H), 2.24 – 2.14 (m, 1H), 2.11 – 1.97 (m, 1H), 1.84 – 1.60 (m, 6H), 1.49 – 1.24 (m, 5H). 49: retention time: 20 min. LCMS: 865.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.85 (brs, 1H), 8.23 (d, <i>J</i> = 8.0 Hz, 1H), 8.14 (brs, 1H), 7.57 – 7.20 (m, 4H), 7.01 (brs, 1H), 6.88 – 6.61 (m, 3H), 6.46 (s, 1H), 5.76 – 5.60 (m, 1H), 4.11 – 4.05 (m, 5H), 4.01 – 3.94 (m, 2H), 3.90 – 3.86 (m, 1H), 3.49 – 3.44 (m, 1H), 2.90 – 2.84 (m, 3H), 2.79 – 2.74 (m, 2H), 2.30 (s, 3H), 2.28 – 2.23 (m,

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		1H), 2.06 – 1.95 (m, 1H), 1.81 – 1.71 (m, 4H), 1.70 – 1.66 (m, 2H), 1.51 – 1.42 (m, 4H), 1.37 – 1.31 (s, 1H).
50&51	int-18 & int-28	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-80%) was used to separate the two isomers. 50: retention time: 17.5 min. LCMS: 865.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.58 (brs, 1H), 8.45 (s, 1H), 7.73 – 7.61 (m, 1H), 7.53 (s, 1H), 7.49 – 7.33 (m, 2H), 7.26 (d, <i>J</i> = 8.0 Hz, 1H), 7.14 (d, <i>J</i> = 8.0 Hz, 1H), 7.09 – 7.00 (m, 1H), 6.99 – 6.83 (m, 2H), 6.81 – 6.74 (m, 1H), 5.71 – 5.44 (s, 1H), 4.74 – 4.54 (m, 1H), 4.49 – 4.12 (m, 1H), 4.08 (s, 3H), 4.01 – 3.93 (m, 2H), 3.52 – 3.43 (m, 2H), 3.34 – 3.22 (m, 2H), 2.88 – 2.79 (m, 3H), 2.55 – 2.52 (m, 1H), 2.32 (s, 3H), 2.29 – 2.24 (m, 1H), 1.76 – 1.72 (m, 5H), 1.64 – 1.52 (m, 3H), 1.51 – 1.40 (m, 1H), 1.33 – 1.29 (m, 3H), 1.20 – 1.16 (m, 1H). 51: retention time: 20 min. LCMS: 865.4 (M+H)⁺. ¹HNMR (400 MHz, DMSO-<i>d</i>₆, 60 °C) δ 11.60 (brs, 1H), 8.45 (s, 1H), 7.71 – 7.62 (s, 1H), 7.60 – 7.46 (m, 2H), 7.41 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 (d, <i>J</i> = 8.0 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.11 – 7.05 (m, 1H), 6.97 – 6.86 (m, 1H), 6.81 – 6.67 (m, 2H), 5.73 – 5.58 (m, 1H), 4.71 – 4.59 (m, 1H), 4.48 – 4.10 (m, 1H), 4.08 (s, 3H), 3.97 (d, <i>J</i> = 8.0 Hz, 2H), 3.50 – 3.43 (m, 2H), 3.31 – 3.26 (m, 1H), 2.87 – 2.81 (m, 3H), 2.55 – 2.53 (m, 1H), 2.34 – 2.30 (m, 4H), 1.77 – 1.69 (m, 4H), 1.59 – 1.51 (m, 3H), 1.50 – 1.40 (m, 3H), 1.31 – 1.28 (m, 2H), 1.19 – 1.16 (m, 1H).
52	int-7-P2 & int-29	LCMS: 907.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.85 (brs, 1H), 8.27 – 8.19 (m, 1H), 8.12 (d, <i>J</i> = 8.0 Hz, 1H), 7.67 – 7.47 (m, 1H), 7.40 – 7.12 (m, 3H), 7.10 – 6.83 (m, 2H), 6.82 – 6.63 (m, 2H), 6.46 – 6.36 (m, 1H), 5.74 – 4.71 (m, 1H), 4.27 - 3.91 (m, 6H), 3.71 (d, <i>J</i> = 8.0 Hz, 2H), 3.50 – 3.22 (m, 1H), 2.97 – 2.88 (m, 2H), 2.81 – 2.67 (m, 3H), 2.34 - 2.29 (m, 3H), 1.75 – 1.61 (m, 8H), 1.52 - 1.43 (m, 2H), 1.42 – 1.37 (m, 2H), 1.28 – 1.24 (m, 6H), 1.19 (s, 3H).
54	Int-51 & int-77	LCMS: 917.4 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.93 (brs, 1H), 8.22 (s, 1H), 7.56 – 7.42 (m, 3H), 7.41 – 6.40 (m, 7H), 6.03 – 5.21 (m, 1H), 4.14 – 3.92 (m, 4H), 3.82 – 3.60 (m, 3H), 3.07 – 2.90 (m, 2H), 2.89 – 2.64 (m, 3H), 2.29 – 2.21 (m, 3H), 1.94 – 1.84 (m, 1H), 1.81 – 1.65 (m, 6H), 1.64 – 1.58 (m, 1H), 1.57 – 1.50 (m, 2H), 1.49 – 1.36 (m, 4H), 1.30 – 1.25 (m, 4H), 1.21 – 1.14 (m, 4H), 1.12 – 0.78 (m, 3H).
55	Int-1 & int-31	LCMS: 882.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.79 (brs, 1H), 7.54 – 7.40 (m, 3H), 7.39 – 7.28 (m, 2H), 7.25 – 7.16 (m, 2H), 7.10 - 6.73 (m, 3H), 6.72 – 6.62 (m, 1H), 5.76 – 5.28 (m, 1H), 4.54 - 4.31 (s, 1H), 4.28 – 4.11 (m, 2H), 4.01 - 3.93 (m, 2H), 3.57 – 3.43 (m, 3H), 3.02 - 2.92 (m, 7H), 2.91 – 2.87 (m, 1H), 2.86 – 2.79 (m, 2H), 2.69 – 2.60 (m, 1H), 2.27 (s, 3H), 1.96 – 1.50 (m, 10H), 1.48 – 1.36 (m, 3H).
56	int-17 & int-30	LCMS: 887.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.64 (brs, 1H), 7.58 - 7.48 (m, 2H), 7.46 – 7.32 (m, 3H), 7.30 – 7.19 (m, 2H), 7.09 - 6.53 (m, 4H), 5.70 – 4.34 (m, 1H), 4.21 (d, <i>J</i> = 8.0 Hz, 2H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.68 – 3.50 (m, 1H), 3.47 – 3.39 (m, 1H), 3.08 – 3.02 (m, 2H), 2.96 – 2.87 (m, 2H), 2.66 – 2.56 (m, 1H), 2.30 (s, 3H), 1.78 – 1.67 (m, 4H), 1.66 – 1.60 (m, 2H), 1.59 – 1.52 (m, 2H), 1.51 – 1.38 (m, 3H), 1.31 – 1.12 (m, 10H).
57	int-1 & int-39	LCMS: 882.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.95 (brs, 1H), 7.58 – 7.47 (m, 3H), 7.46 – 7.42 (m, 1H), 7.40 – 7.36 (m, 1H), 7.26 – 7.20 (m, 2H), 7.15 – 7.07 (m, 2H), 6.82 – 6.73 (m, 2H), 5.69 – 5.42 (m, 1H), 4.49 – 4.36 (m, 1H), 4.02 - 3.96 (m, 4H), 3.95 – 3.92 (m, 1H), 3.52 – 3.47 (m, 3H), 2.98 (s, 6H), 2.89 – 2.82 (m, 3H), 2.76 – 2.73 (m, 1H), 2.29 (s, 3H), 2.23 – 2.16 (m, 1H), 1.99 – 1.91 (m, 1H), 1.84 – 1.71 (m, 8H), 1.51 – 1.43 (m, 3H).

