

CBL-B INHIBITORS AND METHODS OF USES THEREOF**CROSS-REFERENCE**

[0001] This patent application claims the benefit of International Application No. PCT/CN2023/122735, filed September 28, 2023; International Application No. PCT/CN2024/071520, filed January 10, 2024; International Application No. PCT/CN2024/075999, filed February 05, 2024; International Application No. PCT/CN2024/096583, filed May 31, 2024; and International Application No. PCT/CN2024/113575, filed August 21, 2024; which are incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure provides compounds useful as Casitas B-lineage lymphoma (Cbl) inhibitors, pharmaceutical compositions comprising them, and their use in treating a disease or condition associated with Cbl-b activity.

BACKGROUND

[0003] Dysregulated signaling is a prominent feature in cellular transformation and tumorigenesis. The proto-oncogene Casitas B-lineage lymphoma (Cbl) encodes an E3 ubiquitin ligase that downregulates PTK-directed cell signaling through ubiquitination, thereby targeting these kinases for lysosomal or proteasomal degradation. Cbl is a member of the Cbl family of proteins, so characterized based on a highly conserved N-terminal region that contains the structural components required for ubiquitin ligase activity. In simpler eukaryotic organisms, such as *Caenorhabditis elegans* and *Dictyostelium discoideum*, only one Cbl protein is present, but in mammals there are three, including Cbl, Cbl-b and Cbl-c.

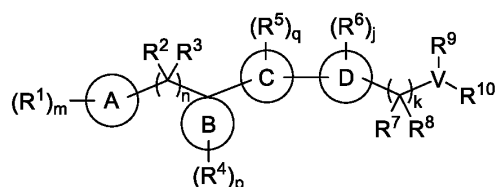
[0004] Cbl-b is an important T cell immune response braker. In contrast to Cbl, which mainly regulates thymocyte development, Cbl-b mainly regulates peripheral T-cell activation through negative regulation of TCR (T-cell receptor) signal transduction pathways. Specifically, Cbl-b inhibits VAV1 activation upon TCR engagement and imposes a requirement for CD28 costimulation for proliferation and IL-2 production in naïve T cells. Cbl-b also ubiquitylates PIK3R1/p85, which inhibits its recruitment to CD28 and TCR ζ , therefore suppressing the activation of PI3K, an important kinase involved in T cell activation and differentiation. Moreover, in activated T-cells, Cbl-b inhibits PLCG1 activation and calcium mobilization upon restimulation and thus promotes T cell anergy. Therefore, Cbl-b restricts unnecessary T cell overactivation under physiological condition. Indeed, Cbl-b KO mice had increased T cell proliferation, spontaneous autoimmunity characterized by auto-antibody production, infiltration of activated T and B lymphocytes into multiple organs. On the other hand, in tumor microenvironment, T cells anergy, exhaustion and exclusion are widely present. Thus,

to unleash T cell's full power through release of the Cbl-b brake as an immune-oncological anti-cancer therapy holds great promise.

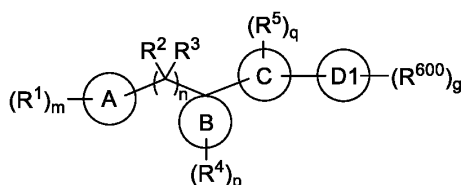
[0005] Accordingly, there is a need for new cancer therapies, specifically using Cbl-b inhibitors.

SUMMARY

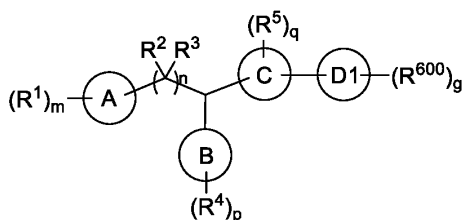
[0006] In one aspect, the present disclosure provides a compound of Formula (I), Formula (II), Formula (III) or Formula (IV), or a pharmaceutically acceptable salt thereof:



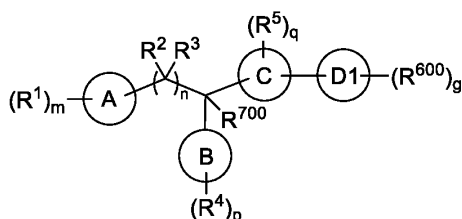
Formula (I)



Formula (II)



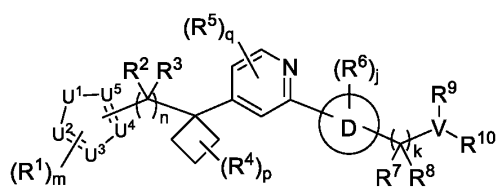
Formula (III)



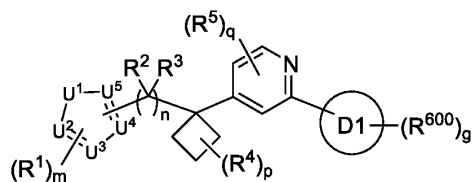
Formula (IV)

as disclosed herein.

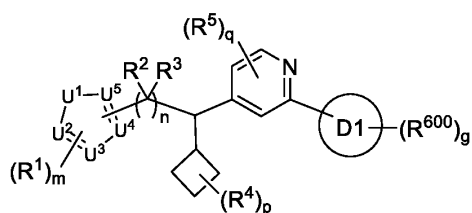
[0007] Also disclosed herein is a compound of Formula (Ia), Formula (IIa), or Formula (IIIa), or a pharmaceutically acceptable salt thereof:



Formula (Ia),



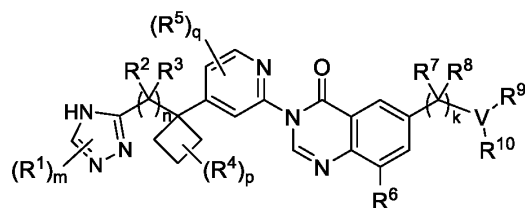
Formula (IIa),



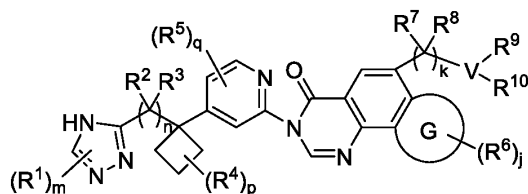
Formula (IIIa),

as disclosed herein.

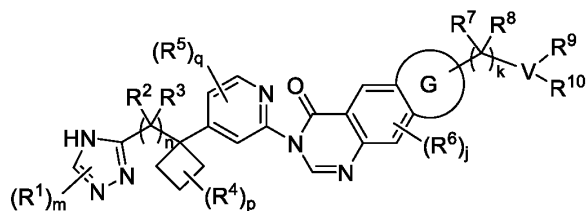
[0008] Also disclosed herein is a compound of Formula (Ib), Formula (Ic), Formula (Id), Formula (IIb), Formula (IIc), Formula (IId), Formula (IIe) or Formula (IIIb), or a pharmaceutically acceptable salt thereof:



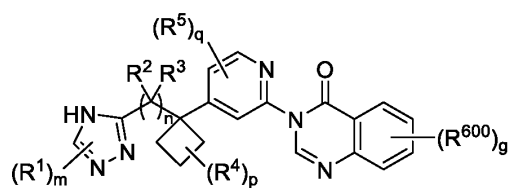
Formula (Ib),



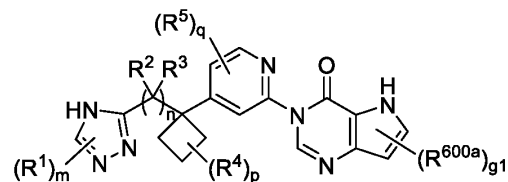
Formula (Ic),



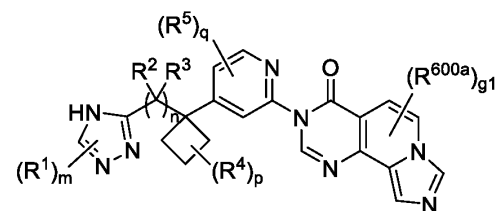
Formula (Id),



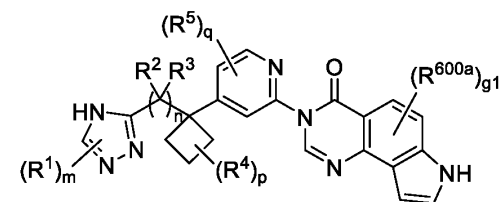
Formula (IIb),



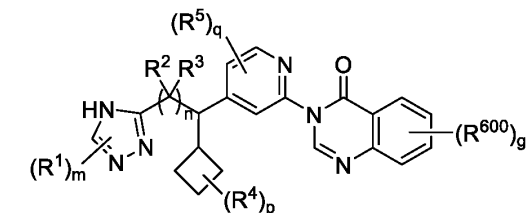
Formula (IIc),



Formula (IId),



Formula (IIe),



Formula (IIIb),

as disclosed herein.

[0009] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein (e.g., a compound of Formula (I), (Ia), (Ib), (Ic) or (Id), a compound of Formula (II), (IIa), (IIb), (IIc), (IId) or Formula (IIe), a compound of Formula (III), (IIIa) or (IIIb), a compound of Formula (IV), or a compound set forth in Table 1, Table 2 or Table 3), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0010] Also disclosed herein is a method of modulating activity of an immune cell, the method comprising contacting the immune cell with an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[0011] Also disclosed herein is a method of treating a cancer, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[0012] Also disclosed herein is a method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[0013] Also disclosed herein is a method of inhibiting abnormal cell proliferation, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[0014] Also disclosed herein is a method of modulating the immune response, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[0015] Also disclosed herein is a method of inhibiting Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[0016] Also disclosed herein is a method for treating a disease or condition associated with Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

INCORPORATION BY REFERENCE

[0017] 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

[0018] In the following description, certain specific details are set forth in order 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.

[0019] 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.

[0020] The terms below, as used herein, have the following meanings, unless indicated otherwise.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] As used herein, the term “C_i-C_j” or “C_{i-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.

[0026] “Oxo” refers to =O.

[0027] “Cyano” refers to -CN.

[0028] “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.

[0029] “Hydroxy” or “hydroxyl”, whether as part of another term or used independently, refers to -OH.

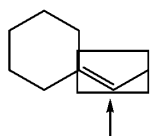
[0030] “Alkyl”, whether as part of another term or used independently, refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, 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, cyano, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0031] “Alkenyl”, whether as part of another term or used independently, refers to a straight-chain, or branched-chain hydrocarbon monoradical 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* configuration, or alternatively, *E* or *Z* configuration about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or

“C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with one or more substituents, such as oxo, halogen, amino, cyano, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0032] “Alkynyl”, whether as part of another term or used independently, refers to a straight-chain or branched-chain hydrocarbon monoradical 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-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂₋₆alkynyl” 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, cyano, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0033] “Alkylidenyl” is alkyl as defined above that is attached via the terminal divalent carbon. Exemplary alkylidenes include, but are not limited to, methylenyl (H₂C=), ethylenyl (CH₃CH=), propylenyl (such as =C(CH₃)₂ and =CHCH₂CH₃), hexylenyl (such as CH₃(CH₂)₄CH=), and the like. For example, in the compound below:



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

[0034] “Alkoxy” or “alkoxyl”, whether as part of another term or used independently, refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Whenever it appears herein, a numerical range such as “C₁₋₆ 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 alkoxy is a C₁₋₃alkoxy. In some embodiments, the alkoxy is a C₁₋₂alkoxy. In some embodiments, the alkoxy 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, heterocycloalkyl, 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.

[0035] “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, which may include fused (for example, an aryl ring fused with a cycloalkyl or another aryl ring), or bridged 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 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, cyano, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0036] “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, a cycloalkyl ring 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, cyano, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0037] “Cycloalkylalkyl” refers to a cycloalkyl attached to alkyl, including -cycloalkyl-alkyl and cycloalkyl-alkyl-. In some embodiments, cycloalkylalkyl refers to -cycloalkyl-alkyl. In some embodiments, cycloalkylalkyl refers to cycloalkyl-alkyl-.

[0038] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0039] “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.

[0040] “Haloalkoxy” refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above.

[0041] “Haloalkynyl” refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

[0042] “Hydroxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0043] “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more aminos. In some embodiments, the alkyl is substituted with one amino. In some embodiments, the

alkyl is substituted with one, two, or three aminos. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0044] “Carboxylate” refers to refers to a $-C(O)O-$ group. A “substituted carboxylate” refers to a $-C(O)O-G$ where G is a carboxylate protecting group. Carboxylate protecting groups are well known to one of ordinary skill in the art. An extensive list of protecting groups for the carboxylate group functionality may be found in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein.

[0045] “Heteroalkyl” 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 one aspect, a heteroalkyl is a C_1-C_6 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, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2NHCH_3$, or $-CH_2CH_2N(CH_3)_2$. 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, $-CN$, $-CF_3$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, $-CN$, $-CF_3$, $-OH$, or $-OMe$. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0046] “Heteroalkenyl” 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 one aspect, a heteroalkenyl is a C_2-C_6 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, $-CH=CHOCH_3$, $-CH=CHOCH_2CH_2OCH_3$, $-CH_2CH_2OCH=CHOCH_3$, $-C(=CH_2)OCH_3$, $-CH=NCH_3$, $-CH_2N=CH_2$, $-CH=CHNHCH_3$, or $-CH=CHN(CH_3)_2$. Unless stated otherwise specifically in the specification, a heteroalkenyl is optionally substituted for example, with oxo, halogen, amino, cyano, 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, $-CN$, $-CF_3$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$. 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.

[0047] “Heteroalkynyl” 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 one aspect, 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, cyano, 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.

[0048] “Heterocyclyl” or “Heterocycloalkyl”, 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 heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic or polycyclic (including but not limited to, bicyclic, tricyclic, or tetracyclic) ring system. In some embodiments, the polycyclic heterocycloalkyl may include fused (for example, a heterocycloalkyl fused with a cycloalkyl or another heterocycloalkyl ring), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C₂-C₁₅ fully saturated heterocycloalkyl or C₂-C₁₅ heterocycloalkenyl), from two to ten carbon atoms (C₂-C₁₀ fully saturated heterocycloalkyl or C₂-C₁₀ heterocycloalkenyl), from two to eight carbon atoms (C₂-C₈ fully saturated heterocycloalkyl or C₂-C₈ heterocycloalkenyl), from two to seven carbon atoms (C₂-C₇ fully saturated heterocycloalkyl or C₂-C₇ heterocycloalkenyl), from two to six carbon atoms (C₂-C₆ fully

saturated heterocycloalkyl or C₂-C₆ heterocycloalkenyl), from two to five carbon atoms (C₂-C₅ fully saturated heterocycloalkyl or C₂-C₅ heterocycloalkenyl), or two to four carbon atoms (C₂-C₄ fully saturated heterocycloalkyl or C₂-C₄ heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, decahydroisoquinolyl, imidazoliny, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranly, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with one or more substituents, such as oxo, halogen, amino, cyano, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl 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 heterocycloalkyl is optionally substituted with one or more substituents, such as halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0049] “Heterocyclalkyl” refers to a heterocycl attached to alkyl, including -heterocycl-alkyl and heterocycl-alkyl-. In some embodiments, heterocyclalkyl refers to -heterocycl-alkyl. In some embodiments, heterocyclalkyl refers to heterocycl-alkyl-.

[0050] “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. In some embodiments, the polycyclic heteroaryl may include fused (for example, a monocyclic heteroaryl fused with a cycloalkyl, heterocycloalkyl, aryl ring or another heteroaryl ring, or a monocyclic aryl fused with a heterocycloalkyl or heteroaryl ring), or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridonyl, pyridinyl, hydroxypyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with one or more substituents, such as halogen, amino, cyano, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, 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.

[0051] The term “partially saturated” 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.

[0052] 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.

[0053] 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.

[0054] 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.

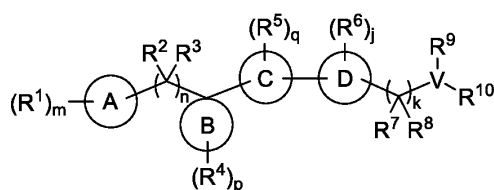
[0055] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving 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.

[0056] As used herein, a “disease or condition associated with cbl-b activity” or, alternatively, “a cbl-b-mediated disease or disorder” means any disease or other deleterious condition in which cbl-b, or a mutant thereof, is known or suspected to play a role.