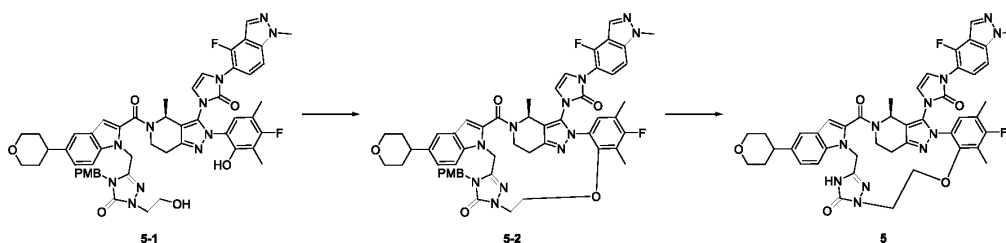
Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
58	int-18 & int-26	LCMS: 825.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.65 (brs, 1H), 7.53 (s, 1H), 7.46 – 7.29 (m, 5H), 7.27 (d, <i>J</i> = 8.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.06 – 6.82 (m, 2H), 6.81 – 6.53 (m, 2H), 5.75 – 5.51 (m, 1H), 4.51 – 4.08 (m, 3H), 4.02 – 3.92 (m, 2H), 3.77 – 3.28 (m, 4H), 3.00 – 2.80 (m, 3H), 2.66 – 2.56 (m, 1H), 2.33 – 2.26 (m, 3H), 1.80 – 1.70 (m, 5H), 1.69 – 1.57 (m, 3H), 1.56 – 1.39 (m, 3H), 1.35 – 1.03 (m, 4H).
59	int-18 & int-32	LCMS: 861.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.66 (brs, 1H), 7.80 – 7.60 (m, 1H), 7.53 (brs, 1H), 7.45 – 7.34 (m, 3H), 7.27 (d, <i>J</i> = 8.0 Hz, 1H), 7.11 – 6.96 (m, 1H), 6.95 – 6.73 (m, 2H), 6.72 – 6.58 (m, 1H), 5.75 – 5.48 (m, 1H), 4.49 – 4.27 (m, 1H), 4.01 – 3.95 (m, 3H), 3.93 – 3.87 (m, 1H), 3.74 – 3.57 (m, 1H), 3.51 – 3.46 (m, 2H), 2.93 – 2.79 (m, 2H), 2.78 – 2.70 (m, 1H), 2.29 (s, 3H), 2.22 – 2.13 (m, 1H), 1.99 – 1.91 (m, 1H), 1.81 – 1.70 (m, 6H), 1.70 – 1.40 (m, 5H), 1.33 – 1.26 (m, 1H), 1.25 – 1.09 (m, 3H).
73	Int-17 & int-33	LCMS: 931.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 8.28 (s, 1H), 7.68 – 7.44 (m, 2H), 7.45 – 7.28 (m, 2H), 7.27 – 7.22 (m, 1H), 7.21 – 7.15 (m, 1H), 7.06 – 6.51 (m, 4H), 6.09 – 5.19 (m, 1H), 4.42 – 4.19 (m, 2H), 4.15 – 3.85 (m, 4H), 3.79 – 3.67 (m, 2H), 3.09 – 2.98 (m, 2H), 2.97 – 2.88 (m, 1H), 2.55 – 2.52 (m, 1H), 2.28 (s, 3H), 1.81 – 1.65 (m, 6H), 1.64 – 1.48 (m, 5H), 1.48 – 1.37 (m, 2H), 1.37 – 1.05 (m, 11H), 1.04 – 0.91 (m, 1H).
73-1 & 73-2	Int-17 & int-33	73 was separated by chiral SFC (Column: ChiralPak AD, 250*30 mm I.D., 10 μm; Mobile phase: A for CO ₂ and B for Isopropanol (0.1% NH ₃ H ₂ O); Gradient: B 35%; Flow rate: 120 mL/min; Back pressure: 100 bar; Column temperature: 38°C) to afford 73-1 & 73-2 . 73-1 , retention Time: 1.879. LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.78 (brs, 1H), 8.29 (s, 1H), 7.72 – 7.46 (m, 2H), 7.45 – 7.30 (m, 2H), 7.28 – 7.21 (m, 1H), 7.20 – 7.14 (m, 1H), 6.95 – 6.51 (m, 4H), 6.02 – 5.25 (m, 1H), 4.44 – 4.31 (m, 1H), 4.29 – 4.15 (m, 1H), 4.14 – 3.92 (m, 4H), 3.85 – 3.57 (m, 3H), 3.12 – 2.89 (m, 3H), 2.29 (s, 3H), 1.87 – 1.49 (m, 12H), 1.48 – 1.37 (m, 2H), 1.34 – 1.23 (m, 5H), 1.22 – 1.08 (m, 5H), 1.01 – 0.89 (m, 1H). 73-2 , retention Time: 2.743; LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.81 (brs, 1H), 8.29 (s, 1H), 7.66 – 7.47 (m, 2H), 7.46 – 7.36 (m, 1H), 7.35 – 7.23 (m, 2H), 7.22 – 7.14 (m, 1H), 7.09 – 6.84 (m, 2H), 6.80 – 6.63 (m, 2H), 5.93 – 5.20 (m, 1H), 4.40 – 4.21 (m, 2H), 4.16 – 3.93 (m, 4H), 3.87 – 3.61 (m, 3H), 3.09 – 2.86 (m, 3H), 2.28 (s, 3H), 1.84 – 1.67 (m, 6H), 1.66 – 1.52 (m, 5H), 1.51 – 1.39 (m, 3H), 1.38 – 1.26 (m, 5H), 1.23 – 1.12 (m, 5H), 1.05 – 0.93 (m, 1H).
74&75	int-18 & int-33	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-50%) was used to separate the two isomers. 74 : retention time: 20 min. LCMS: 903.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 8.28 (s, 1H), 7.55 (brs, 2H), 7.41 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 7.04 – 6.56 (m, 4H), 5.97 – 5.23 (m, 1H), 4.37 – 4.22 (m, 2H), 4.06 (s, 3H), 3.97 (dt, <i>J</i> = 12.0, 4.0 Hz, 2H), 3.84 – 3.63 (m, 1H), 3.52 – 3.43 (m, 2H), 3.07 – 2.77 (m, 3H), 2.53 – 2.51 (m, 1H), 2.27 (s, 3H), 1.82 – 1.54 (m, 10H), 1.53 – 1.36 (m, 3H), 1.35 – 1.28 (m, 1H), 1.26 – 1.07 (m, 3H), 1.06 – 0.77 (m, 2H). 75 : retention time: 22 min. LCMS: 903.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.59 (brs, 1H), 8.28 (s, 1H), 7.54 (m, 2H), 7.44 – 7.26 (m, 2H), 7.23 (d, <i>J</i> = 8.0 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.92 – 6.53 (m, 4H), 6.05 – 5.53 (m, 1H), 4.41 – 4.15 (m, 2H), 4.05 (s, 3H), 3.95 (d, <i>J</i> = 8.0 Hz, 2H), 3.88 – 3.56 (m, 1H), 3.53 – 3.39 (m, 2H), 3.02 – 2.91 (m, 2H), 2.86 – 2.79 (m, 1H), 2.53 –

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		2.51 (m, 1H), 2.28 (s, 3H), 1.82 – 1.46 (m, 12H), 1.45 – 1.33 (m, 2H), 1.25 – 0.90 (m, 5H).
76	int-19 & int-22	LCMS: 865.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.28 (s, 1H), 8.14 (d, <i>J</i> = 8.0 Hz, 1H), 7.62 – 7.44 (m, 1H), 7.36 – 7.17 (m, 3H), 7.01 – 6.50 (m, 4H), 6.44 (s, 1H), 5.80 – 5.66 (m, 1H), 5.08 – 4.75 (m, 1H), 4.38 – 4.23 (m, 2H), 4.14 – 4.01 (m, 4H), 4.00 – 3.93 (m, 2H), 3.50 – 3.42 (m, 2H), 2.97 – 2.88 (m, 1H), 2.81 – 2.71 (m, 3H), 2.55 – 2.51 (m, 1H), 2.27 (s, 3H), 1.84 – 1.62 (m, 8H), 1.48 – 1.28 (s, 5H).
78 & 78-1	int-1 & int-34	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-80%) was used to separate the two isomers. 78 : retention time: 18 min. LCMS: 891.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.19 (s, 1H), 7.54 – 7.44 (m, 2H), 7.42 – 7.30 (m, 3H), 7.20 (d, <i>J</i> = 8.0 Hz, 1H), 7.06 – 6.96 (m, 1H), 6.92 – 6.52 (m, 3H), 5.89 – 5.25 (m, 1H), 4.29 – 4.02 (m, 4H), 4.01 – 3.93 (m, 3H), 3.85 – 3.79 (m, 1H), 3.78 – 3.55 (m, 1H), 3.52 – 3.44 (m, 2H), 2.88 – 2.82 (m, 3H), 2.27 (s, 3H), 2.25 – 2.18 (m, 1H), 2.05 – 1.98 (m, 1H), 1.82 – 1.68 (m, 7H), 1.60 – 1.36 (m, 6H), 1.17 – 1.05 (m, 1H), 1.02 – 0.91 (m, 1H). 78-1 : retention time: 20 min. LCMS: 891.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.18 (s, 1H), 7.52 – 7.23 (m, 5H), 7.16 (d, <i>J</i> = 8.0 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.71 – 6.59 (m, 3H), 5.72 – 5.69 (m, 1H), 4.03 – 3.98 (m, 4H), 3.98 – 3.95 (m, 3H), 3.82 – 3.80 (m, 2H), 3.19 – 3.15 (m, 2H), 2.86 – 2.77 (m, 3H), 2.23 (s, 3H), 2.08 – 2.01 (m, 1H), 1.97 – 1.92 (m, 1H), 1.80 – 1.57 (m, 6H), 1.56 – 1.33 (m, 6H), 1.30 – 1.23 (m, 2H), 1.00 – 0.90 (m, 1H).
79 & 79-1	int-1 & int-33	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-80%) was used to separate the two isomers. 79 : retention time: 14 min. LCMS: 891.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.91 (brs, 1H), 8.27 (s, 1H), 7.60 – 7.44 (m, 3H), 7.29 (d, <i>J</i> = 8.0 Hz, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.03 – 6.52 (m, 4H), 5.89 – 5.14 (m, 1H), 4.36 – 4.20 (m, 2H), 4.14 – 3.90 (m, 6H), 3.87 – 3.61 (m, 1H), 3.56 – 3.40 (m, 2H), 2.93 – 2.80 (m, 2H), 2.54 – 2.51 (m, 1H), 2.26 (s, 3H), 1.90 – 1.59 (m, 10H), 1.58 – 1.34 (m, 5H), 1.11 – 0.89 (m, 2H). 79-1 : retention time: 17 min. LCMS: 891.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 8.28 (s, 1H), 7.61 – 7.41 (m, 3H), 7.40 – 7.25 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 6.82 (s, 1H), 6.74 – 6.66 (m, 2H), 6.62 (brs, 1H), 6.05 – 5.63 (m, 1H), 4.40 – 4.31 (m, 1H), 4.29 – 4.14 (m, 2H), 4.05 (s, 3H), 3.97 – 3.91 (m, 2H), 3.49 – 3.47 (m, 1H), 3.46 – 3.44 (m, 2H), 3.01 – 2.95 (m, 1H), 2.85 – 2.80 (m, 1H), 2.53 – 2.51 (m, 1H), 2.27 (s, 3H), 1.82 – 1.61 (m, 9H), 1.57 – 1.45 (m, 4H), 1.44 – 1.36 (m, 1H), 1.31 – 1.25 (m, 1H), 1.03 – 0.89 (m, 2H).
109	Int-19 & int-33	LCMS: 891.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.85 (brs, 1H), 8.28 (s, 1H), 8.13 (d, <i>J</i> = 8.0 Hz, 1H), 7.6 – 7.45 (m, 1H), 7.40 – 7.23 (m, 2H), 7.19 – 7.10 (m, 1H), 7.03 – 6.86 (m, 1H), 6.79 – 6.50 (m, 3H), 6.49 – 6.30 (m, 1H), 5.98 – 4.99 (m, 1H), 4.35 – 4.23 (m, 2H), 4.05 (s, 3H), 4.01 – 3.93 (m, 2H), 3.92 – 3.77 (m, 1H), 3.69 – 3.52 (m, 1H), 3.50 – 3.41 (m, 2H), 3.05 – 2.82 (m, 2H), 2.81 – 2.71 (m, 1H), 2.26 (s, 3H), 1.82 – 1.59 (m, 9H), 1.55 – 1.34 (m, 5H), 1.32 – 1.27 (m, 3H), 1.88 – 0.99 (m, 1H), 0.82 – 0.70 (m, 1H).
110	Int-17 & int-41	LCMS: 977.6 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 7.91 – 7.69 (m, 1H), 7.61 – 7.44 (m, 2H), 7.42 – 7.35 (m, 1H), 7.33 – 7.21 (m, 2H), 7.15 – 6.95 (m, 2H), 6.87 – 6.33 (m, 3H), 5.88 – 5.11 (m, 1H), 4.38 – 4.25 (m, 2H), 4.19 – 3.79 (m, 2H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.07 – 2.99 (m, 1H), 2.89 – 2.79

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		(m, 1H), 2.73 – 2.59 (m, 4H), 2.27 (s, 3H), 2.22 – 2.13 (m, 1H), 1.96 – 1.89 (m, 1H), 1.83 – 1.66 (m, 4H), 1.65 – 1.45 (m, 6H), 1.44 – 1.40 (m, 1H), 1.39 – 1.31 (m, 4H), 1.30 – 1.27 (m, 4H), 1.26 – 1.25 (m, 1H), 1.24 – 1.21 (m, 2H), 1.20 (s, 3H), 1.17 – 1.12 (m, 1H), 1.01 – 0.89 (m, 1H).
111	Int-17 & int-34	LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 8.20 (s, 1H), 7.62 – 7.51 (m, 1H), 7.46 – 7.30 (m, 4H), 7.27 – 7.20 (m, 1H), 7.10 – 6.93 (m, 1H), 6.92 – 6.52 (m, 3H), 5.99 – 5.19 (m, 1H), 4.26 – 3.99 (m, 5H), 3.96 – 3.77 (m, 2H), 3.73 (d, <i>J</i> = 8.0 Hz, 2H), 3.09 – 2.98 (m, 1H), 2.88 – 2.79 (m, 2H), 2.28 (s, 3H), 2.25 – 2.17 (m, 1H), 2.07 – 1.95 (m, 1H), 1.78 – 1.67 (m, 4H), 1.65 – 1.51 (m, 5H), 1.47 – 1.39 (m, 2H), 1.38 – 1.30 (m, 2H), 1.28 (s, 3H), 1.23 – 1.06 (m, 6H), 1.00 – 0.89 (m, 1H).
111-1 & 111-2	Int-17 & int-34	111 was separated by chiral SFC (Column: ChiralPak AD, 250*30 mm I.D., 10 μm; Mobile phase: A for CO ₂ and B for Isopropanol (0.1% NH ₃ H ₂ O); Gradient: B 35%; Flow rate: 120 mL /min; Back pressure: 100 bar; Column temperature: 38°C) to afford 111-1 & 111-2 . 111-1 , retention Time: 2.438. LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.59 (brs, 1H), 8.20 (s, 1H), 7.64 – 7.48 (m, 1H), 7.47 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 7.03 – 6.90 (m, 1H), 6.88 – 6.58 (m, 3H), 6.02 – 5.20 (m, 1H), 4.15 – 3.92 (m, 5H), 3.92 – 3.61 (m, 4H), 3.06 – 2.97 (m, 1H), 2.83 (s, 2H), 2.30 – 2.19 (m, 4H), 2.04 – 1.94 (m, 1H), 1.77 – 1.46 (m, 10H), 1.45 – 1.34 (m, 2H), 1.33 – 1.24 (m, 5H), 1.22 – 1.10 (m, 5H), 0.99 – 0.89 (m, 1H). 111-2 , retention Time: 3.520; LCMS: 933.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.61 (brs, 1H), 8.19 (s, 1H), 7.65 – 7.48 (m, 1H), 7.43 – 7.28 (m, 4H), 7.25 (d, <i>J</i> = 8.0 Hz, 1H), 7.07 – 6.56 (m, 4H), 5.86 – 5.15 (m, 1H), 4.15 – 3.95 (m, 5H), 3.89 – 3.63 (m, 4H), 3.07 – 2.98 (m, 1H), 2.89 – 2.78 (m, 2H), 2.30 – 2.16 (m, 4H), 2.04 – 1.95 (m, 1H), 1.78 – 1.66 (m, 4H), 1.65 – 1.50 (m, 5H), 1.49 – 1.35 (m, 3H), 1.34 – 1.23 (m, 5H), 1.22 – 1.14 (m, 5H), 1.01 – 0.90 (m, 1H).
112	Int-22 & int-50	LCMS: 891.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.91 (brs, 1H), 8.29 (s, 1H), 7.55 (d, <i>J</i> = 8.0 Hz, 1H), 7.46 (s, 1H), 7.37 (s, 1H), 7.32 – 7.21 (m, 2H), 7.01 – 6.65 (m, 4H), 5.84 – 5.14 (m, 1H), 4.65 – 4.37 (m, 1H), 4.36 – 4.24 (m, 2H), 4.06 (s, 3H), 3.95 – 3.81 (m, 2H), 3.64 – 3.54 (m, 3H), 3.00 (t, <i>J</i> = 8.0 Hz, 2H), 2.97 – 2.92 (m, 2H), 2.89 – 2.83 (m, 1H), 2.81 – 2.78 (m, 1H), 2.28 (s, 3H), 2.15 (t, <i>J</i> = 8.0 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.86 – 1.57 (m, 6H), 1.52 – 1.40 (m, 5H).
113	Int-23 & int-50	LCMS: 891.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.91 (brs, 1H), 8.19 (s, 1H), 7.49 – 7.29 (m, 5H), 7.09 – 6.98 (m, 1H), 6.93 – 6.63 (m, 3H), 5.80 – 5.30 (m, 1H), 4.64 – 4.31 (m, 1H), 4.12 – 3.98 (m, 4H), 3.92 – 3.78 (m, 3H), 3.59 (t, <i>J</i> = 12.0 Hz, 2H), 3.07 – 2.96 (m, 3H), 2.93 – 2.76 (m, 4H), 2.28 (s, 3H), 2.25 – 2.18 (s, 1H), 2.17 – 2.10 (m, 2H), 2.09 – 1.99 (m, 1H), 1.97 – 1.62 (m, 6H), 1.50 – 1.39 (m, 5H).
114	Int-1 & int-42	LCMS: 903.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.93 (brs, 1H), 8.54 (s, 1H), 7.77 (d, <i>J</i> = 2.0 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.58 – 7.46 (m, 4H), 7.35 – 7.29 (m, 1H), 7.25 – 7.19 (m, 1H), 7.14 – 7.03 (s, 1H), 6.89 – 6.65 (m, 2H), 6.64 – 6.38 (m, 2H), 5.71 – 5.21 (m, 1H), 4.11 – 3.95 (m, 6H), 3.50 – 3.48 (m, 2H), 2.92 – 2.81 (m, 2H), 2.78 – 2.68 (m, 1H), 2.27 (s, 3H), 2.25 – 2.11 (m, 1H), 2.05 – 1.65 (m, 9H), 1.63 – 1.44 (m, 4H), 1.43 – 1.35 (m, 1H), 1.13 – 0.90 (m, 2H).
115	Int-17 & int-42	LCMS: 945.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.64 (brs, 1H), 8.53 (s, 1H), 7.77 (s, 1H), 7.70 – 7.45 (m, 4H), 7.43 – 7.23 (m, 3H), 7.15 – 6.98 (m, 1H), 6.85 – 6.47 (m, 4H), 5.91 – 5.59 (m, 1H), 5.42 – 5.08 (m, 1H), 4.06