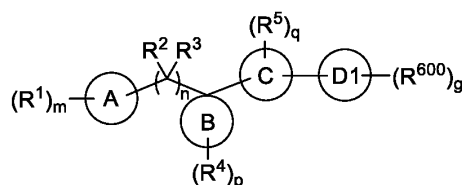
Compounds

[0057] Described herein are compounds, or a pharmaceutically acceptable salt thereof useful in the treatment of a disease or condition associated with Cbl-b.

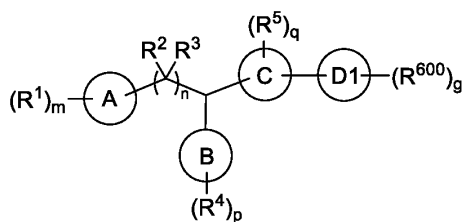
[0058] Disclosed herein is a compound of Formula (I), (II), or (III):



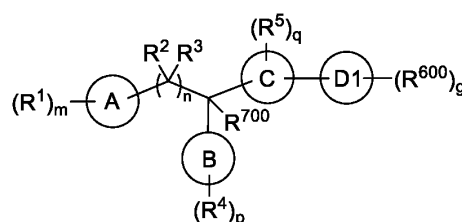
Formula (I),



Formula (II),



Formula (III),



Formula (IV),

or a pharmaceutically acceptable salt thereof,

wherein:

each R¹ is independently selected from halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more R;

Ring A is cycloalkyl, heterocyclyl, aryl or heteroaryl;

each of R² and R³ is independently selected from hydrogen, halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more R;

Ring B is cycloalkyl or heterocyclyl;

each R⁴ is independently selected from halogen, cyano, oxo, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, or haloalkyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, and haloalkyl are optionally substituted with one or more R;

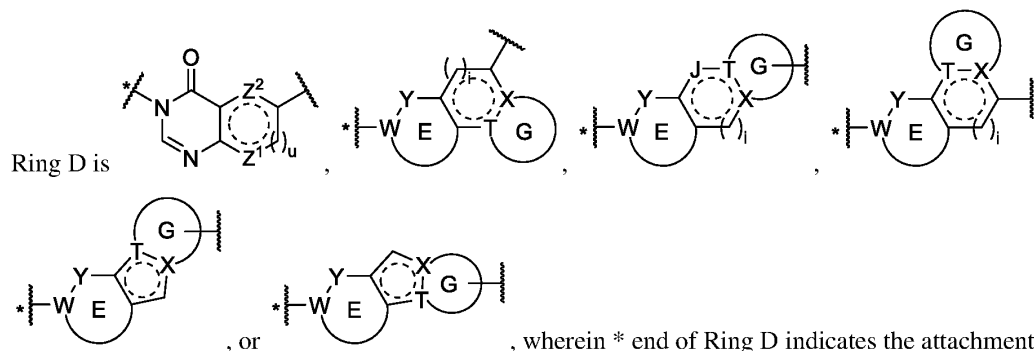
or

two R^4 together with the same atom to which they are both attached form a C_2 - C_6 alkylidenyl

optionally substituted with one or more R;

Ring C is aryl or heteroaryl;

each R^5 is independently selected from halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl are optionally substituted with one or more R; or



Z^1 is $C(H)_{1-2}$ or $N(H)_{0-1}$;

Z^2 is $C(H)_{1-2}$, $N(H)_{0-1}$, O, or S;

W is $C(H)_{0-1}$ or N;

Y is $N(H)_{0-1}$, O, S, $C(O)$, $S(O)_{1-2}$ or $P(O)_{1-2}$;

J is $C(H)_{0-1}$ or N;

X is $C(H)_{0-1}$ or N;

T is $C(H)_{0-1}$ or N;

Ring E is heterocyclyl or heteroaryl;

Ring G is cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with one or more R;

each R^6 is independently selected from halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R;

each of R^7 and R^8 is independently selected from hydrogen, deuterium, halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, haloalkyl or cycloalkyl;

V is CH or N;

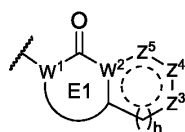
each of R^9 and R^{10} is independently selected from hydrogen, deuterium, alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, or heterocyclylalkyl, wherein the cycloalkyl, heterocyclyl, cycloalkylalkyl, and heterocyclylalkyl are optionally substituted with one or more R; or

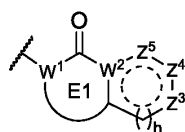
R^9 and R^{10} together with the atom to which they are attached form a cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl is optionally substituted with one or more R;

R^a is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are independently optionally substituted with one or more R;

each of R^b and R^c is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are independently optionally substituted with one or more R; or

R^b and R^c taken together with the atom to which they are attached form a heterocyclyl optionally substituted with one or more R;



Ring D1 is , wherein == indicates a single bond or a double bond;

Ring E1 is a 5- to 6- membered heteroaryl or a 5- to 6- membered heterocyclyl;

Z^3 is $C(H)_{1-2}$ or $N(H)_{0-1}$;

Z^4 is $C(H)_{1-2}$, $N(H)_{0-1}$, O, or S;

Z^5 is $C(H)_{1-2}$, $N(H)_{0-1}$, O, or S;

W^1 is $C(H)_{0-1}$ or N;

W^2 is $C(H)_{0-1}$ or N;

each R^{600} is independently selected from halogen, cyano, heterocyclyl, $-SR^a$, $-NH_2$, $-N(alkyl)_2$, $-NH(cycloalkyl)$, $-C(O)NH_2$, $-C(O)NH(alkyl)$, unsubstituted alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, hydroxylalkyl, haloalkoxy, $-alkynyl-N(alkyl)_2$, haloalkynyl, $-alkynyl-heterocyclyl$, or cycloalkyl, wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R^7 ;

or, two R^{600} taken together with the atom(s) to which they are attached form a cycloalkyl, heterocyclyl or heteroaryl optionally substituted with one or more R;

R^{700} is halogen, alkyl, haloalkyl, cycloalkyl or heterocyclyl, wherein the alkyl, haloalkyl, cycloalkyl and heterocyclyl are independently optionally substituted with one or more R;

each of R and R^7 is independently halogen, cyano, oxo, $-OH$, $-S(=O)(alkyl)$, $-S(=O)_2(alkyl)$, $-S(=O)_2N(alkyl)_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, $-NH_2$, $-N(alkyl)_2$, $-NH(alkyl)$, $-C(=O)(alkyl)$, $-C(=O)OH$, $-C(=O)O(alkyl)$, alkyl, alkoxy, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, or heterocyclyl;

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

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

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

k is 0, 1, 2 or 3;

u is 0, 1 or 2;

h is 0 or 1; and

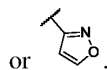
i is 0, 1 or 2.

[0059] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring A is heteroaryl. In some embodiments, Ring A is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl. In some embodiments, Ring A is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl, or 5-membered heteroaryl. In some embodiments, Ring A is monocyclic heteroaryl. In some embodiments, Ring A is polycyclic heteroaryl.

[0060] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring A is 5- to 7-membered monocyclic heteroaryl. In some embodiments, Ring A is 5- to 6-membered monocyclic heteroaryl. In some embodiments, Ring A is 5-membered monocyclic heteroaryl. In some embodiments, Ring A is 6-membered monocyclic heteroaryl.

[0061] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring A is triazolyl, isoxazolyl, pyrrolyl, thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, or dihydropyrrolotriazolyl.

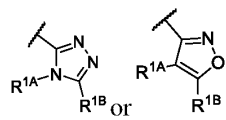
[0062] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring A is



[0063] In some embodiments of the compound of Formula (I), (II), (III) or (IV), each R¹ is independently selected from -CN, -OH, -OR^a, -NR^eR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl. In some embodiments, each R¹ is independently selected from C₁-C₆alkyl or C₁-C₆haloalkyl. In some embodiments, each R¹ is independently selected from C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl, C₁-C₂alkyl, C₁alkyl, C₂alkyl, C₃alkyl, C₄alkyl, C₅alkyl, C₆alkyl, C₁-C₆haloalkyl, C₁-C₅haloalkyl, C₁-C₄haloalkyl, C₁-C₃haloalkyl, C₁-C₂haloalkyl, C₁haloalkyl, C₂haloalkyl, C₃haloalkyl, C₄haloalkyl, or C₅haloalkyl. In some embodiments, each R¹ is independently selected from CH₃, CF₂H or CFH₂.

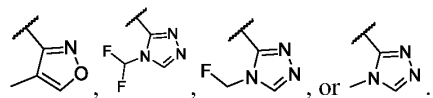
[0064] In some embodiments of the compound of Formula (I), (II), (III) or (IV), m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[0065] In some embodiments of the compound of Formula (I), (II), (III) or (IV), $(R^1)_m$ - is



, each R^{1A} and R^{1B} is independently selected from hydrogen or R^1 .

[0066] In some embodiments of the compound of Formula (I), (II), (III) or (IV), $(R^1)_m$ - is



[0067] In some embodiments of the compound of Formula (I), (II), (III) or (IV), n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1.

[0068] In some embodiments of the compound of Formula (I), (II), (III) or (IV), each of R^2 and R^3 is independently selected from hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6} heteroalkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3- to 6- membered heterocyclyl, C_{6-10} aryl or 5- to 9- membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more R. In some embodiments, each of R^2 and R^3 is independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 3- to 6- membered heterocyclyl, wherein the alkyl, haloalkyl and cycloalkyl are optionally substituted with one or more R.

[0069] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring B is a cycloalkyl. In some embodiments, Ring B is C_{3-9} cycloalkyl, C_{3-8} cycloalkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl, C_{3-5} cycloalkyl, or C_{3-4} cycloalkyl. In some embodiments, Ring B is C_9 cycloalkyl, C_8 cycloalkyl, C_7 cycloalkyl, C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl. In some embodiments, Ring B is monocyclic cycloalkyl. In some embodiments, Ring B is polycyclic cycloalkyl.

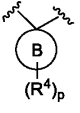
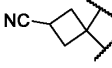
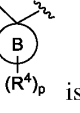
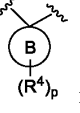
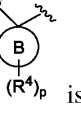
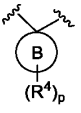
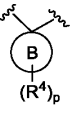
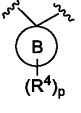
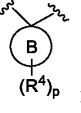
[0070] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring B is a cyclobutanyl. In some embodiments, Ring B is a cyclobutenyl. In some embodiments, Ring B is a cyclopropyl.

[0071] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring B is a heterocyclyl. In some embodiments, Ring B is a 3- to 9- membered heterocyclyl, 3- to 8- membered heterocyclyl, 3- to 7- membered heterocyclyl, 3- to 6- membered heterocyclyl, 3- to 5- membered heterocyclyl, 3- to 4- membered heterocyclyl, 5- to 6- membered heterocyclyl, 3- membered heterocyclyl, 4- membered heterocyclyl, 5- membered heterocyclyl, 6- membered heterocyclyl, 7- membered heterocyclyl, 8- membered heterocyclyl, or 9- membered heterocyclyl. In some embodiments, Ring B is monocyclic heterocyclyl. In some embodiments, Ring B is polycyclic heterocyclyl. In some embodiments, the heterocyclyl comprises 1 or 2 O atom or N atom. In some

embodiments, the heterocyclyl comprises 1 O atom. In some embodiments, the heterocyclyl comprises 1 N atom.

[0072] In some embodiments of the compound of Formula (I), (II), (III) or (IV), p is 0, 1, 2 or 3. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3.

[0073] In some embodiments of the compound of Formula (I), (II), (III) or (IV), each R^4 is independently selected from halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-NR^bR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6} heteroalkynyl, or C_{1-6} haloalkyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, and haloalkyl are optionally substituted with one or more R. In some embodiments, each R^4 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl, wherein the alkyl, alkenyl, alkynyl, and haloalkyl are optionally substituted with one or more R. In some embodiments, each R^4 is independently selected from C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, or C_{1-3} haloalkyl, wherein the alkyl, alkenyl, alkynyl, and haloalkyl are optionally substituted with one or more R. In some embodiments, each R^4 is cyano.

[0074] In some embodiments of the compound of Formula (I) or (II),  is , , , or . In some embodiments,  is . In some embodiments,  is . In some embodiments,  is . In some embodiments,  is . In some embodiments,  is . In some embodiments,  is . In some embodiments,  is .

[0075] In some embodiments of the compound of Formula (III) or Formula (IV),  is , , , or .

[0076] In some embodiments of the compound of Formula (I), (II), (III) or (IV), two R^4 together with the same atom to which they are both attached form a C_2 - C_6 alkylidenyl optionally substituted with one or more R. In some embodiments, two R^4 together with the same atom to which they are both attached form a C_2 - C_6 alkylidenyl optionally substituted with one or more halogen. In some

embodiments, two R^4 together with the same atom to which they are both attached form a C_2-C_4 alkylidenyl optionally substituted with one or more halogen. In some embodiments, two R^4 together

with the same atom to which they are both attached form a  optionally substituted with one or more halogen.

[0077] In some embodiments of the compound of Formula (I) or (II),  is , or .

In some embodiments,  is . In some embodiments,  is .

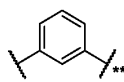
[0078] In some embodiments of the compound of Formula (III) or (IV),  is  or .

[0079] In some embodiments of the compound of Formula (IV), R^{700} is halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 3- to 6- membered heterocyclyl, wherein the alkyl, haloalkyl, cycloalkyl and heterocyclyl are independently optionally substituted with one or more R. In some embodiments, R^{700} is F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CHF_2CH_3$, cyclopropyl, or cyclobutyl.

[0080] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring C is an aryl. In some embodiments, Ring C is C_{6-12} aryl, C_{6-11} aryl, C_{6-10} aryl, C_{6-9} aryl, C_{6-8} aryl, or C_{6-7} aryl. In some embodiments, Ring C is C_{12} aryl, C_{11} aryl, C_{10} aryl, C_9 aryl, C_8 aryl, C_7 aryl or C_6 aryl. In some embodiments, Ring C is monocyclic aryl. In some embodiments, Ring C is polycyclic aryl.

[0081] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring C is phenyl.

[0082] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring C is



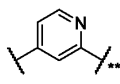
, and ** end of Ring C indicates the attachment point of Ring C to Ring D or Ring D1.

[0083] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring C is a heteroaryl. In some embodiments, Ring C is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl. In some embodiments, Ring C is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl, or 5-membered heteroaryl. In some embodiments, Ring C is monocyclic heteroaryl. In some embodiments, Ring C is polycyclic heteroaryl.

[0084] In some embodiments of the compound of Formula (I), (II), (III) or (IV), Ring C is 5- to 7-membered monocyclic heteroaryl. In some embodiments, Ring C is 5- to 6-membered monocyclic heteroaryl. In some embodiments, Ring C is 5-membered monocyclic heteroaryl. In some embodiments, Ring C is 6-membered monocyclic heteroaryl.

[0085] In some embodiment of the compound of Formula (I), (II), (III) or (IV), Ring C is pyridinyl.

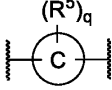
[0086] In some embodiment of the compound of Formula (I), (II), (III) or (IV), Ring C is



, and ** end of Ring C indicates the attachment point of Ring C to Ring D or Ring D1.

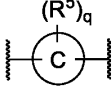
[0087] In some embodiment of the compound of Formula (I), (II), (III) or (IV), each R^5 is independently selected from halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl are optionally substituted with one or more R. In some embodiment, each R^5 is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 3-6 membered heterocyclyl, wherein the alkyl, haloalkyl, cycloalkyl or heterocyclyl are optionally substituted with one or more R.