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		(s, 3H), 3.78 – 3.67 (m, 2H), 2.87 – 2.82 (m, 1H), 2.78 – 2.67 (m, 2H), 2.32 – 2.18 (m, 4H), 2.01 – 1.92 (s, 1H), 1.85 – 1.66 (m, 5H), 1.65 – 1.47 (m, 6H), 1.46 – 1.34 (m, 3H), 1.33 – 1.25 (m, 5H), 1.19 (s, 3H), 1.00 – 0.91 (m, 1H).
116	Int-1 & int-43	LCMS: 921.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.94 (brs, 1H), 7.64 – 7.40 (m, 3H), 7.29 (d, <i>J</i> = 8.0 Hz, 1H), 7.26 – 7.13 (m, 2H), 7.12 – 6.94 (m, 2H), 6.90 – 6.32 (m, 3H), 5.93 – 5.09 (m, 1H), 4.36 – 3.87 (m, 5H), 3.86 – 3.58 (m, 1H), 3.53 – 3.41 (m, 2H), 2.92 – 2.78 (m, 2H), 2.75 – 2.64 (m, 1H), 2.26 (s, 3H), 2.23 – 2.13 (m, 1H), 1.98 – 1.87 (m, 1H), 1.87 – 1.66 (m, 7H), 1.65 – 1.53 (m, 1H), 1.52 – 1.43 (m, 3H), 1.42 – 1.34 (m, 1H), 1.21 – 1.06 (m, 1H), 1.05 – 0.86 (m, 2H).
117	Int-17 & int-43	LCMS: 963.2 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 7.74 – 7.45 (m, 2H), 7.43 – 7.35 (m, 1H), 7.34 – 7.28 (m, 1H), 7.27 – 7.13 (m, 2H), 7.12 – 6.89 (m, 2H), 6.88 – 6.23 (m, 3H), 5.85 – 5.06 (m, 1H), 4.14 – 3.93 (m, 3H), 3.80 – 3.62 (m, 3H), 3.11 – 2.98 (m, 1H), 2.90 – 2.78 (m, 1H), 2.76 – 2.64 (m, 1H), 2.27 (s, 3H), 2.24 – 2.11 (m, 1H), 2.06 – 1.82 (m, 2H), 1.81 – 1.47 (m, 9H), 1.45 – 1.35 (m, 2H), 1.33 – 1.12 (m, 9H), 1.11 – 0.83 (m, 2H).
118 & 118-1	Int-33 & int-51	Prep-HPLC (column: Welch Triart C18 250*21.2 mm*10 μm; mobile phase: [water (0.1% FA) - ACN]; B%: 60%-80%) was used to separate the two isomers. 118 : retention time: 20 min. LCMS: 919.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.94 (brs, 1H), 8.29 (s, 1H), 7.61 – 7.45 (m, 3H), 7.31 (d, <i>J</i> = 8.0 Hz, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.07 – 6.47 (m, 4H), 5.95 – 5.18 (m, 1H), 4.39 – 4.19 (m, 2H), 4.15 – 3.89 (m, 4H), 3.84 – 3.57 (m, 3H), 3.09 – 3.00 (m, 2H), 2.97 – 2.88 (m, 1H), 2.27 (s, 3H), 1.89 – 1.78 (m, 2H), 1.77 – 1.70 (m, 4H), 1.69 – 1.61 (m, 2H), 1.60 – 1.53 (m, 2H), 1.52 – 1.46 (m, 3H), 1.45 – 1.40 (m, 1H), 1.34 – 1.27 (m, 4H), 1.21 (s, 3H), 1.09 – 0.91 (m, 2H). 118-1 : retention time: 22 min. LCMS: 919.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.90 (brs, 1H), 8.30 (s, 1H), 7.63 – 7.41 (m, 3H), 7.42 – 7.26 (m, 1H), 7.25 – 7.15 (m, 2H), 6.92 – 6.79 (m, 1H), 6.78 – 6.59 (m, 3H), 6.12 – 5.45 (m, 1H), 4.42 – 4.32 (m, 1H), 4.30 – 4.19 (m, 1H), 4.07 (s, 3H), 4.07 – 3.88 (m, 1H), 3.87 – 3.64 (m, 3H), 3.07 – 2.94 (m, 3H), 2.29 (s, 3H), 1.87 – 1.77 (m, 2H), 1.75 – 1.67 (m, 4H), 1.66 – 1.58 (m, 2H), 1.57 – 1.47 (m, 5H), 1.46 – 1.40 (m, 1H), 1.30 – 1.27 (m, 4H), 1.19 (s, 3H), 1.06 – 0.91 (m, 2H).
133	Int-70 & int-17	LCMS: 974.4 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.60 (brs, 1H), 7.63 – 7.48 (m, 1H), 7.44 – 7.33 (m, 2H), 7.30 – 7.20 (m, 1H), 7.06 – 6.64 (m, 6H), 5.91 – 5.17 (m, 1H), 4.24 – 3.79 (m, 2H), 3.76 – 3.69 (m, 3H), 3.54 – 3.44 (m, 4H), 3.07 – 3.01 (m, 1H), 2.83 – 2.75 (m, 2H), 2.27 (s, 3H), 2.26 – 2.20 (m, 1H), 1.93 – 1.85 (m, 1H), 1.76 – 1.67 (m, 4H), 1.66 – 1.52 (m, 9H), 1.45 – 1.37 (m, 2H), 1.32 – 1.24 (m, 6H), 1.21 – 1.14 (m, 5H), 1.03 – 0.93 (m, 1H).
134	Int-53 & int-34	LCMS: 932.1 (M+H) ⁺ . ¹ HNMR (500 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.62 (brs, 1H), 8.18 (s, 1H), 7.78 – 7.53 (m, 1H), 7.44 – 7.30 (m, 5H), 7.03 – 6.61 (m, 4H), 6.06 (s, 1H), 5.86 – 5.19 (m, 1H), 4.10 – 3.97 (m, 5H), 3.88 – 3.77 (m, 4H), 2.86 – 2.79 (m, 2H), 2.44 – 2.41 (m, 2H), 2.26 (s, 3H), 2.24 – 2.16 (s, 1H), 2.04 – 1.98 (m, 1H), 1.77 – 1.63 (m, 2H), 1.60 – 1.49 (m, 2H), 1.46 – 1.35 (m, 3H), 1.32 – 1.25 (m, 9H), 1.21 – 1.11 (m, 2H), 1.02 – 0.91 (m, 1H).
135	Int-51 & int-34	LCMS: 919.3 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.93 (brs, 1H), 8.18 (s, 1H), 7.53 – 7.44 (m, 2H), 7.40 – 7.29 (m, 3H), 7.24 – 7.16 (m, 1H), 7.04 – 6.95 (m, 1H), 6.89 – 6.55 (m, 3H), 5.74 – 5.25 (m, 1H), 4.13 – 3.96

Compound No.	Starting material	MW [M+H] ⁺ & ¹ H NMR
		(m, 5H), 3.85 – 3.68 (m, 4H), 3.07 – 3.01 (m, 1H), 2.87 – 2.80 (m, 2H), 2.26 (s, 3H), 2.22 – 2.16 (m, 1H), 2.05 – 1.94 (m, 1H), 1.85 – 1.68 (m, 5H), 1.66 – 1.53 (m, 3H), 1.52 – 1.48 (m, 1H), 1.47 – 1.36 (m, 4H), 1.28 (s, 3H), 1.19 (s, 3H), 1.02 – 0.83 (m, 2H).
136	Int-7-P2 & int-34	LCMS: 919.5 (M+H) ⁺ . ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆ , 60 °C) δ 11.82 (brs, 1H), 8.18 (s, 1H), 8.12 (d, <i>J</i> = 8.0 Hz, 1H), 7.46 – 7.22 (m, 4H), 7.08 – 6.76 (m, 2H), 6.74 – 6.46 (m, 2H), 6.45 – 6.28 (m, 1H), 5.93 – 4.93 (m, 1H), 4.37 – 3.85 (m, 5H), 3.84 – 3.77 (m, 1H), 3.74 – 3.66 (m, 2H), 3.64 – 3.35 (m, 1H), 2.99 – 2.88 (m, 1H), 2.87 – 2.75 (m, 2H), 2.25 (s, 3H), 2.23 – 2.17 (m, 1H), 2.06 – 1.96 (m, 1H), 1.78 – 1.62 (m, 4H), 1.61 – 1.52 (m, 1H), 1.51 – 1.45 (m, 2H), 1.44 – 1.33 (m, 4H), 1.32 – 1.21 (m, 5H), 1.19 (s, 3H), 0.92 – 0.73 (m, 2H).

Example 1.2: Synthesis of Compound 5**[0289] Step 1: 5-1**

[0290] 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]⁺.

[0291] Step 2: 5-2

[0292] 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-*d*₆) 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).

[0293] Step 3: Compound 5

[0294] To a solution of **5-2** (5 mg, 5.12 μ mol) in DCM (0.05 ml) and TFA (0.05 ml) was added trifluoromethanesulfonic acid (1.59 μ l, 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 $\times$ 2). The organic layer was washed with brine (2 mL), dried over Na₂SO₄, filtered and concentrated to afford **Compound 5**. LCMS: 856.3 [M+H]⁺.

Example 2.1: cAMP assay

[0295] The changes of cAMP in human GLP-1 cells (cAMP Hunter™ 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.

[0296] Experimental Methods:

[0297] 1. Cell Thawing

[0298] 1) Pre-warm complete medium (DMEM/F12+10% FBS+500 μ g/mL G418) in a 37 °C water bath for 30 minutes.

[0299] 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.

[0300] 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. 10mL of the assay complete medium was added into a T75 flask and incubated at 37 °C and 5% CO₂.

[0301] 4) Maintain the cells in culture until they are 80% confluent.

[0302] 2. Cell Propagation

[0303] 1) Remove the T75 flask from the cell culture incubator and place in a sterile tissue culture hood.

[0304] 2) Gently aspirate media from the T75 flask.

[0305] 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.

[0306] 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.

[0307] 5) Incubate the flask at 37°C and 5% CO₂ for 2 to 3 minutes or until the cells have detached.

[0308] 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.

[0309] 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.

[0310] 8) The cells were passed for twice and then used for the cell experiment.

[0311] 3. Compound Treatment

[0312] 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.

[0313] The starting concentration of the compounds was 10 μ M, 3-fold dilution, 10 concentration points, and duplicate. The 100 nL compounds were transferred to the 384-well plate using Echo.

[0314] 4. Cell Culture

[0315] 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.

[0316] 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.

[0317] 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.

[0318] 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 (μ L)
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

[0319] 5. Reaction

[0320] 1) Transfer 10 μ L of cell solution to 384-well plate.

[0321] 2) Centrifuge at 600 rpm for 3 minutes and incubate 60 minutes at room temperature.

[0322] 3) Add 5 μ L 4X Eu-cAMP tracer solution and 5 μ L 4X ULIGHT™-anti-cAMP solution to 384-well plate.

TABLE 6 Detection reagent

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

[0323] 4) Centrifuge at 600rpm for 3 minutes and incubate 60 minutes at room temperature.

[0324] cAMP signal was detected with Envision. GraphPad Prism (version 6.0) was used for the data analysis.

[0325] 6. Detection of agonist activity in vitro:

[0326] 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.

[0327] $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{HillSlope}))}$

Table 7

Compound No.	EC ₅₀
1	B
2	B
3	B
4	A
19	A
20	B
23	B
24	B
25	D
26	B
27	D
28	A
29	B
30	B
31	A
33	B
34	B
37	B
42	B
43	B
44	A
45	B
46	A
48	B
50	B
51	C
52	B
54	A

56	A
57	B
58	B
59	B
73	A
73-1	C
73-2	A
74	A
75	C
76	A
78	A
78-1	C
79	A
79-1	D
109	B
110	A
111	A
111-1	C
111-2	A
112	A
113	B
114	B
115	B
116	B
117	B
118	A
118-1	B
133	A
134	B
135	A
136	B
142	A

EC₅₀: 0 < A ≤ 10 nM; 10 nM < B ≤ 50 nM; 50 nM < C ≤ 100 nM; 100 nM < D ≤ 200 nM

[0328] Other compounds disclosed herein also show GLP-1R agonist activity.

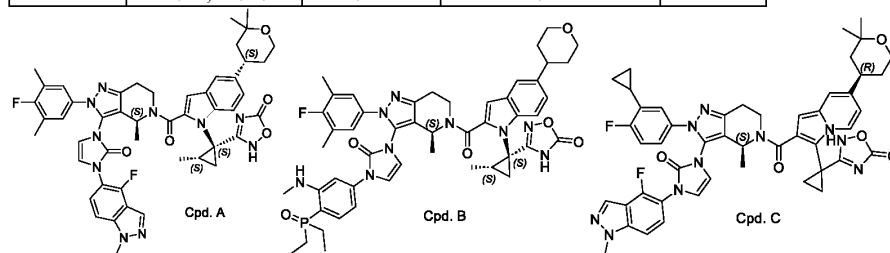
Example 2.2: Pharmacokinetic profile evaluation

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 noncompartmental analysis modules in FDA certified pharmacokinetic program Phoenix WinNonlin 7.0 (Pharsight, USA).

The data for Example C is shown in **Table 8**.

Table 8. Monkey PK profile

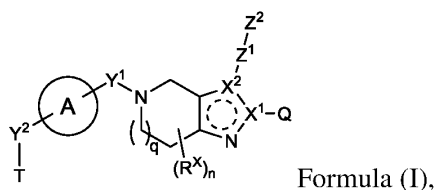
Example	Dose (mg/kg)	PO $T_{1/2}$ (h)	AUC_{0-t} (ng*h/mL)	Oral F%
Cpd. A	IV 0.5, PO 1.5	6.2	1154	22
Cpd. B	IV 0.5, PO 1.5	4.8	161	17
Cpd. C	IV 0.5, PO 1.5	1	104	8
28	IV 0.1, PO 0.1	8.4	717	35
31	IV 0.5, PO 1.5	1.4	197	12
73	PO 0.1	10.9	902	
111	IV 0.1, PO 0.1	9.1	2917	88



Compared to reference compound Cpd. A, Cpd. B and Cpd. C, examples disclosed herein showed better monkey pharmacokinetic profiles.

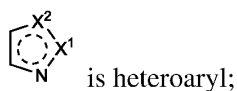
WHAT IS CLAIMED IS:

1. A compound of 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, heterocyclylalkyl or heteroarylalkyl, wherein the alkyl, heterocyclyl, heteroaryl, heterocyclylalkyl 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, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)(R^d)$, $-S(=O)_2(R^d)$, 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 or alkoxy;

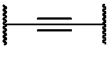
or two R^Z together with the same atom to which they are both attached form a C_2-C_6 alkylidenyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, SF_5 , haloalkyl, alkyl or alkoxy;

or one R^T together with one R^Q form a linking moiety L connecting T and Q;

or one R^Z together with one R^Q form a linking moiety L connecting Z^2 and Q;

or one R^T together with one R^X form a linking moiety L connecting T and R^X ;

each L is a bond or a linear C₁₋₂₀ bivalent hydrocarbon chain optionally substituted with one or more R^y, wherein one or more methylene units of the chain are optionally and

independently replaced by cycloalkyl, heterocyclyl, -C(R^L)=C(R^L)-, , -O-, -S-, -N(R^L)-, -C(=O)-, -OC(=O)-, -C(=O)O-, -S(=O)-, -S(=O)₂-, -N(R^L)C(=O)-, -C(=O)N(R^L)-, -N(R^L)S(=O)₂-, or -S(=O)₂N(R^L)-;