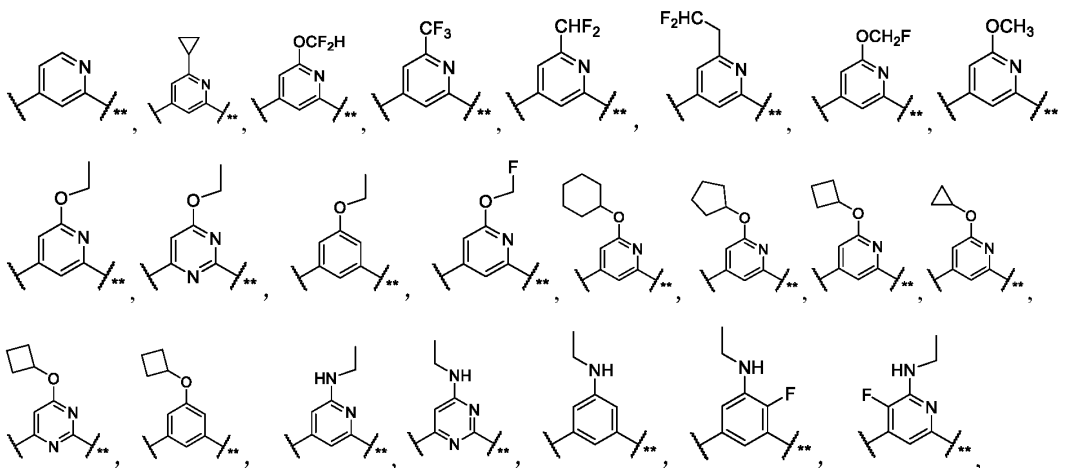
[0088] In some embodiment of the compound of Formula (I), (II), (III) or (IV), q is 0, 1, 2 or 3. In some embodiment, q is 0, 1, or 2. In some embodiment, q is 0. In some embodiment, q is 1. In some embodiment, q is 2.

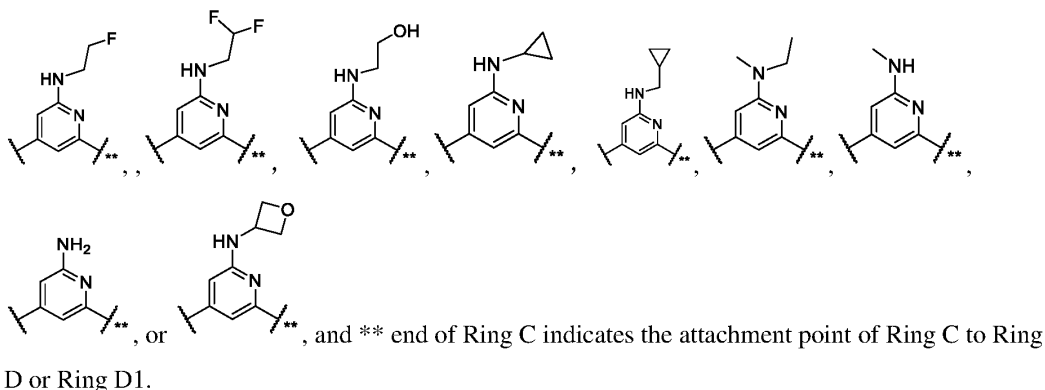
[0089] In some embodiment of the compound of Formula (I), (II), (III) or (IV),  is



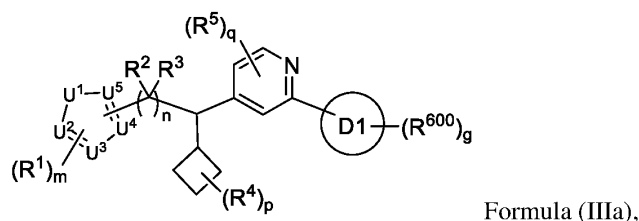
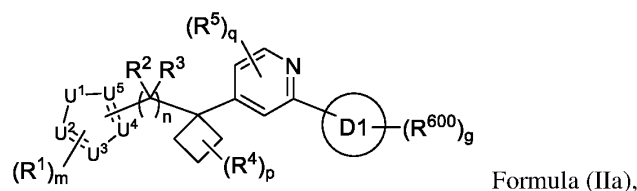
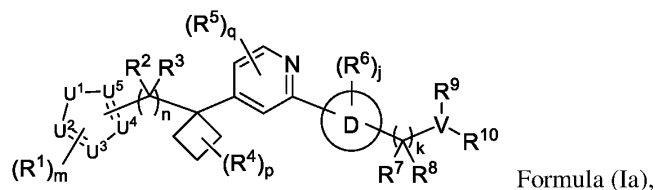
, each R^{5A} , R^{5B} and R^{5C} is independently selected from hydrogen or R^5 , and ** end of Ring C indicates the attachment point of Ring C to Ring D or Ring D1.

[0090] In some embodiment of the compound of Formula (I), (II), (III) or (IV),  is





[0091] In some embodiment, the compound has a Formula (Ia), Formula (IIa) or Formula (IIIa):



wherein U¹ is O, S, NH or CH₂; and each of U², U³, U⁴ and U⁵ is independently N or CH.

[0092] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIE), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is alkyl or haloalkyl.

[0093] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is alkyl. In some embodiments, R¹ is C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl or C₁-C₂alkyl. In some embodiments, R¹ is C₆alkyl, C₅alkyl, C₄alkyl, C₃alkyl, C₂alkyl or C₁alkyl.

[0094] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIE), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is -CH₃.

[0095] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIE), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is haloalkyl. In some embodiments, R¹ is

C₁-C₆haloalkyl, C₁-C₅haloalkyl, C₁-C₄haloalkyl, C₁-C₃haloalkyl or C₁-C₂haloalkyl. In some embodiments, R¹ is independently C₆haloalkyl, C₅haloalkyl, C₄haloalkyl, C₃haloalkyl, C₂haloalkyl or C₁haloalkyl.

[0096] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is -CHF₂.

[0097] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), m is 1, and R¹ is -CH₂F.

[0098] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), n is 0.

[0099] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), n is 1, and both R² and R³ are hydrogen.

[0100] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 1, and R⁴ is alkyl or alkynyl.

[0101] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 1, and R⁴ is alkyl. In some embodiments, R⁴ is C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl or C₁-C₂alkyl. In some embodiments, R⁴ is C₆alkyl, C₅alkyl, C₄alkyl, C₃alkyl, C₂alkyl or C₁alkyl.

[0102] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 1, and R⁴ is -CH₃.

[0103] In some embodiments, p is 1, and R⁴ is alkynyl. In some embodiments, R⁴ is C₂-C₆alkynyl, C₂-C₅alkynyl, C₂-C₄alkynyl, or C₂-C₃alkynyl. In some embodiments, R⁴ is C₆alkynyl, C₅alkynyl, C₄alkynyl, C₃alkynyl, or C₂alkynyl.

[0104] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 1, and R⁴ is ethynyl.

[0105] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 2, and two R⁴ together with the same atom to which

they are both attached form a  optionally substituted with one or more halogen.

[0106] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), p is 2, and two R⁴ together with the same atom to which

they are both attached form a  or .

[0107] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 0.

[0108] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is -OR^a.

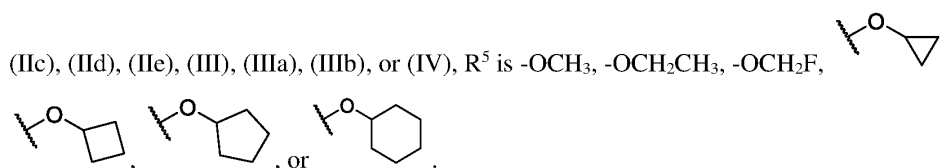
[00109] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, R⁵ is -OR^a, and R^a is alkyl, haloalkyl, or cycloalkyl.

[00110] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), R^a is alkyl. In some embodiments, R^a is C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl or C₁-C₂alkyl. In some embodiments, R^a is C₆alkyl, C₅alkyl, C₄alkyl, C₃alkyl, C₂alkyl or C₁alkyl.

[00111] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), R^a is haloalkyl. In some embodiments, R^a is C₁-C₆haloalkyl, C₁-C₅haloalkyl, C₁-C₄haloalkyl, C₁-C₃haloalkyl or C₁-C₂haloalkyl. In some embodiments, R^a is independently C₆haloalkyl, C₅haloalkyl, C₄haloalkyl, C₃haloalkyl, C₂haloalkyl or C₁haloalkyl.

[00112] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), R^a is cycloalkyl. In some embodiments, R^a is C₃₋₉ cycloalkyl, C₃₋₈ cycloalkyl, C₃₋₇ cycloalkyl, C₃₋₆ cycloalkyl, C₃₋₅ cycloalkyl, or C₃₋₄ cycloalkyl. In some embodiments, R^a is C₉ cycloalkyl, C₈ cycloalkyl, C₇ cycloalkyl, C₆ cycloalkyl, C₅ cycloalkyl, C₄ cycloalkyl or C₃ cycloalkyl. In some embodiments, R^a is monocyclic cycloalkyl.

[00113] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb),



[00114] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is cycloalkyl.

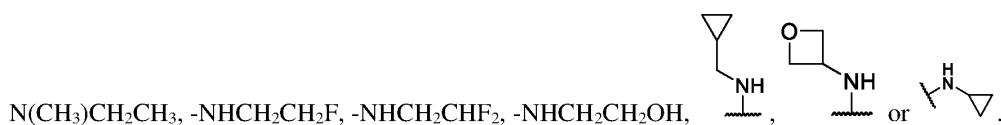
[00115] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), R⁵ is C₃₋₉ cycloalkyl, C₃₋₈ cycloalkyl, C₃₋₇ cycloalkyl, C₃₋₆ cycloalkyl, C₃₋₅ cycloalkyl, or C₃₋₄ cycloalkyl. In some embodiments, R⁵ is C₉ cycloalkyl, C₈ cycloalkyl, C₇ cycloalkyl, C₆ cycloalkyl, C₅ cycloalkyl, C₄ cycloalkyl or C₃ cycloalkyl. In some embodiments, R⁵ is monocyclic cycloalkyl.

[00116] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is cyclopropyl.

[00117] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is -NR^bR^c. In some embodiments, R^b is hydrogen, and R^c is hydrogen. In some embodiments, R^b is hydrogen, and R^c is alkyl, haloalkyl, cycloalkyl, or heterocyclyl, wherein the alkyl, cycloalkyl, and heterocyclyl are independently optionally substituted with one or more R. In some embodiments, R^b is hydrogen, and R^c is C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, cycloalkyl, and heterocyclyl are independently optionally substituted with one or more R. In some

embodiments, R^b is hydrogen, and R^c is alkyl, haloalkyl or cycloalkyl. In some embodiments, R^c is alkyl, wherein the alkyl is independently optionally substituted with one or more R. In some embodiments, R^c is alkyl. In some embodiments, R^c is C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl, C_1 - C_2 alkyl, C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl, wherein the alkyl is independently optionally substituted with one or more R. In some embodiments, R^c is C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl or C_1 - C_2 alkyl. In some embodiments, R^c is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl. In some embodiments, R^c is haloalkyl. In some embodiments, R^c is C_1 - C_6 haloalkyl, C_1 - C_5 haloalkyl, C_1 - C_4 haloalkyl, C_1 - C_3 haloalkyl or C_1 - C_2 haloalkyl. In some embodiments, R^c is independently C_6 haloalkyl, C_5 haloalkyl, C_4 haloalkyl, C_3 haloalkyl, C_2 haloalkyl or C_1 haloalkyl. In some embodiments, R^c is cycloalkyl. In some embodiments, R^c is C_{3-9} cycloalkyl, C_{3-8} cycloalkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl, C_{3-5} cycloalkyl, or C_{3-4} cycloalkyl. In some embodiments, R^c is C_9 cycloalkyl, C_8 cycloalkyl, C_7 cycloalkyl, C_6 cycloalkyl, C_5 cycloalkyl, C_4 cycloalkyl or C_3 cycloalkyl. In some embodiments, R^c is monocyclic cycloalkyl. In some embodiments, R^c is monocyclic C_{3-6} cycloalkyl, monocyclic C_{3-5} cycloalkyl, or monocyclic C_{3-4} cycloalkyl. In some embodiments, R^c is heterocyclyl. In some embodiments, R^c is 3- to 6- membered heterocyclyl, 3- to 5- membered heterocyclyl, 3- to 4- membered heterocyclyl, 5- to 6- membered heterocyclyl, 6- membered heterocyclyl, 5- membered heterocyclyl, 4- membered heterocyclyl, or 3- membered heterocyclyl.

[00118] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), q is 1, and R^5 is selected from NH_2 , $-NHCH_2CH_3$, -



[00119] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIe), (III), (IIIa), (IIIb), or (IV), each R is independently halogen, cyano, oxo, -OH, - $S(=O)(alkyl)$, $-S(=O)_2(alkyl)$, $-S(=O)_2N(alkyl)_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, $-NH_2$, - $N(alkyl)_2$, $-NH(alkyl)$, $-C(=O)(alkyl)$, $-C(=O)OH$, $-C(=O)O(alkyl)$, alkyl, alkoxy, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, or heterocyclyl. In some embodiments of a compound disclosed herein, each R is independently halogen, cyano, -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, or C_3 - C_6 cycloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, cyano, -OH, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_1 - C_6 haloalkyl. In some embodiments, each R is independently halogen, cyano, -OH, or C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -OH, or C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen or C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R is independently halogen. In some embodiments, R is independently halogen, cyano, oxo, -OH, $-S(=O)(C_1-C_6alkyl)$, $-S(=O)_2(C_1-C_6alkyl)$, - $S(=O)_2N(C_1-C_6alkyl)_2$, $-S(=O)_2NH(C_1-C_6alkyl)$, $-S(=O)_2N(C_1-C_6alkyl)_2$, $-NH_2$, $-N(C_1-C_6alkyl)_2$, -

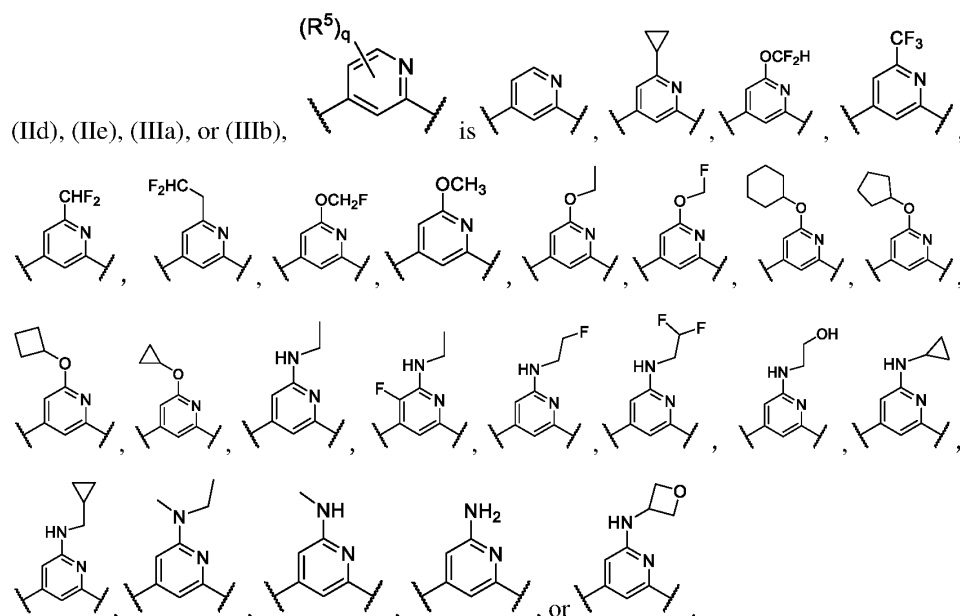
NH(C₁-C₆alkyl), -C(=O)(C₁-C₆alkyl), -C(=O)OH, -C(=O)O(C₁-C₆alkyl), C₁-C₆alkyl, C₁-C₆alkoxyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocyclyl. In some embodiments, R is independently halogen, cyano, -OH, C₁-C₆alkyl (such as -CH₃ or -CH₂CH₃, etc.), C₁-C₆alkoxyl (such as -OCH₃ or -OCH₂CH₃, etc.), C₁-C₆hydroxyalkyl (such as -CF₃ or -CH₂CF₃, etc.), C₃-C₆cycloalkyl (such as cyclopropyl, cyclobutyl,

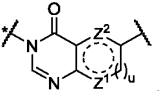
or cyclopentyl etc.), or 3- to 6-membered heterocyclyl (such as , , or , etc.).

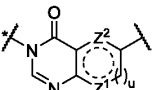
[00120] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIE), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is alkyl or haloalkyl, wherein the alkyl or haloalkyl are optionally substituted with one or more R.