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

each R^y is independently halogen, oxo, cyano, nitro, -OR^{y1}, -OC(=O)R^{y1}, -OC(=O)OR^{y1}, -OC(=O)N(R^{y2})₂, -SR^{y1}, -S(=O)R^{y1}, -S(=O)₂R^{y1}, -S(=O)₂N(R^{y2})₂, -S(=O)(=NR^{y2})R^{y1}, -N(R^{y2})₂, -NR^{y2}C(=O)N(R^{y2})₂, -NR^{y2}C(=O)R^{y1}, -NR^{y2}C(=O)OR^{y1}, -NR^{y2}S(=O)₂R^{y1}, -N=S(=O)(R^{y1})₂, -C(=O)R^{y1}, -C(=O)OR^{y2}, -C(=O)N(R^{y2})₂, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, SF₅, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R^{y3};

each R^{y1} is independently hydrogen, alkyl, SF₅, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl or heterocyclyl, each optionally substituted with one or more R^{y3};

each R^{y2} is independently hydrogen, alkyl, SF₅, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, or -alkyl-heterocyclyl, optionally substituted with one or more R^{y3};

or two R^{y2} on the same atom are taken together with the atom to which they are attached to form a heterocyclyl optionally substituted with one or more R^{y3}; and

each R^{y3} is independently halogen, cyano, hydroxy, oxo, -SF₅, -SH, -S(=O)-alkyl, -S(=O)₂-alkyl, -S(=O)₂NH₂, -S(=O)₂NH-alkyl, -S(=O)₂N(alkyl)₂, -S(=O)(=N-alkyl)(alkyl), -NH₂, -NH-alkyl, -N(alkyl)₂, -N=S(=O)(alkyl)₂, -C(=O)-alkyl, -C(=O)OH, -C(=O)O-alkyl, -C(=O)NH₂, -C(=O)NH-alkyl, -C(=O)N(alkyl)₂, -P(=O)(alkyl)₂, alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxyalkyl, aminoalkyl, heteroalkyl or cycloalkyl;

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;

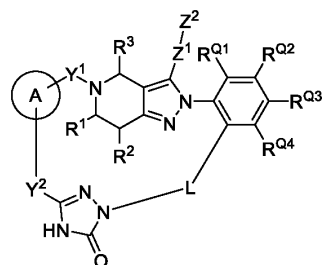
each R^d is independently hydrogen, alkyl, or cycloalkyl;

n is any integer of 0-6; and

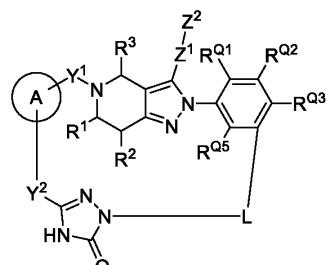
q is any integer of 1-3;

provided that the compound comprises at least one linking moiety L .

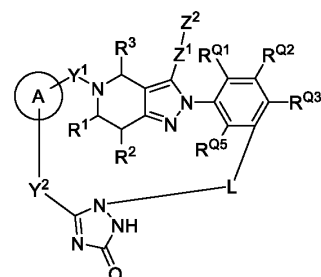
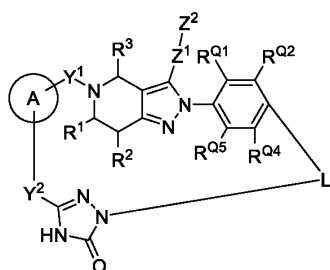
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is aryl optionally substituted with one or more R^Q .
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Q is phenyl optionally substituted with one or more R^Q .
4. The compound 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 .
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.
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein one R^T and one R^Q form a linking moiety L connecting T and Q .
7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula selected from:



Formula (A-1),



Formula (A-2),



Formula (A-3) or

Formula (A-4),

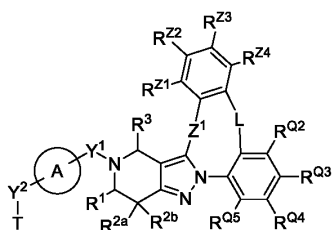
wherein:

each of R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} and R^{Q5} is independently hydrogen or R^Q ;

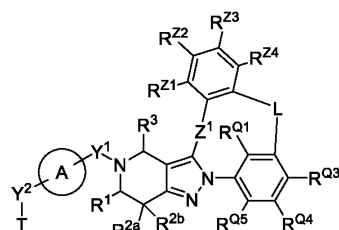
or R^{Q1} and R^{Q2} , R^{Q2} and R^{Q3} , R^{Q3} and R^{Q4} , or R^{Q4} and R^{Q5} together with the intervening atoms form a cycloalkyl, heterocyclyl, aryl, or heteroaryl, each optionally substituted with one or more group independently selected from halogen, hydroxy, cyano, alkyl, haloalkyl, hydroxylalkyl, alkoxy or cycloalkyl;

each of R^1 , R^2 and R^3 is independently hydrogen or R^X .

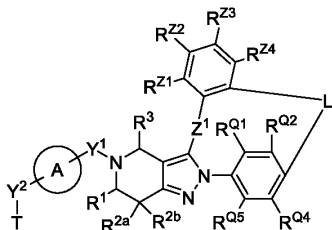
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is aryl optionally substituted with one or more R^Q , Z^2 is aryl optionally substituted with one or more R^Z , and one R^Z and one R^Q form a linking moiety L connecting Z^2 and Q.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula selected from:



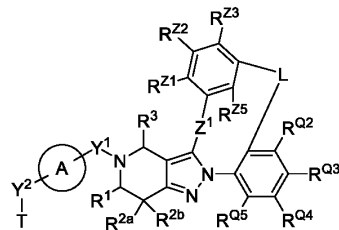
Formula (B-1),



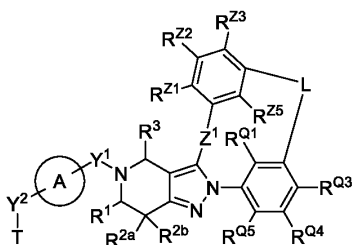
Formula (B-2),



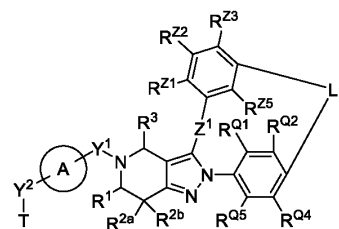
Formula (B-3),



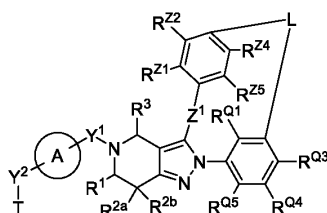
Formula (B-4),



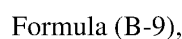
Formula (B-5),



Formula (B-6),

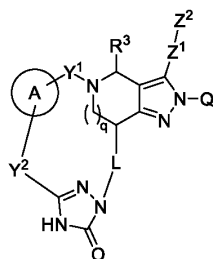


Formula (B-8) or



10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R¹ and R^{2a} are taken together with the atoms they attached to form a cycloalkyl or heterocyclyl.
11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are taken together with the atom they attached to form a cycloalkyl or heterocyclyl.
12. The compound of claim 7 or 9, or a pharmaceutically acceptable salt thereof, wherein each of R^{Q1}, R^{Q2}, R^{Q3}, R^{Q4} and R^{Q5} is independently hydrogen, halogen, alkyl or cycloalkyl.
13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein one R^T together with one R^X form a linking moiety L connecting T and R^X.

14. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula(C-1):

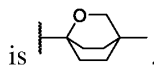


Formula (C-1),

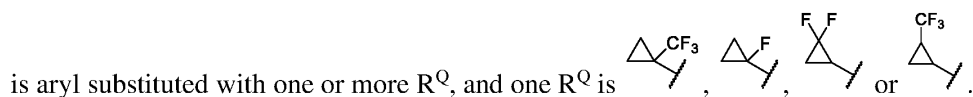
wherein R^3 is hydrogen or R^x .

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein L is $\text{---}L^{11}\text{---}L^{12}\text{---}L^{13}\text{---}L^{14}\text{---}L^{15}\text{---}$, each of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is independently selected from a bond, -S-, -C(=O)-, -O-, -NH-, -S(=O)₂-, -S(=O)-, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, or heterocyclyl are optionally substituted with one or more R^y .
16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein each of L^{11} , L^{12} , L^{13} , L^{14} , and L^{15} is independently selected from a bond, -S-, -C(=O)-, -O-, -NH-, -S(=O)₂-, -S(=O)-, -CH₂-, -CH₂CH₂-, -CH=CH-, $\text{---}\equiv\text{---}$ or , wherein -NH-, -CH₂-, -CH₂CH₂-, -CH=CH-, or  are optionally substituted with one or more R^y .
17. The compound of any one of claims 7, 9, 14-16, or a pharmaceutically acceptable salt thereof, wherein L is -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂C=CH-, -CH₂CH₂O-, -OCH₂CH₂-, -NHCH₂CH₂-, or -CH₂CH₂NH-, -CH₂CH₂CH₂O-, -OCH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂O-, -OCH₂CH₂CH₂CH₂-, -OCH₂CH₂O-, -OCH₂CH₂CH₂O-, -CH=CHCH₂O-, -OCH₂CH=CH-, -CH₂CH₂CH₂NH-, -NHCH₂CH₂CH₂-, -CH₂CH₂OCH₂CH₂-, -CH₂CH₂OCH₂-, -CH₂-cyclobutyl-O- or -CH₂-cyclopropyl-O-, wherein # end of L is connected to Q or Z^2 or R^x .
18. 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 .

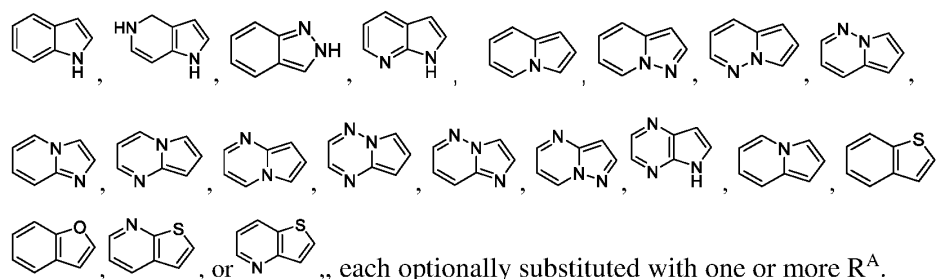
19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein Q



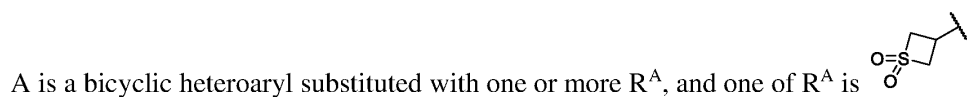
20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is aryl substituted with one or more R^Q , and one R^Q is cycloalkyl substituted with one or more groups independently selected from halogen or haloalkyl.
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein Q



- is aryl substituted with one or more R^Q , and one R^Q is
22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein q is 2 or 3.
23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein Ring A is a bicyclic heteroaryl optionally substituted with one or more R^A .
24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from the group consisting of:



25. The compound of any one of claims 1-24, 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} .
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein each R^{A1} is independently oxo, alkyl or alkoxy.
27. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring

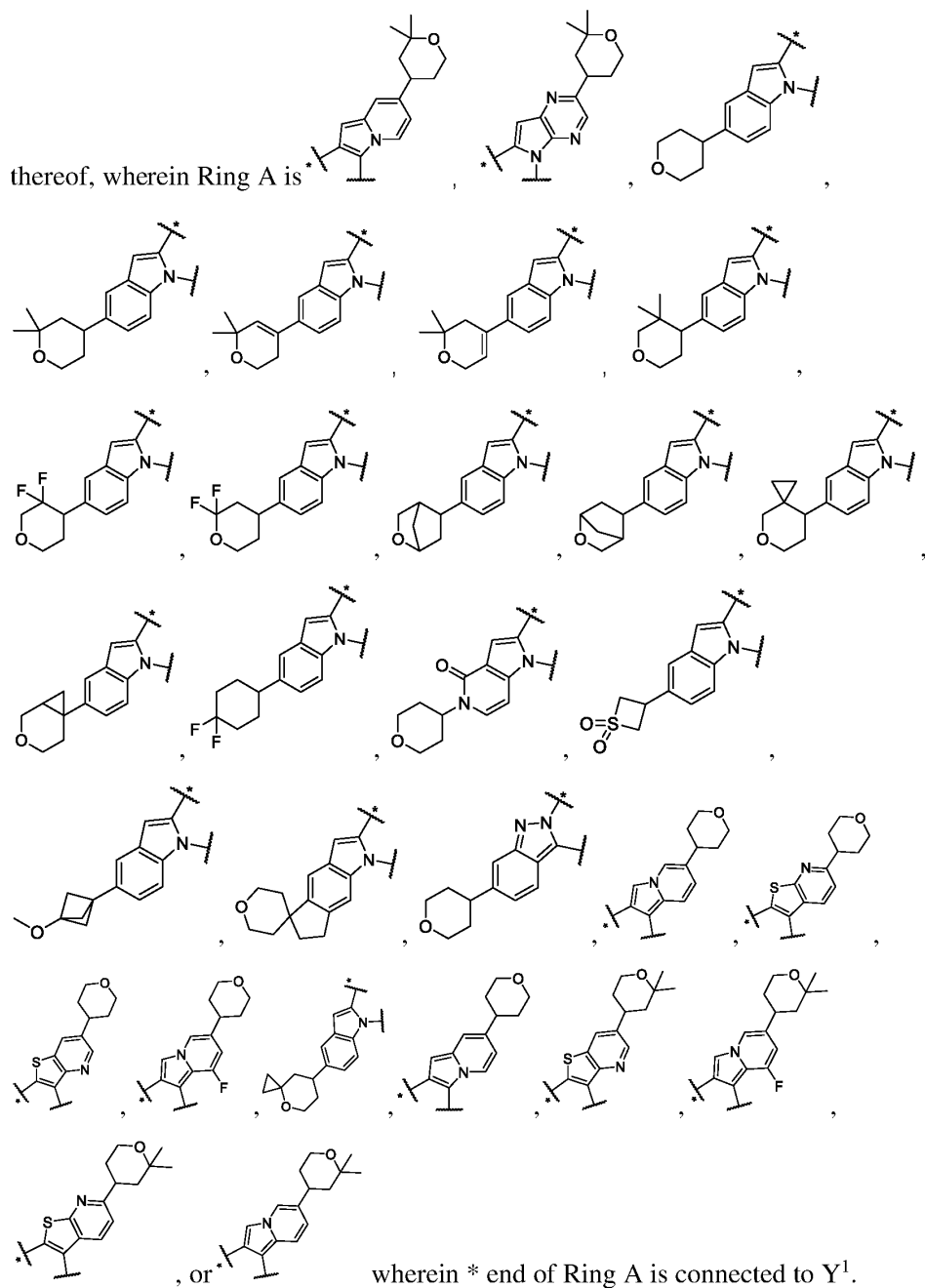


A is a bicyclic heteroaryl substituted with one or more R^A , and one of R^A is

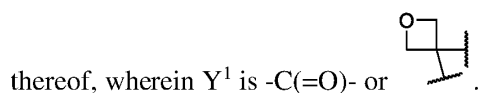
or

; or Ring A is a tricyclic or tetracyclic heteroaryl optionally substituted with one or more R^A .

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt



29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt

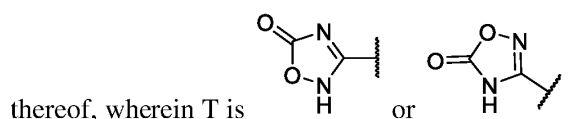


30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein Y² is alkyl or cycloalkyl optionally substituted with alkyl.

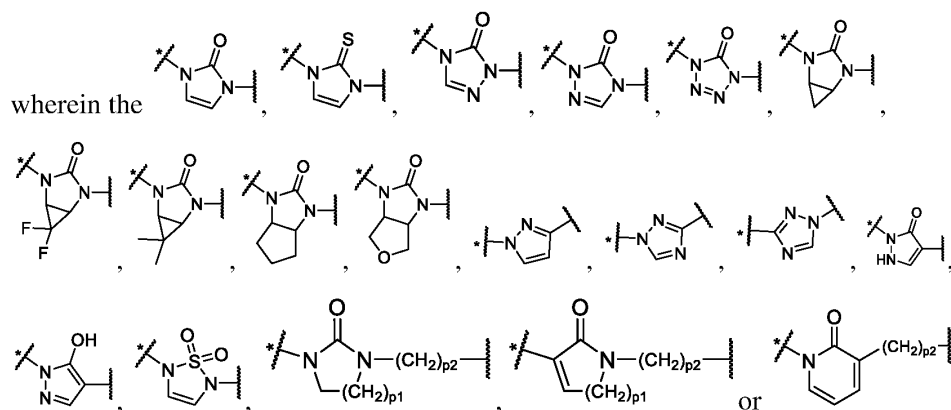
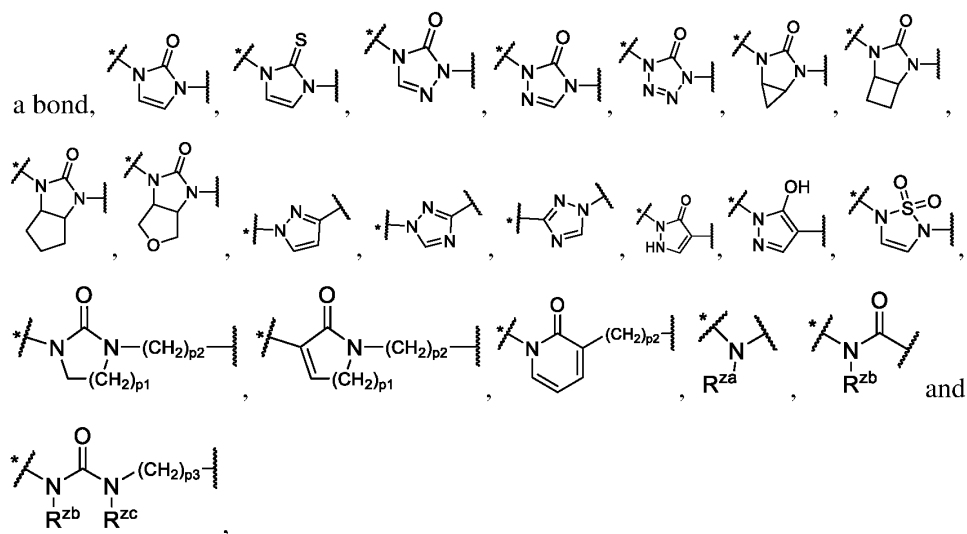
31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein Y^2