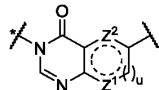
[00121] In some embodiments of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IIE), (III), (IIIa), (IIIb), or (IV), q is 1, and R⁵ is -CHF₂, -CH₂CHF₂, or -CF₃.

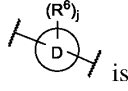
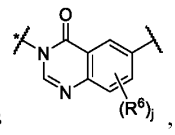
[00122] In some embodiments of the compound of Formula (Ia), (Ib), (Ic), (Id), (IIa), (IIb), (IIc),

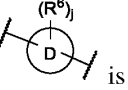
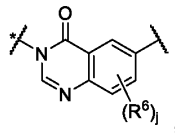


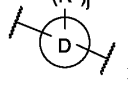
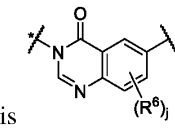
[00123] In some embodiments of the compound of Formula (I), Ring D is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C.

[00124] In some embodiments of the compound of Formula (I), Ring D is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C, and u is 1.

[00125] In some embodiments of the compound of Formula (I), Ring D is , Z^1 is -C(H)₁₋₂-, Z^2 is -C(H)₁₋₂-, and * end of Ring D indicates the attachment point of Ring D to Ring C.

[00126] In some embodiments of the compound of Formula (I), , is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C.

[00127] In some embodiment of the compound of Formula (I), , is , and each R^6 is independently halogen, -OR^a, alkyl, or haloalkyl, wherein each of alkyl and haloalkyl is independently optionally substituted with one or more R, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

[00128] In some embodiments of the compound of Formula (I), , is , and each R^6 is independently halogen, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of alkyl and haloalkyl independently optionally substituted with one or more R, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

[00129] In some embodiments of the compound of Formula (I), one or more of R^6 is independently halogen.

[00130] In some embodiments of the compound of Formula (I), j is 1, and R^6 is -F.

[00131] In some embodiments of the compound of Formula (I), one or more of R^6 is independently -OR^a. In some embodiments, R^a is alkyl or haloalkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

[00132] In some embodiments of the compound of Formula (I), one or more of R^6 is independently -OR^a, and R^a is alkyl. In some embodiments, R^a is independently C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl or C₁-C₂alkyl, each independently optionally substituted with one or more R. In some embodiments, R^a is independently C₆alkyl, C₅alkyl, C₄alkyl, C₃alkyl, C₂alkyl or C₁alkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

[00133] In some embodiments of the compound of Formula (I), j is 1, and R^6 is -OCH₃.

[00134] In some embodiments of the compound of Formula (I), one or more of R^6 is independently C₁-C₆alkyl, C₁-C₅alkyl, C₁-C₄alkyl, C₁-C₃alkyl or C₁-C₂alkyl, each independently optionally

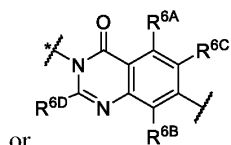
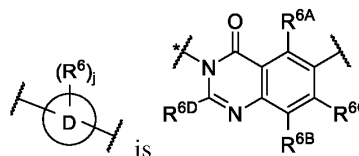
substituted with one or more R. In some embodiments, one or more of R⁶ is independently C₆alkyl, C₅alkyl, C₄alkyl, C₃alkyl, C₂alkyl or C₁alkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

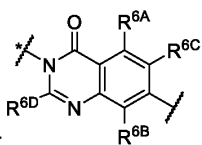
[00135] In some embodiments of the compound of Formula (I), j is 1, and R⁶ is -CH₃.

[00136] In some embodiments of the compound of Formula (I), one or more of R⁶ is independently C₁-C₆haloalkyl, C₁-C₅haloalkyl, C₁-C₄haloalkyl, C₁-C₃haloalkyl or C₁-C₂haloalkyl, each independently optionally substituted with one or more R. In some embodiments, one or more of R⁶ is independently C₆haloalkyl, C₅haloalkyl, C₄haloalkyl, C₃haloalkyl, C₂haloalkyl or C₁haloalkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, cyano, oxo, or -OH.

[00137] In some embodiments of the compound of Formula (I), j is 1, and R⁶ is C₁-C₆haloalkyl, C₁-C₅haloalkyl, C₁-C₄haloalkyl, C₁-C₃haloalkyl or C₁-C₂haloalkyl. In some embodiments, j is 1, and R⁶ is C₁haloalkyl. In some embodiments, j is 1, and R⁶ is -CF₃ or -CHF₂.

[00138] In some embodiments of the compound of Formula (I),



or , each R^{6A}, R^{6B}, R^{6C} and R^{6D} is independently selected from hydrogen or R⁶, and * end of Ring D indicates the attachment point of Ring D to Ring C.

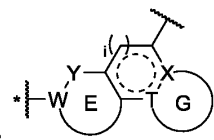
[00139] In some embodiments of the compound of Formula (I), R^{6A} is hydrogen.

[00140] In some embodiments of the compound of Formula (I), R^{6B} is hydrogen, halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, or heterocyclyl wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more R. In some embodiments, R^{6B} is hydrogen, halogen, cyano, -OR^a, -SR^a, -NR^bR^c, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ heteroalkyl, C₂₋₆ heteroalkenyl, C₂₋₆ heteroalkynyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocyclyl wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R. In some embodiments, R^{6B} is hydrogen, halogen, -OR^a, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, and 3-6 membered heterocyclyl wherein the alkyl, haloalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R. In some embodiments, R^{6B} is hydrogen, halogen, CF₃, CH₃, OCH₃, CHF₂, or cyclopropyl.

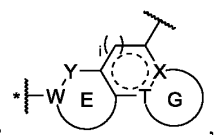
[00141] In some embodiments of the compound of Formula (I), R^{6C} is hydrogen, halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl,

cycloalkyl, or heterocyclyl wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more R. In some embodiments, R^{6C} is hydrogen, halogen, C₁₋₆alkyl, or C₁₋₆haloalkyl wherein the alkyl, and haloalkyl are optionally substituted with one or more R. In some embodiments, R^{6B} is hydrogen, F, Cl, Br, I or CH₃.

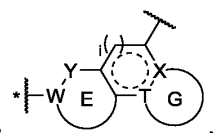
[00142] In some embodiments of the compound of Formula (I), R^{6D} is hydrogen.



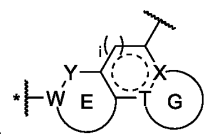
[00143] In some embodiments of the compound of Formula (I), Ring D is wherein * end of Ring D indicates the attachment point of Ring D to Ring C.



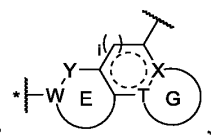
[00144] In some embodiments of the compound of Formula (I), Ring D is wherein * end of Ring D indicates the attachment point of Ring D to Ring C, and i is 1.



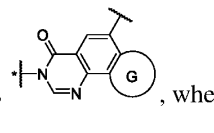
[00145] In some embodiments of the compound of Formula (I), Ring D is wherein W is N, and Y is C(O), and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.



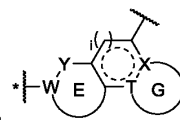
[00146] In some embodiments of the compound of Formula (I), Ring D is wherein Ring E is a 6-membered heteroaryl, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.



[00147] In some embodiments of the compound of Formula (I), Ring D is wherein X is C, and T is C, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.



[00148] In some embodiments of the compound of Formula (I), Ring D is wherein * end of Ring D indicates the attachment point of Ring D to Ring C.



[00149] In some embodiments of the compound of Formula (I), Ring D is cycloalkyl, heterocyclyl or heteroaryl, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.

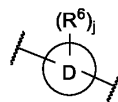
[00150] In some embodiments of the compound of Formula (I), Ring G is cycloalkyl. In some embodiments, Ring G is C_{5-11} cycloalkyl, C_{5-10} cycloalkyl, C_{5-9} cycloalkyl, C_{5-8} cycloalkyl, C_{5-7} cycloalkyl, or C_{5-6} cycloalkyl. In some embodiments, Ring G is C_{11} cycloalkyl, C_{10} cycloalkyl, C_9 cycloalkyl, C_8 cycloalkyl, C_7 cycloalkyl, C_6 cycloalkyl or C_5 cycloalkyl. In some embodiments, Ring G is monocyclic cycloalkyl.

[00151] In some embodiments of the compound of Formula (I), Ring G is heterocyclyl. In some embodiments, Ring G is 5- to 10-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heterocyclyl. In some embodiments, Ring G is 10-membered heterocyclyl, 9-membered heterocyclyl, 8-membered heterocyclyl, 7-membered heterocyclyl, 6-membered heterocyclyl, or 5-membered heterocyclyl. In some embodiments, Ring G is monocyclic heterocyclyl.

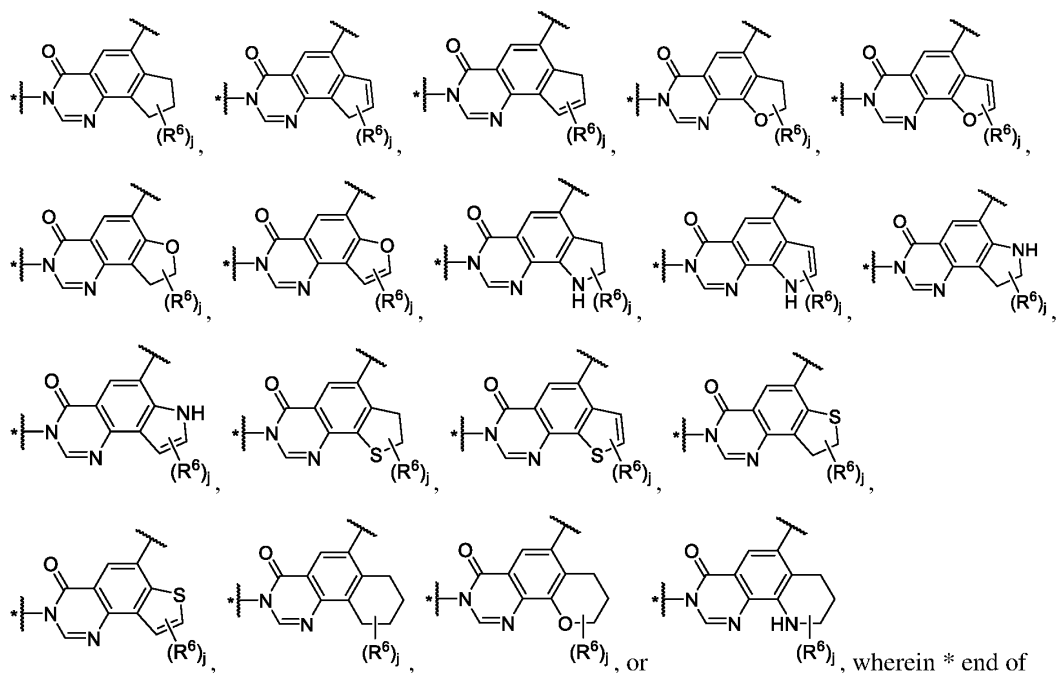
[00152] In some embodiments of the compound of Formula (I), Ring G is 5- to 7-membered monocyclic heterocyclyl. In some embodiments, Ring G is 5- to 6-membered monocyclic heterocyclyl. In some embodiments, Ring G is 5-membered monocyclic heterocyclyl. In some embodiments, Ring G is 6-membered monocyclic heterocyclyl.

[00153] In some embodiments of the compound of Formula (I), Ring G is heteroaryl. In some embodiments, Ring G is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl. In some embodiments, Ring G is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl, or 5-membered heteroaryl. In some embodiments, Ring G is monocyclic heteroaryl. In some embodiments, Ring G is polycyclic heteroaryl. In some embodiments, Ring G is bicyclic heteroaryl.

[00154] In some embodiments of the compound of Formula (I), Ring G is 5- to 7-membered monocyclic heteroaryl. In some embodiments, Ring G is 5- to 6-membered monocyclic heteroaryl. In some embodiments, Ring G is 5-membered monocyclic heteroaryl. In some embodiments, Ring G is 6-membered monocyclic heteroaryl.



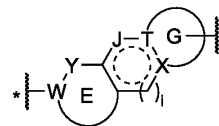
[00155] In some embodiments of the compound of Formula (I), is selected from:



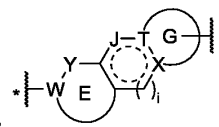
Ring D indicates the attachment point of Ring D to Ring C.

[00156] In some embodiments of the compound of Formula (I), j is 0, 1 or 2, and each R^6 is independently halogen, alkyl or haloalkyl.

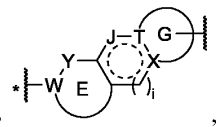
[00157] In some embodiments of the compound of Formula (I), each R^6 is independently halogen. In some embodiments, each R^6 is independently fluoro or chloro.



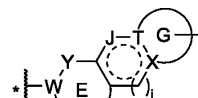
[00158] In some embodiments of the compound of Formula (I), Ring D is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C.

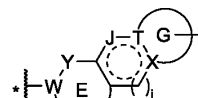


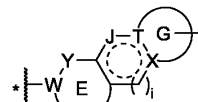
[00159] In some embodiments of the compound of Formula (I), Ring D is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C, and i is 1.

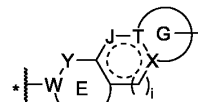


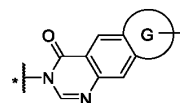
[00160] In some embodiments of the compound of Formula (I), Ring D is , W is -N-, Y is -C(O)-, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.

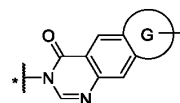


[00161] In some embodiments of the compound of Formula (I), Ring D is , Ring E is a 6-membered heteroaryl, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.



[00162] In some embodiments of the compound of Formula (I), Ring D is , J is CH, X is C, T is C, and * end of Ring D indicates the attachment point of Ring D to Ring C. In some embodiments, i is 1.



[00163] In some embodiments of the compound of Formula (I), Ring D is , wherein * end of Ring D indicates the attachment point of Ring D to Ring C.

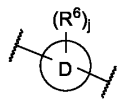
[00164] In some embodiments of the compound of Formula (I), Ring G is cycloalkyl. In some embodiments, Ring G is C₅₋₁₁ cycloalkyl, C₅₋₁₀ cycloalkyl, C₅₋₉ cycloalkyl, C₅₋₈ cycloalkyl, C₅₋₇ cycloalkyl, or C₅₋₆ cycloalkyl. In some embodiments, Ring G is C₁₁ cycloalkyl, C₁₀ cycloalkyl, C₉ cycloalkyl, C₈ cycloalkyl, C₇ cycloalkyl, C₆ cycloalkyl or C₅ cycloalkyl. In some embodiments, Ring G is monocyclic cycloalkyl.

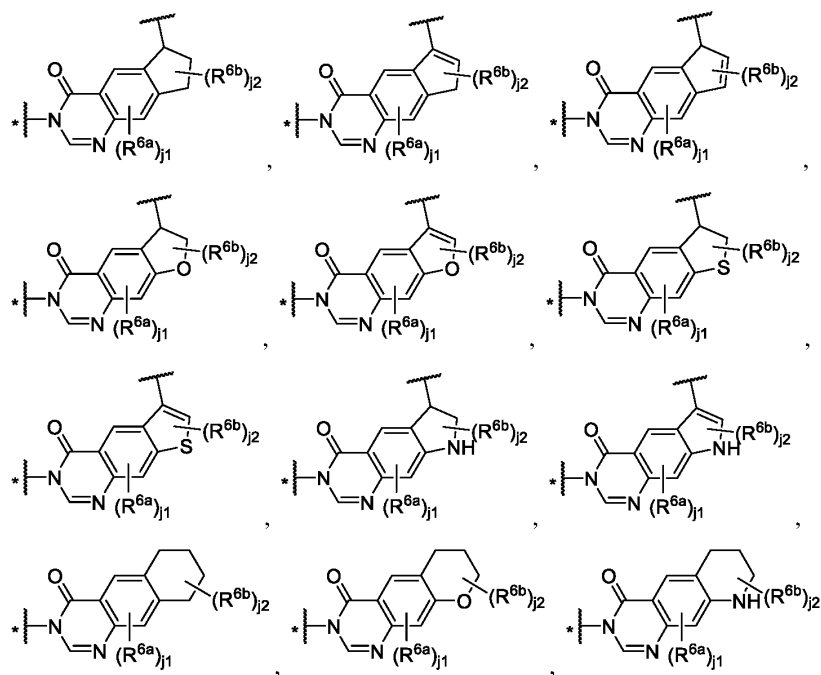
[00165] In some embodiments of the compound of Formula (I), Ring G is heterocyclyl. In some embodiments, Ring G is 5- to 10-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heterocyclyl. In some embodiments, Ring G is 10-membered heterocyclyl, 9-membered heterocyclyl, 8-membered heterocyclyl, 7-membered heterocyclyl, 6-membered heterocyclyl, or 5-membered heterocyclyl. In some embodiments, Ring G is monocyclic heterocyclyl.