32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein T is heterocyclyl or heteroaryl, each optionally substituted with one or more R^T .
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein each R^T is independently oxo, halogen or alkyl.
34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt



35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^X is C_{1-6} alkyl.
36. The compound of any one of claims 1-34, 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} .
37. The compound of any one of claims 1-34, 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} .
38. The compound of any one of claims 1-37, 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.
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof, wherein Z^1 is selected from the group consisting of:



are optionally substituted 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;

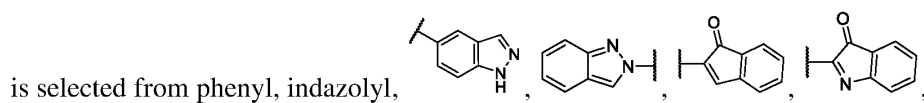
R^{za} is hydrogen, C_{1-6} alkyl, or $(C_{1-6}$ alkyl)carbonyl;

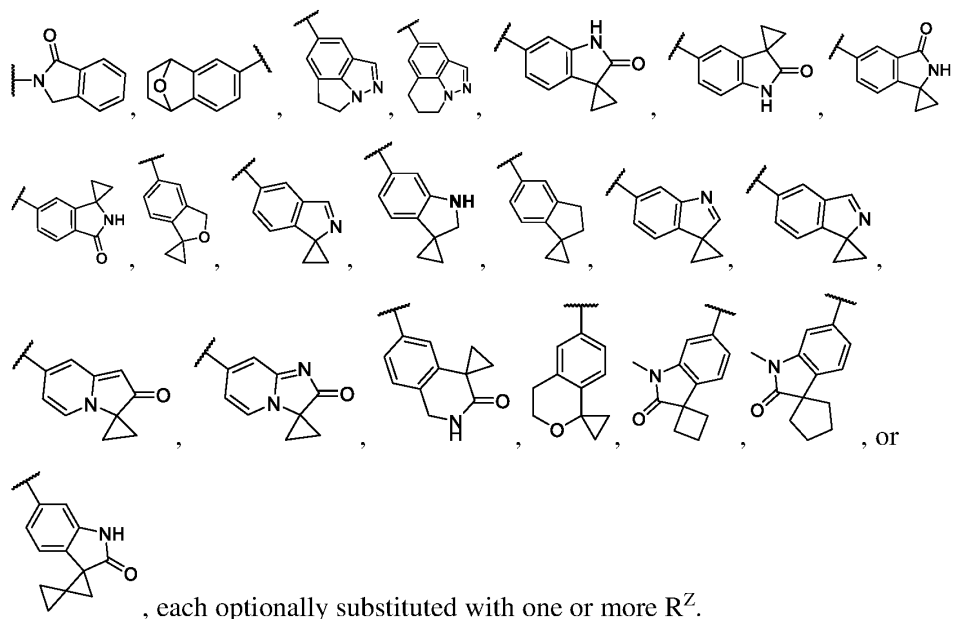
R^{zb} and R^{zc} are independently hydrogen or C_{1-6} alkyl; and

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

40. The compound of any one of claims 1-7 and 11-39, or a pharmaceutically acceptable salt thereof, wherein Z^2 is aryl or heteroaryl, each optionally substituted with one or more R^Z .

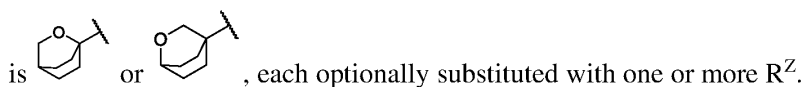
41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein Z^2





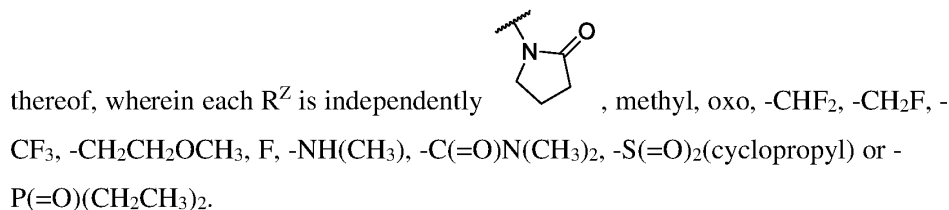
42. The compound of any one of claims 1-7 and 11-39, or a pharmaceutically acceptable salt thereof, wherein Z^2 is cycloalkyl or heterocyclyl, each optionally substituted with one or more R^Z .

43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein Z^2

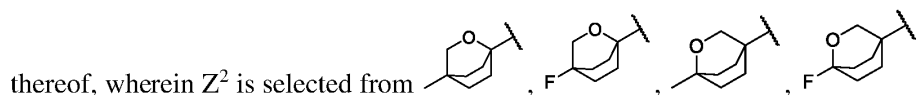


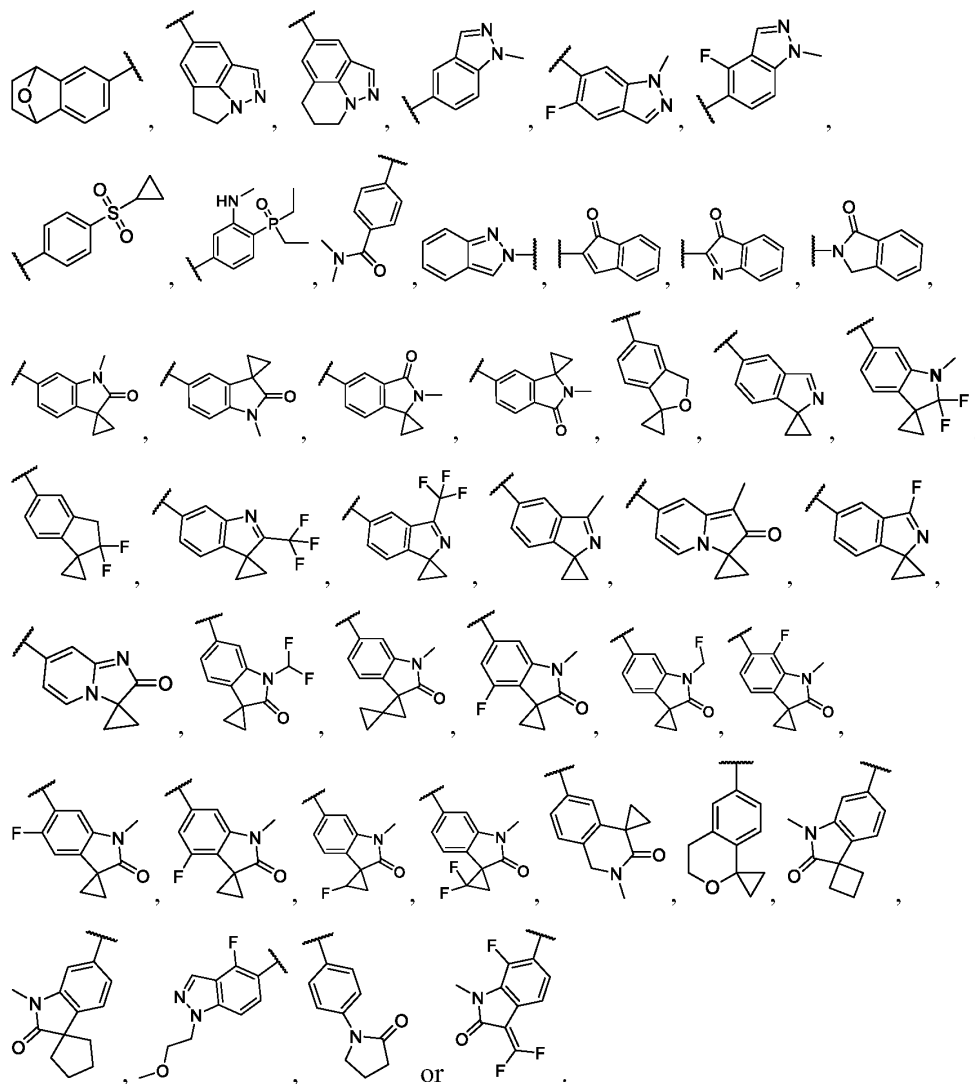
44. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, wherein each R^Z is independently halogen, alkyl, oxo, haloalkyl, $-N(R^d)_2$, $-C(=O)N(R^d)_2$, $-S(=O)_2(R^d)$, $-P(=O)(R^d)_2$ or heterocyclyl optionally substituted with one or more groups independently selected from halogen, hydroxy, oxo, alkyl or alkoxy.

45. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt



46. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt





47. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from any compound set forth in Table 1.1, Table 1.2, Table 2.1, Table 2.2 and Table 3.
48. A pharmaceutical composition comprising the compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
49. 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 1-47 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 48.
50. The method of claim 49, 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.