[00166] In some embodiments of the compound of Formula (I), Ring G is 5- to 7-membered monocyclic heterocyclyl. In some embodiments, Ring G is 5- to 6-membered monocyclic heterocyclyl. In some embodiments, Ring G is 5-membered monocyclic heterocyclyl. In some embodiments, Ring G is 6-membered monocyclic heterocyclyl.

[00167] In some embodiments of the compound of Formula (I), Ring G is heteroaryl. In some embodiments, Ring G is 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl. In some embodiments, Ring G is 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl, or 5-membered heteroaryl. In some embodiments, Ring G is monocyclic heteroaryl. In some embodiments, Ring G is polycyclic heteroaryl. In some embodiments, Ring G is bicyclic heteroaryl.

[00168] In some embodiments of the compound of Formula (I), Ring G is 5- to 7-membered monocyclic heteroaryl. In some embodiments, Ring G is 5- to 6-membered monocyclic heteroaryl. In some embodiments, Ring G is 5-membered monocyclic heteroaryl. In some embodiments, Ring G is 6-membered monocyclic heteroaryl.

[00169] In some embodiments of the compound of Formula (I),  is selected from:



wherein * end of Ring D indicates the attachment point of Ring D to Ring C;

each of R^{6a} and R^{6b} is independently R^6 ;

j_1 is 0, 1, or 2; and

j_2 is 0, 1, 2, 3 or 4.

[00170] In some embodiments of the compound of Formula (I), both j_1 and j_2 are 0.

[00171] In some embodiments of the compound of Formula (I), j_1 is 1, j_2 is 0, and R^{6a} is alkyl. In some embodiments, R^{6a} is C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl or C_1 - C_2 alkyl. In some embodiments, R^6 is independently C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[00172] In some embodiments of the compound of Formula (I), j_1 is 1, j_2 is 0, and R^{6a} is $-CH_3$.

[00173] In some embodiments of the compound of Formula (I), k is 0.

[00174] In some embodiments of the compound of Formula (I), k is 1, and each of R^7 and R^8 is independently selected from hydrogen or alkyl.

[00175] In some embodiments of the compound of Formula (I), k is 1, and both R^7 and R^8 are hydrogen.

[00176] In some embodiments of the compound of Formula (I), k is 1, R^7 is hydrogen, and R^8 is alkyl. In some embodiments, R^8 is C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl or C_1 - C_2 alkyl. In some embodiments, R^8 is C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

[00177] In some embodiments of the compound of Formula (I), k is 1, R^7 is hydrogen, and R^8 is $-CH_3$.

[00178] In some embodiments of the compound of Formula (I), k is 1, and both R^7 and R^8 are alkyl. In some embodiments, R^7 and R^8 are independently C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl or C_1 - C_2 alkyl. In some embodiments, R^7 and R^8 are independently C_6 alkyl, C_5 alkyl, C_4 alkyl, C_3 alkyl, C_2 alkyl or C_1 alkyl.

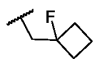
[00179] In some embodiments of the compound of Formula (I), k is 1, and both R^7 and R^8 are $-CH_3$.

[00180] In some embodiments of the compound of Formula (I), V is N.

[00181] In some embodiments of the compound of Formula (I), V is N, R^9 is hydrogen, and R^{10} is cycloalkylalkyl or cycloalkyl, each optionally substituted with one or more R, and each R is independently selected from halogen, alkyl or haloalkyl.

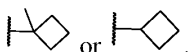
[00182] In some embodiments of the compound of Formula (I), V is N, R^9 is hydrogen, and R^{10} is cycloalkylalkyl optionally substituted with one or more R, and each R is independently selected from halogen, alkyl or haloalkyl. In some embodiments, R^{10} is $-C_1$ - C_3 alkyl- C_{3-9} cycloalkyl, $-C_1$ - C_3 alkyl- C_{3-8} cycloalkyl, $-C_1$ - C_3 alkyl- C_{3-7} cycloalkyl, $-C_1$ - C_3 alkyl- C_{3-6} cycloalkyl, $-C_1$ - C_3 alkyl- C_{3-5} cycloalkyl, or $-C_1$ - C_3 alkyl- C_{3-4} cycloalkyl, each independently optionally substituted with one or more R. In some embodiments, R^5 is $-C_1$ - C_3 alkyl- C_9 cycloalkyl, $-C_1$ - C_3 alkyl- C_8 cycloalkyl, $-C_1$ - C_3 alkyl- C_7 cycloalkyl, $-C_1$ - C_3 alkyl- C_6 cycloalkyl, $-C_1$ - C_3 alkyl- C_5 cycloalkyl, $-C_1$ - C_3 alkyl- C_4 cycloalkyl or $-C_1$ - C_3 alkyl- C_3 cycloalkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, alkyl or haloalkyl.

[00183] In some embodiments of the compound of Formula (I), V is N, R^9 is hydrogen, and R^{10} is



[00184] In some embodiments of the compound of Formula (I), V is N, R^9 is hydrogen, and R^{10} is cycloalkyl optionally substituted with one or more R, and each R is independently selected from halogen, alkyl or haloalkyl. In some embodiments, R^{10} is $-C_{3-9}$ cycloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{3-7}$ cycloalkyl, $-C_{3-6}$ cycloalkyl, $-C_{3-5}$ cycloalkyl, or $-C_{3-4}$ cycloalkyl, each independently optionally substituted with one or more R. In some embodiments, R^5 is $-C_9$ cycloalkyl, $-C_8$ cycloalkyl, $-C_7$ cycloalkyl, $-C_6$ cycloalkyl, $-C_5$ cycloalkyl, $-C_4$ cycloalkyl or $-C_3$ cycloalkyl, each independently optionally substituted with one or more R. In some embodiments, each R is independently halogen, alkyl or haloalkyl.

[00185] In some embodiments of the compound of Formula (I), V is N, R^9 is hydrogen, and R^{10} is



[00186] In some embodiments of the compound of Formula (I), V is N, and R⁹ and R¹⁰ together with the atom to which they are attached form a heterocyclyl optionally substituted with one or more R, and each R is independently selected from halogen, alkyl or haloalkyl.

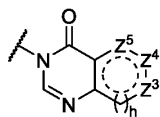
[00187] In some embodiments of the compound of Formula (I), V is N, and R⁹ and R¹⁰ together with the atom to which they are attached form a 5- to 10-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heterocyclyl, each independently optionally substituted with one or more R. In some embodiments, R⁹ and R¹⁰ together with the atom to which they are attached form a 10-membered heterocyclyl, 9-membered heterocyclyl, 8-membered heterocyclyl, 7-membered heterocyclyl, 6-membered heterocyclyl, or 5-membered heterocyclyl, each independently optionally substituted with one or more R. In some embodiments, R⁹ and R¹⁰ together with the atom to which they are attached form a 5- to 7-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, R⁹ and R¹⁰ together with the atom to which they are attached form a 5- to 6-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, R⁹ and R¹⁰ together with the atom to which they are attached form a 5-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, R⁹ and R¹⁰ together with the atom to which they are attached form a 6-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, each R is independently selected from halogen, alkyl or haloalkyl.

[00188] In some embodiments of the compound of Formula (I), V is N, and R⁹ and R¹⁰ together with the atom to which they are attached form a piperidine optionally substituted with one or more R.

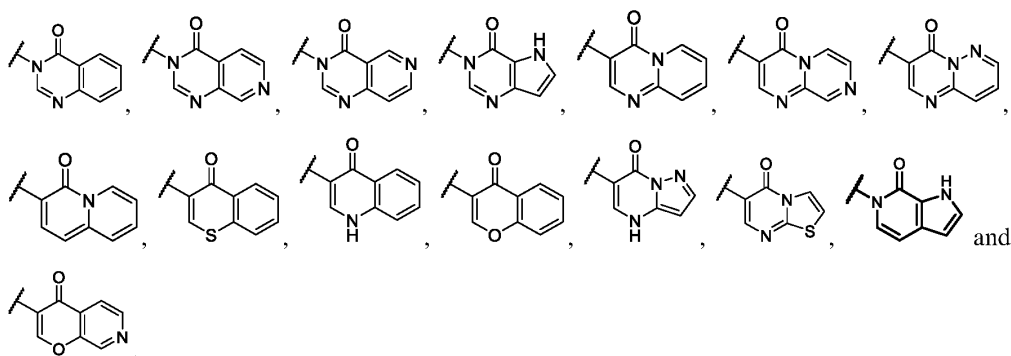
[00189] In some embodiments of the compound of Formula (I), V is N, and R⁹ and R¹⁰ together with the atom to which they are attached form a piperidine substituted with one -CH₃.

[00190] In some embodiments of the compound of Formula (II), (III) or (IV), Ring E1 is a 5- or 6-membered heteroaryl or a 5- or 6-membered heterocyclyl. In some embodiments, Ring E1 is a 6-membered heteroaryl or a 6-membered heterocyclyl. In some embodiments, Ring E1 is a 5-membered heteroaryl or a 5-membered heterocyclyl.

[00191] In some embodiments of the compound of Formula (II), (III) or (IV), Ring D1 is

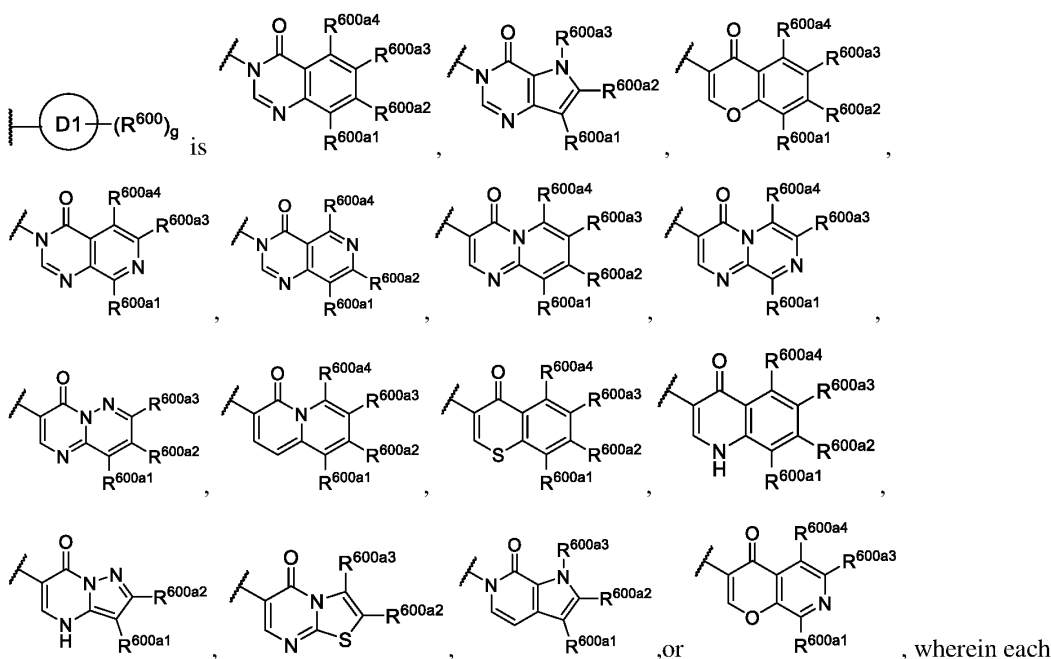


[00192] In some embodiments of the compound of Formula (II), (IIa), (III), (IIIa) or (IV), Ring D1 is selected from the group consisting of:



[00193] In some embodiments of the compound of Formula (II), (IIa), (III), (IIIa) or (IV), g is 0, 1, or 2.

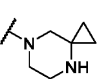
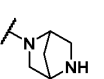
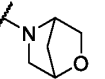
[00194] In some embodiments of the compound of Formula (II), (IIa), (III), or (IIIa),



R^{600a1} , R^{600a2} , R^{600a3} , and R^{600a4} is independently selected from hydrogen or R^{600} .

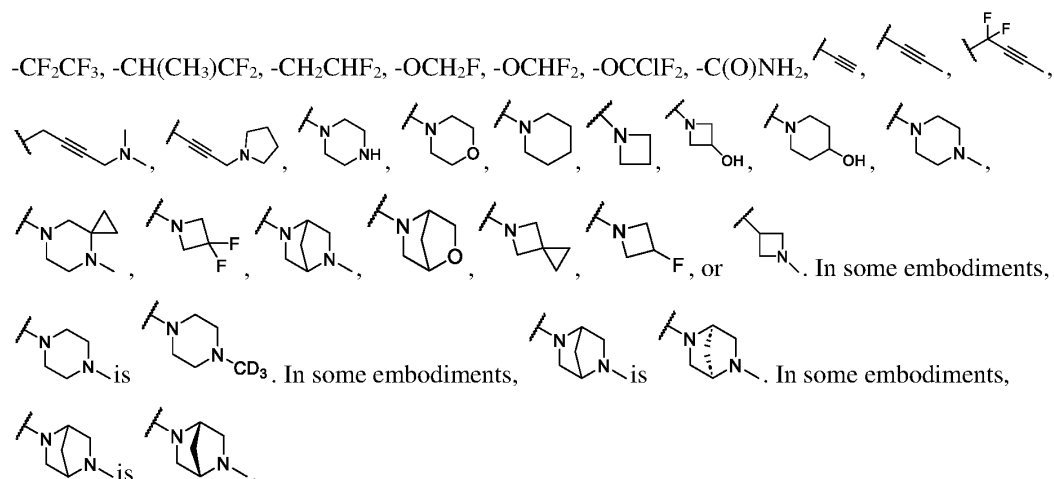
[00195] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), or (IIIa), (IIIb), or (IV), each R^{600} is independently selected from halogen, cyano, heterocyclyl, $-SR^a$, $-NH_2$, $-N(alkyl)_2$, $-NH(cycloalkyl)$, $-C(O)NH_2$, $-C(O)NH(alkyl)$, unsubstituted alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, hydroxylalkyl, haloalkoxy, $-alkynyl-N(alkyl)_2$, haloalkynyl, $-alkynyl-heterocyclyl$, or cycloalkyl, wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R^1 . In some embodiments, each R^{600} is independently selected from halogen, cyano, piperazinyl, $-SR^a$, $-NH_2$, $-N(alkyl)_2$, $-NH(cycloalkyl)$, $-C(O)NH_2$, $-C(O)NH(alkyl)$, unsubstituted alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, hydroxylalkyl, haloalkoxy, $-alkynyl-N(alkyl)_2$, haloalkynyl, $-alkynyl-heterocyclyl$, or cycloalkyl. In some embodiments, each R^{600} is independently selected from halogen, cyano, heterocyclyl, $-C(O)NH_2$, unsubstituted alkyl, alkynyl, haloalkyl, hydroxylalkyl, haloalkoxy, $-alkynyl-$

N(alkyl)₂, haloalkynyl, -alkynyl-heterocyclyl or cycloalkyl, wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R'. In some embodiments, each R⁶⁰⁰ is independently selected from halogen, cyano, -, -C(O)NH₂, unsubstituted C₁₋₆ alkyl (such as unsubstituted C₁₋₅ alkyl, unsubstituted C₁₋₄ alkyl, unsubstituted C₁₋₃ alkyl, or unsubstituted C₁₋₂ alkyl, etc), C₂₋₆ alkynyl (such as C₂₋₅ alkynyl, C₂₋₄ alkynyl or C₂₋₃ alkynyl, etc), C₁₋₆ haloalkyl (such as C₁₋₅ haloalkyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl or C₁₋₂ haloalkyl, etc), C₁₋₆ hydroxylalkyl (such as C₁₋₅ hydroxylalkyl, C₁₋₄ hydroxylalkyl, C₁₋₃ hydroxylalkyl or C₁₋₂ hydroxylalkyl, etc), C₁₋₆ haloalkoxyl (such as C₁₋₅ haloalkoxyl, C₁₋₄ haloalkoxyl, C₁₋₃ haloalkoxyl or C₁₋₂ haloalkoxyl, etc), -C₂₋₆ alkynyl-N(C₁₋₆ alkyl)₂, C₂₋₆ haloalkynyl (such as C₂₋₅ haloalkynyl, C₂₋₄ haloalkynyl or C₂₋₃ haloalkynyl, etc), -C₂₋₆ alkynyl-(3- to 6-membered heterocyclyl), C₃₋₆ cycloalkyl (such as C₃₋₅ cycloalkyl or C₃₋₄ cycloalkyl), or 3- to 6-membered heterocyclyl (such as 3- to 5-membered heterocyclyl or 3- to 4-membered heterocyclyl), wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R'. In some embodiments, each R⁶⁰⁰ is independently selected from halogen, cyano, C₁₋₃ alkyl, C₁₋₃ hydroxylalkyl, -C₂₋₃ alkynyl-N(C₁₋₃ alkyl)₂, C₂₋₃ haloalkynyl, and -C₂₋₃ alkynyl-(5- to 6-membered heterocyclyl). In some embodiments, each R⁶⁰⁰ is a C₃₋₆ cycloalkyl (such as C₃ cycloalkyl, C₄ cycloalkyl, C₅ cycloalkyl, C₆ cycloalkyl, C₃₋₅ cycloalkyl, or C₃₋₆ cycloalkyl, etc), which is optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each R⁶⁰⁰ is a 3- to 6-membered heterocyclyl (such as 3-membered heterocyclyl, 4-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, 3- to 5-membered heterocyclyl, or 5- to 6-membered heterocyclyl, etc), which is optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each R⁶⁰⁰ is piperazinyl, piperidinyl, or azetidiny, which are optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each R⁶⁰⁰ is a spirocyclic bicyclic heterocyclyl (such as 6- to 15-membered spirocyclic bicyclic heterocyclyl, 6-membered spirocyclic bicyclic heterocyclyl, 7-membered spirocyclic bicyclic heterocyclyl, 8-membered spirocyclic bicyclic heterocyclyl, or 9-membered spirocyclic bicyclic heterocyclyl), each is optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each R⁶⁰⁰ is a bridged bicyclic heterocyclyl (such as 6- to 15-membered bridged bicyclic heterocyclyl, 6-membered bridged bicyclic heterocyclyl, 7-membered bridged bicyclic heterocyclyl, 8-membered bridged bicyclic heterocyclyl, or 9-membered bridged bicyclic heterocyclyl), which is optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each R⁶⁰⁰ is a fused bicyclic heterocyclyl (such as 6- to 15-membered fused bicyclic heterocyclyl, 6-membered fused bicyclic heterocyclyl, 7-membered fused bicyclic heterocyclyl, 8-membered fused bicyclic heterocyclyl, or 9-membered fused bicyclic heterocyclyl), each is optionally substituted with one or more (e.g., two or three, etc) R'. In some embodiments, each

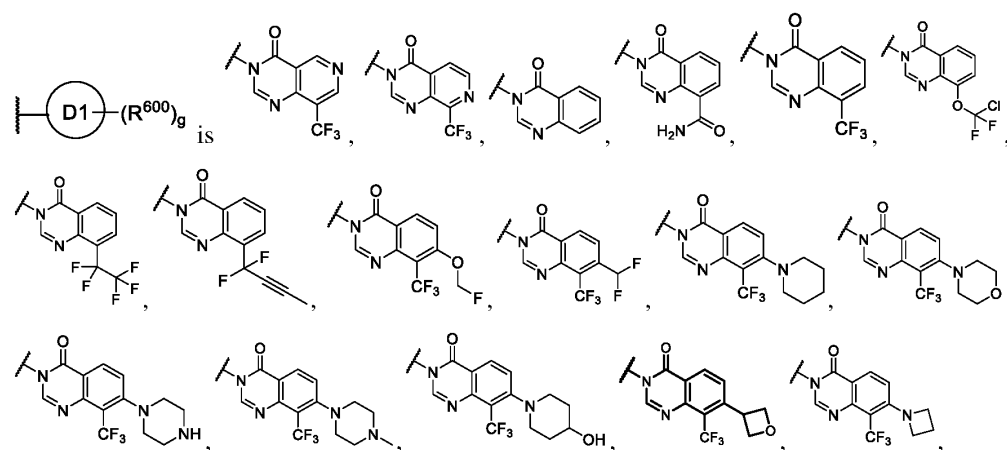
R⁶⁰⁰ is , , or , each is optionally substituted with one or more (e.g., two or three, etc) R'.

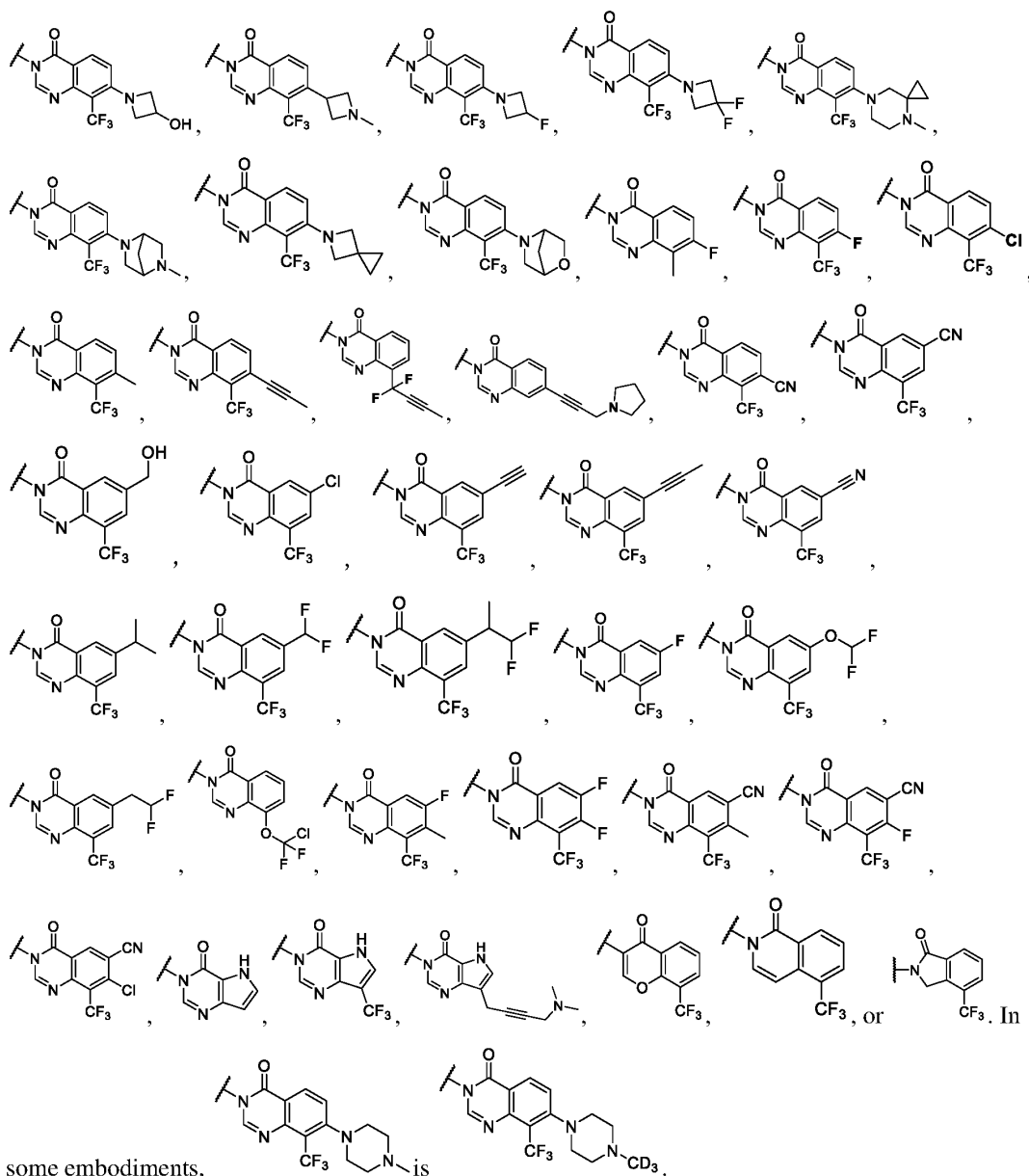
[00196] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), or (IIIa), (IIIb), or (IV), each R' is independently halogen, cyano, oxo, -OH, -S(=O)(alkyl), -S(=O)₂(alkyl), -S(=O)₂N(alkyl)₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, -NH₂, -N(alkyl)₂, -NH(alkyl), -C(=O)(alkyl), -C(=O)OH, -C(=O)O(alkyl), alkyl, alkoxy, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, or heterocyclyl. In some embodiments, each R' is independently halogen, cyano, oxo, -OH, -NH₂, alkyl, alkoxy, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, or heterocyclyl. In some embodiments, each R' is independently halogen, -OH, -NH₂, C₁₋₆ alkyl (such as C₁₋₅ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl, C₁₋₂ alkyl, or C₁ alkyl, etc), C₁₋₆ haloalkyl (such as C₁₋₅ haloalkyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl or C₁₋₂ haloalkyl, etc), or C₁₋₆ hydroxylalkyl (such as C₁₋₅ hydroxylalkyl, C₁₋₄ hydroxylalkyl, C₁₋₃ hydroxylalkyl or C₁₋₂ hydroxylalkyl, etc). In some embodiments, R' is independently halogen, -OH, -NH₂, -CH₃, or -CH₂CH₃. In some embodiments, -CH₃ is -CD₃.

[00197] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), or (IIIa), (IIIb), or (IV), each R⁶⁰⁰ is independently selected from -Cl, -F, -CN, -CH₃, -CH(CH₃)₂, -CH₂OH, -CF₃, -CHF₂,



[00198] In some embodiments of the compound of Formula (II), (IIa), (III), or (IIIa), or (IV),





[00199] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R^{600} taken together with the atom to which they are attached form a cycloalkyl, heterocyclyl or heteroaryl, each optionally substituted with one or more R.

[00200] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R^{600} taken together with the atom to which they are attached form a cycloalkyl optionally substituted with one or more R. In some embodiments, two R^{600} taken together with the atom to which they are attached form a C_{3-6} cycloalkyl (such as C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl, C_{3-5} cycloalkyl, or C_{5-6} cycloalkyl, etc) optionally substituted with one or more R.

[00201] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R⁶⁰⁰ taken together with the atom to which they are attached form a heterocyclyl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 5- to 10-membered heterocyclyl, 5- to 9-membered heterocyclyl, 5- to 8-membered heterocyclyl, 5- to 7-membered heterocyclyl, or 5- to 6-membered heterocyclyl, each optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 10-membered heterocyclyl, 9-membered heterocyclyl, 8-membered heterocyclyl, 7-membered heterocyclyl, 6-membered heterocyclyl, or 5-membered heterocyclyl, each optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a monocyclic heterocyclyl optionally substituted with one or more R.

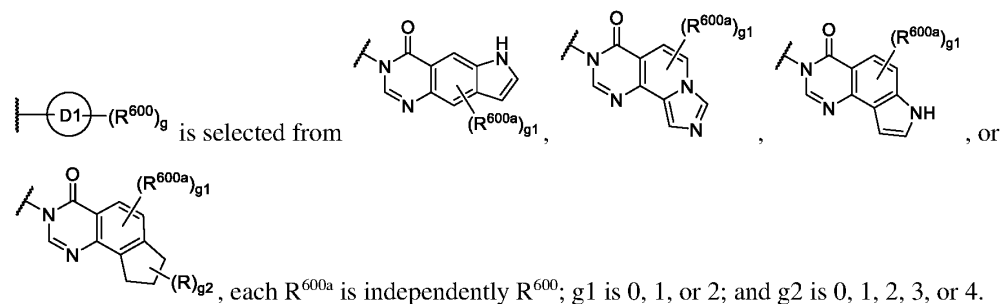
[00202] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R⁶⁰⁰ taken together with the atom to which they are attached form a 5- to 7-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 5- to 6-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 5-membered monocyclic heterocyclyl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 6-membered monocyclic heterocyclyl optionally substituted with one or more R.

[00203] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R⁶⁰⁰ taken together with the atom to which they are attached form a heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 5- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl, each optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 10-membered heteroaryl, 9-membered heteroaryl, 8-membered heteroaryl, 7-membered heteroaryl, 6-membered heteroaryl, or 5-membered heteroaryl, each optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a monocyclic heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a polycyclic heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a bicyclic heteroaryl optionally substituted with one or more R.

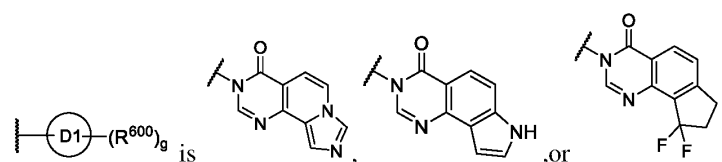
[00204] In some embodiments of the compound of Formula (II), (IIa), (IIb), (III), (IIIa), (IIIb), or (IV), two R⁶⁰⁰ taken together with the atom to which they are attached form a 5- to 7-membered monocyclic heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰

taken together with the atom to which they are attached form a 5- to 6-membered monocyclic heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 5-membered monocyclic heteroaryl optionally substituted with one or more R. In some embodiments, two R⁶⁰⁰ taken together with the atom to which they are attached form a 6-membered monocyclic heteroaryl optionally substituted with one or more R.

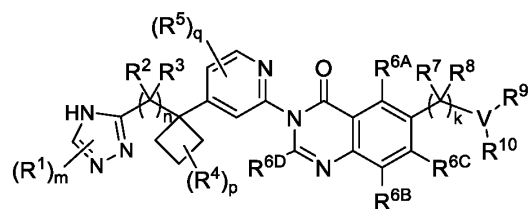
[00205] In some embodiments of the compound of Formula (II), (IIa), (III), (IIIa), or (IV),



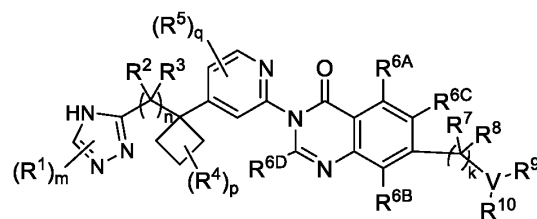
[00206] In some embodiments of the compound of Formula (II), (IIa), (III), (IIIa), or (IV),



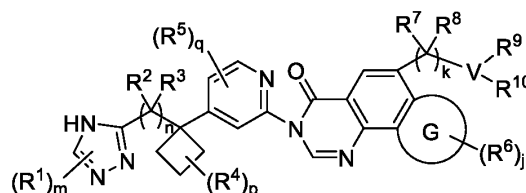
[00207] In some embodiments of the compound of Formula (I), (II), (III) or (IV), herein provided a compound having a formula selected from:



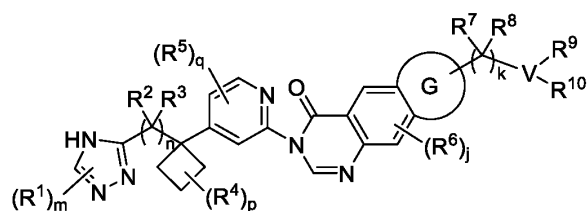
Formula (Ib),



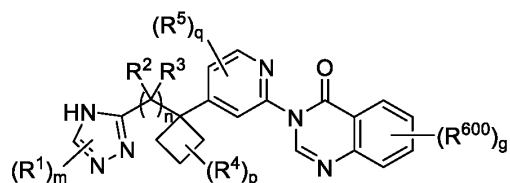
Formula (Ibb),



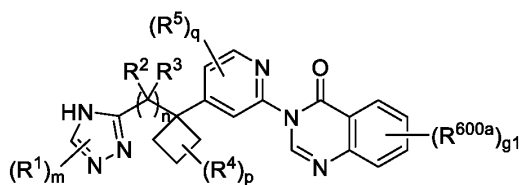
Formula (Ic),



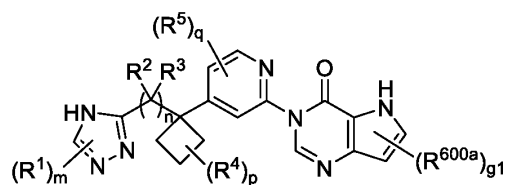
Formula (Id),



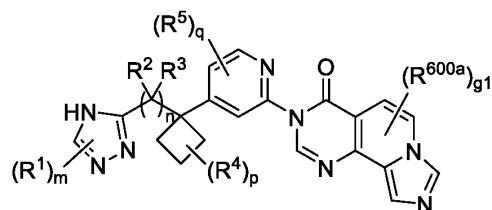
Formula (IIb),



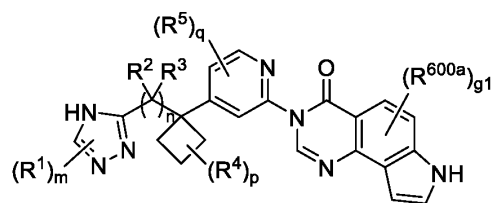
Formula (IIbb),



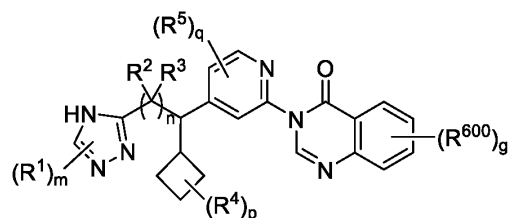
Formula (IIc),



Formula (IId),



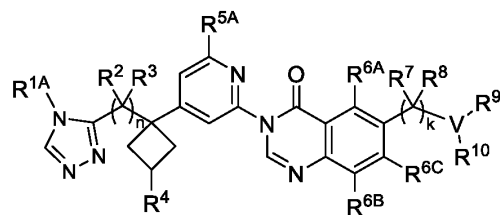
Formula (IIe),



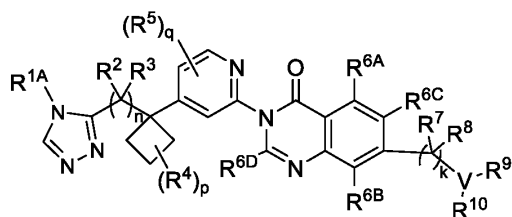
Formula (IIIb),

or a pharmaceutically acceptable salt thereof, wherein g is 0, 1, 2, 3, or 4, R¹ to R¹⁰, R^{6A} to R^{6D}, R⁶⁰⁰, R^{600a}, V, Ring G, m, n, p, q, k and g1 are as defined herein.

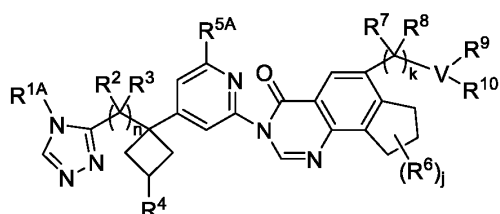
[00208] In some embodiments of the compound of Formula (I), (II), (III) or (IV), herein provided a compound having a formula selected from:



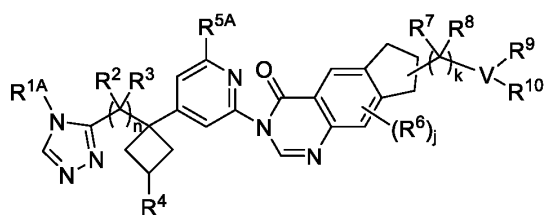
Formula (Ib-1),



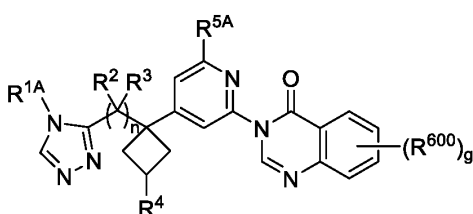
Formula (Ibb-1),



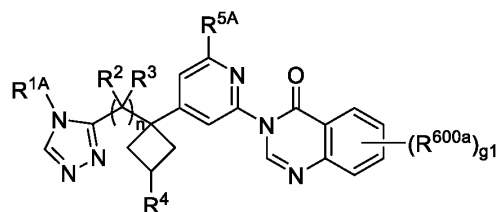
Formula (Ic-1),



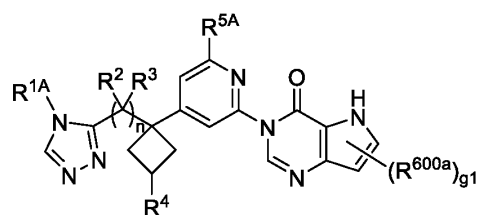
Formula (Id-1),



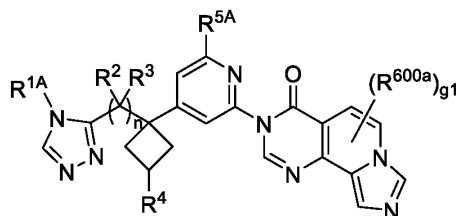
Formula (IIb-1),



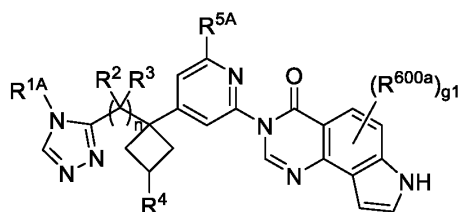
Formula (IIbb-1),



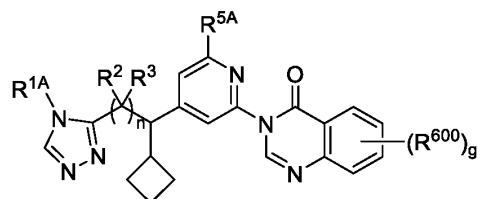
Formula (IIc-1),



Formula (IId-1),



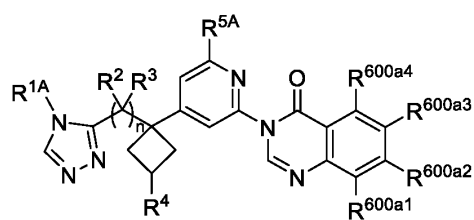
Formula (IIE-1),



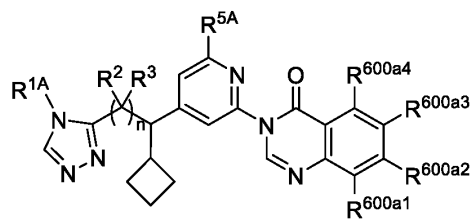
Formula (IIb-1),

or a pharmaceutically acceptable salt thereof, wherein g is 0, 1, 2, 3, or 4, R^1 to R^{10} , V , R^{5A} to R^{5C} , R^{6A} to R^{6D} , R^{600} , R^{600a} , Ring G, n , k and $g1$ are as defined herein.

[00209] In some embodiments of the compound Formula (II) or (III), herein provided a compound having a formula selected from:



Formula (IIb-1-1),



Formula (IIIb-1-1),

or a pharmaceutically acceptable salt thereof, wherein each R^{600a1} , R^{600a2} , R^{600a3} , and R^{600a4} is independently selected from hydrogen or R^{600} ; n, R^{1A} , R^2 , R^3 , R^4 and R^{5A} are as defined herein.

[00210] In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 1, Table 2 or Table 3.

Table 1 Exemplary Compounds

Compound No.	Structure	Compound No.	Structure
1.		3.	
4.		5.	
6.		7.	
8.		9.	
10.		11.	
12.		13.	
14.		15.	
18.		19.	
21.		22.	

23.		25.	
34.		36.	
37.		40.	
41.		42.	
43.		44.	
45.		46.	
47.		48.	
49.		50.	
51.		52.	
53.		54.	
55.		56.	

57.		58.	
59.		60.	
61.		62.	
63.		64.	
65.		66.	
67.		68.	
69.		70.	
71.		72.	
73.			

[00211] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 2.

Table 2 Exemplary Compounds

Compound No.	Structure	Compound No.	Structure
16.		17.	
20.		24.	
26.		27.	
28.		29.	
30.		31.	
32.		33.	
35.		38.	
39.		74.	
75.		76.	
77.		78.	

79.		80.	
81.		82.	
83.		84.	
85.		86.	
87.		88.	
89.		90.	
91.		92.	
93.		94.	
95.		96.	

97.		98.	
99.		100.	
101.		102.	
103.		104.	
105.		106.	
107.		108.	
109.		110.	
111.		112.	
113.		114.	

115.		116.	
117.		118.	
119.		120.	
121.		122.	
123.		124.	
125.		126.	
127.		128.	
129.		130.	

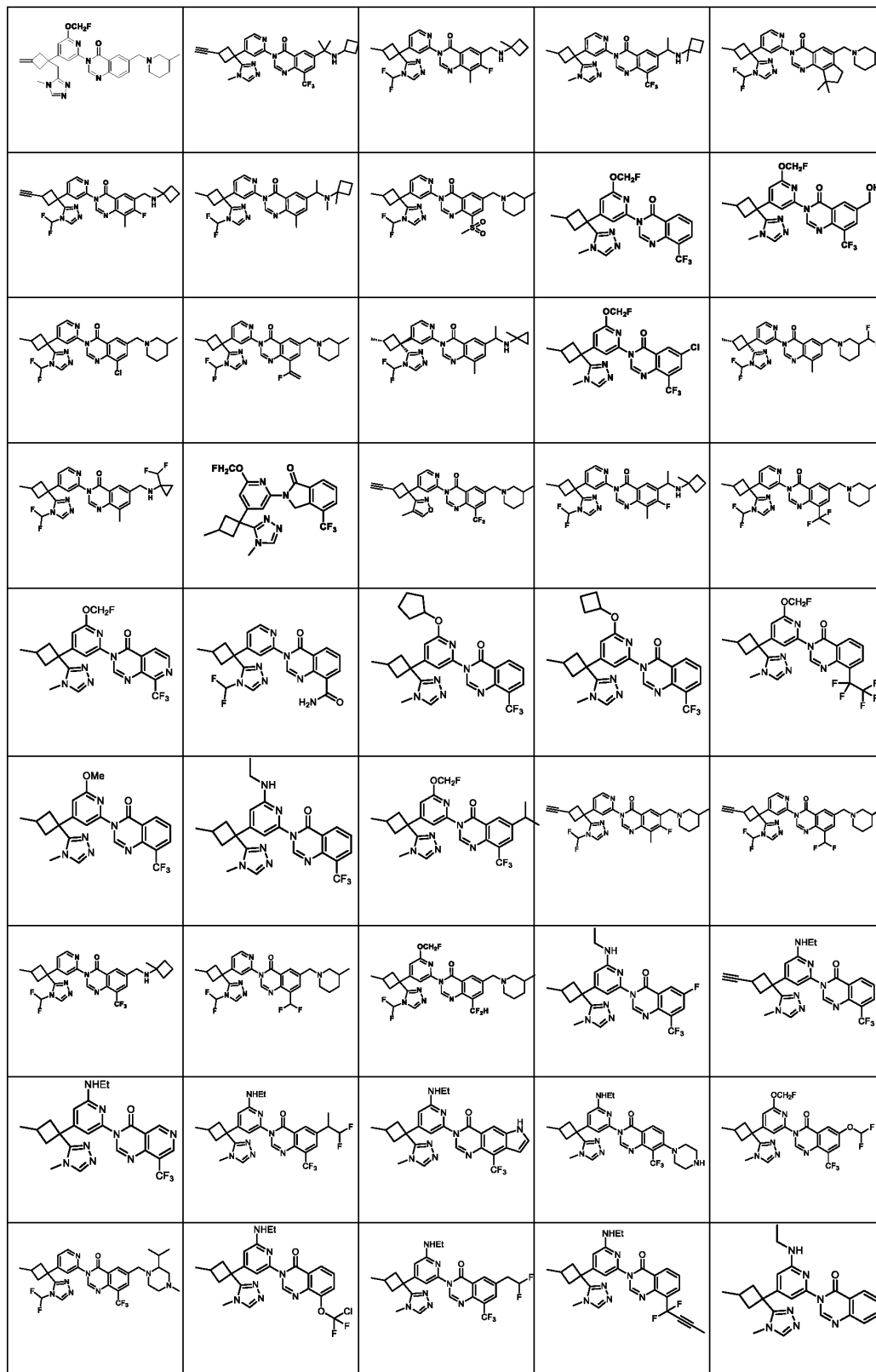
131.		132.	
133.		134.	
135.		136.	
137.		138.	
139.		140.	
141.		142.	
143.		144.	

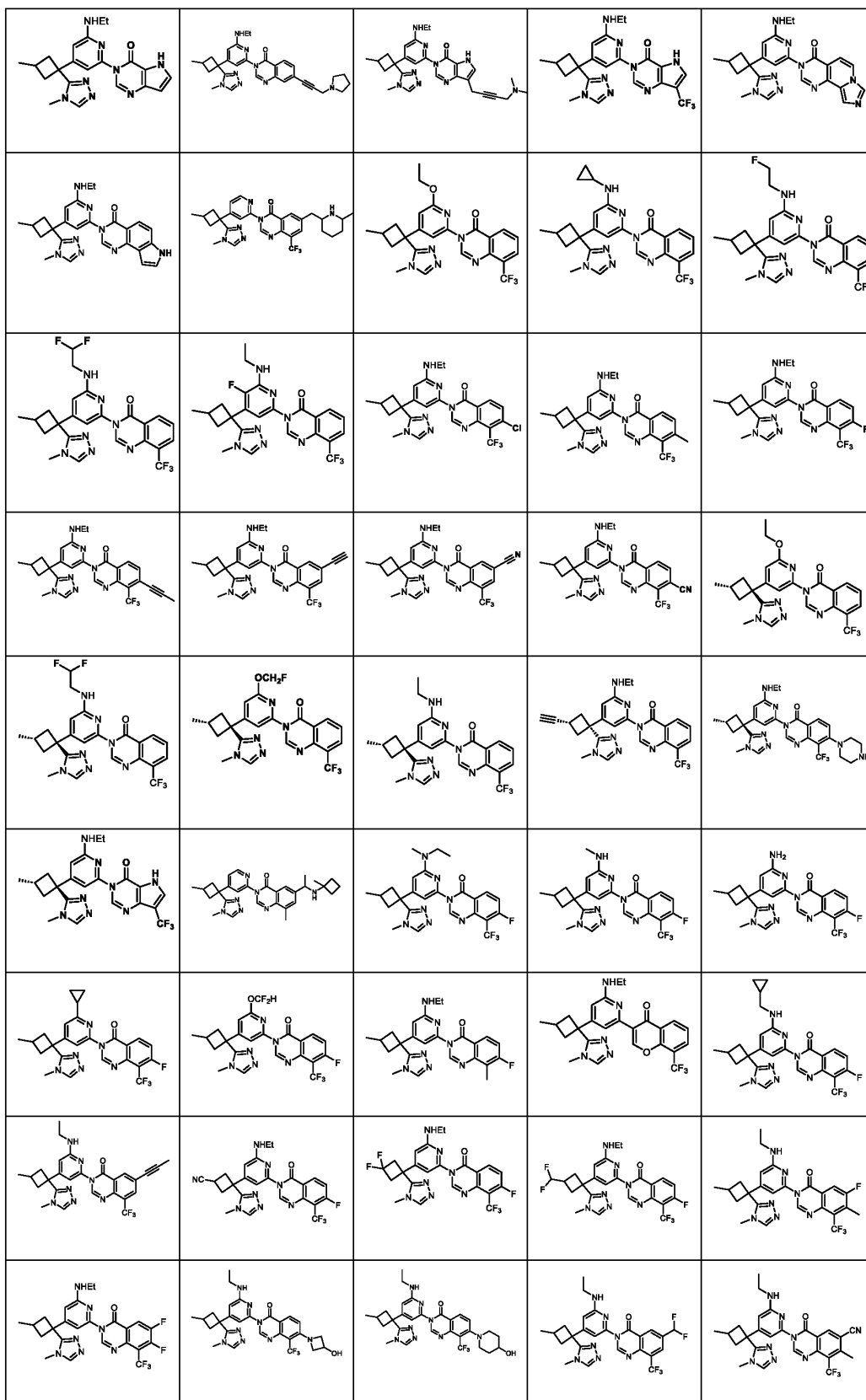
145.		146.	
147.		148.	
149.		150.	
151.		152.	
153.		154.	
155.		156.	
157.		158.	

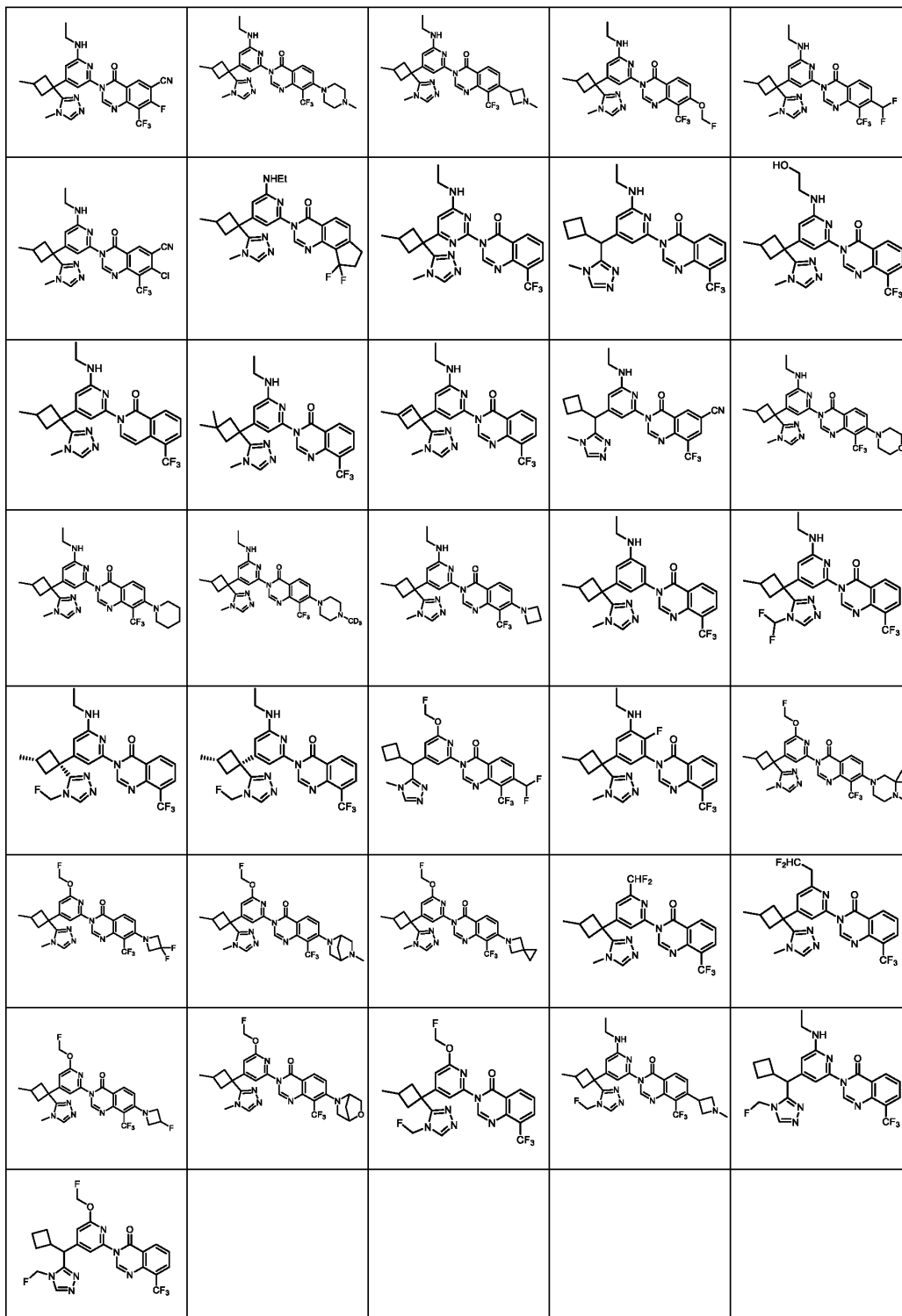
[illegible]

[00212] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is one of the compounds in Table 3.

Table 3 Exemplary Compounds







Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00213] 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 situations, 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. The carbon-carbon bonds of the compounds provided may be depicted herein using a solid line (—), a wedged bond (▲), a hashed wedged bond (⋯), a bold bond (▬) or a hashed bond (⋯). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g., specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of a wedged bond (▲) or a hashed wedged bond (⋯) is means to indicate absolute stereochemistry. The use of a bold bond (▬) or a hashed bond (⋯) is means to indicate relative stereochemistry.

Isotopically enriched compounds

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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

[00219] 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.

[00220] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of 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.

[00221] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with organic or inorganic acid, 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, glucoheptonate, 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, 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, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[00222] 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.

[00223] 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 metal or alkaline earth metal 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.

[00224] 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.

Tautomers

[00225] 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.

Method of Treatment

[00226] Disclosed herein are methods of modulating the activity of an immune cell (e.g., a T-cell, a B-cell, or a NK-cell) such as by contacting the immune cell with an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition thereof.

[00227] Also disclosed herein is a method of treating a cancer, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00228] Also disclosed herein is a method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00229] Also disclosed herein is a method of inhibiting abnormal cell proliferation, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00230] Also disclosed herein is a method of modulating the immune response, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00231] Also disclosed herein is a method of inhibiting Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00232] Also disclosed herein is a method for treating a disease or condition associated with Cbl-b activity, the method comprising administering an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to the subject in need thereof.

[00233] In some embodiments, the disease or condition associated with Cbl-b activity is cancer.

[00234] In some embodiments, the cancer is a hematologic cancer. In some embodiments, the cancer is a lymphoma, a leukemia, or a myeloma. In some embodiments, the cancer is a non-

hematologic cancer. In some embodiments, the cancer is a sarcoma, a carcinoma, or a melanoma. In some embodiments, the cancer is solid tumor cancer.

[00235] Hematologic cancers include, but are not limited to, one or more leukemias such as B-cell acute lymphoid leukemia (“BALL”), T-cell acute lymphoid leukemia (“TALL”), acute lymphoid leukemia (ALL); one or more chronic leukemias including, but not limited to, chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and “preleukemia,” which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells.

[00236] Non-hematologic cancers include but are not limited to, a neuroblastoma, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer (e.g., NSCLC), pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, uterine cancer, adrenal cancer, and head and neck cancer.

Dosing

[00237] In certain 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.

Routes of Administration

[00238] 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.

[00239] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation.

Pharmaceutical Compositions/Formulations

[00240] 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.

[00241] 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.

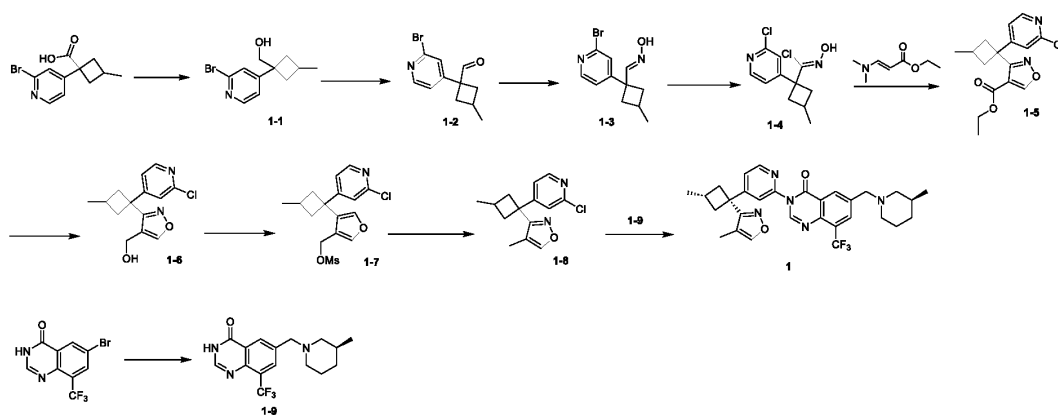
Examples

[00242] 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.

Synthesis of Compounds

Example 1



[00243] To a solution of 1-(2-bromopyridin-4-yl)-3-methylcyclobutane-1-carboxylic acid (7 g, 25.9 mmol) in THF (2 mL) was added BH_3 (259 mL, 259 mmol, 1.0 M in THF) at 25 °C under N_2 . The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of MeOH at 25 °C. The mixture was concentrated under reduced pressure to afford **Compound 1-1** (3.1 g, 46.7%), which was used directly for next step without further purification; LCMS: 256.1/258.1 $[\text{M}+\text{H}]^+$.

[00244] To a solution of **Compound 1-1** (5 g, 19.5 mmol) in DCM (100 mL) was added DMP (16.6 g, 39.0 mmol) at 0°C. The resulting mixture was stirred at 25°C for 12 hrs. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product, which was purified by flash silica gel chromatography to afford **Compound 1-2** (4.5 g, 90.7%); LCMS: 254.0/256.0 $[\text{M}+\text{H}]^+$.

[00245] To a solution of hydroxylamine hydrochloride (1.4 g, 19.7 mmol) and TEA (2.70 mL, 19.7 mmol) in DCM (50 mL) was added **Compound 1-2** (5 g, 19.7 mmol) at 0°C. The resulting mixture was stirred at room temperature for 16 hrs. The reaction mixture was poured to water (100 mL) and extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium

sulfate, filtered and concentrated under reduced pressure to give **Compound 1-3** (4.5 g, 85.0%), which was used directly to the next step without further purification; LCMS: 269.0/271.0 [M+H]⁺.

[00246] To a solution of **Compound 1-3** (4 g, 14.9 mmol) in DMF (50 mL) was added NCS (6.0 g, 44.6 mmol) at 25°C under N₂. After being stirred at 60 °C for 3 hrs, the reaction mixture was used directly to the next step without further purification; LCMS: 259.0 [M+H]⁺.

[00247] To a solution of **Compound 1-4** (5 g, 19.4 mmol) in CHCl₃ (30 mL) was added ethyl (2*E*)-3-(dimethylamino)prop-2-enoate (4.2 g, 29.1 mmol) and TEA (4.03 mL, 29.1 mmol). The mixture was stirred at room temperature for 16 hrs. The reaction was quenched by the addition of saturated NH₄Cl (aq.). Then the resulting mixture was extracted with DCM (50 mL × 2). The combined organic layers were washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography to afford **Compound 1-5** (2.2 g, 35.4%); LCMS: 321.2 [M+H]⁺.

[00248] To a solution of **Compound 1-5** (600 mg, 1.9 mmol) in THF (10 mL) was added DIBAL-H (2 mL, 2.0 mmol) slowly at -78 °C over 1 min. The resulting mixture was stirred at -78°C for 2 hrs. The reaction mixture was quenched by the addition of 2M NaOH (aq., 2 mL) at 25°C. After being diluted with EtOAc (30 mL), the mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product, which was purified by reversed-phase chromatography to afford **Compound 1-6** (200 mg, 38.4%); LCMS: 279.1 [M+H]⁺.

[00249] To a solution of **Compound 1-6** (150 mg, 0.5 mmol) in DCM (5 mL) was added TEA (0.08 mL, 0.6 mmol) and MsCl (67.8 mg, 0.6 mmol) at 25 °C. The reaction was stirred at 25°C for 2 hrs. The mixture was quenched by the addition of water (10 mL) and extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give **Compound 1-7** (160 mg, 83.3%); LCMS: 357.0 [M+H]⁺.

[00250] To a solution of **Compound 1-7** (170 mg, 0.5 mmol) in DMSO (2 mL) was added NaBH₄ (36.0 mg, 0.9 mmol) at 25°C. The reaction was stirred at 60°C for 1 h. The reaction mixture was purified by reverse phase chromatography to afford **Compound 1-8** (60 mg, 47.9%); LCMS: 263.0 [M+H]⁺.

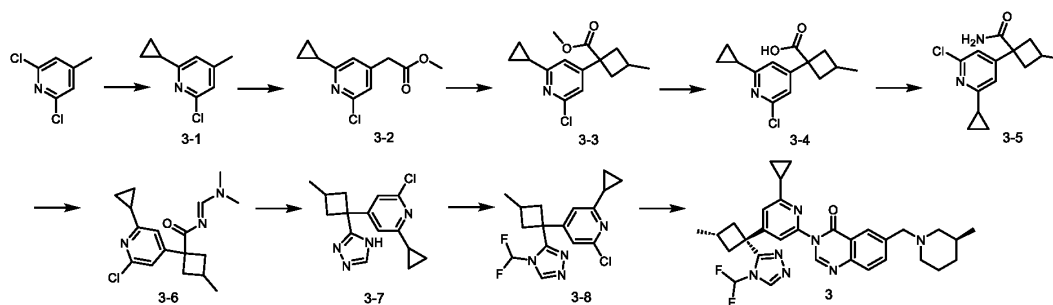
[00251] To a solution of potassium (*S*)-trifluoro[(3-methyl-1-piperidyl)methyl]borate (1.8 g, 8.365 mmol), 6-bromo-8-(trifluoromethyl)quinazolin-4(3*H*)-one (1.2 g, 4.180 mmol) and K₂CO₃ (1.7 g, 12.547 mmol) in dioxane (10 mL) and water (2 mL) was added cataXciumA (0.3 g, 0.836 mmol) and Pd(OAc)₂ (0.1 g, 0.418 mmol). The mixture was stirred at 120°C for 12 hrs under nitrogen atmosphere. The reaction mixture was partitioned between EtOAc (70 mL) and water (50 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 1-9** (1.03 g, 76.0%). LCMS: 272.1 [M+H]⁺.

[00252] To a solution of **Compound 1-8** (50 mg, 0.19 mmol) and **Compound 1-9** (49.5 mg, 0.152 mmol) in dioxane (2 mL) was added CuI (36.3 mg, 0.19 mmol), K₂CO₃ (52.6 mg, 0.38 mmol) and

methyl[(1*R*,2*R*)-2-(methyamino)cyclohexyl]amine (16.2 mg, 0.11 mmol) at 25°C under N₂. The reaction was stirred at 120°C for 16 hrs. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give the crude product, which was purified by pre-HPLC to afford the

Compound 1. LCMS: 552.4 [M+H]⁺; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.86 – 8.44 (m, 3H), 8.09 (s, 1H), 7.95 (s, 1H), 7.43 – 7.27 (m, 2H), 4.43 – 3.39 (m, 2H), 2.95 – 2.79 (m, 2H), 2.75 – 2.45 (m, 4H), 2.32 – 1.55 (m, 10H), 1.15 (d, *J* = 5.6 Hz, 3H), 1.06 – 0.70 (m, 4H).

Example 3



[00253] To a solution of 2,6-dichloro-4-methylpyridine (10 g, 61.73 mmol) in Water (15 mL) and Toluene (150 mL) was added cyclopropyltrifluoro- λ^4 -borane, potassium salt (10 g, 67.90 mmol), Pd(OAc)₂ (1.4 g, 6.17 mmol), cataXciumA (2.2 g, 6.17 mmol) and Cs₂CO₃ (60.3 g, 185.18 mmol). The reaction was stirred at 110°C for 2 hrs under N₂. The reaction mixture was partitioned between NH₄Cl (aq.) 100 mL and EtOAc (200 mL). The organic phase was separated, washed with NH₄Cl (aq.) (100 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 3-1** (5.1 g, 49.3%). LCMS: 168.1 [M+H]⁺.

[00254] To a solution of **Compound 3-1** (5.1 g, 30.43 mmol) in anhydrous THF (30 mL) was slowly added LDA (22.8 mL, 45.64 mmol) at -78°C under N₂. The mixture was stirred at -78 °C for 0.5 h. A solution of methyl methoxymethanoate (13.7 g, 152.15 mmol) was added dropwise. The mixture was stirred for another 1 h at 0 °C. The mixture was quenched by the addition of H₂O (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 3-2** (2.1 g, 30.6%). LCMS: 226.1 [M+H]⁺.

[00255] To a solution of **Compound 3-2** (2.5 g, 11.07 mmol) in DMF (25 mL) was added Cs₂CO₃ (7.2 g, 22.15 mmol). The mixture was stirred at 0 °C for 0.5 h under N₂. After the slowly addition of 1,3-dibromo-2-methylpropane (7.2 g, 33.23 mmol) at 25°C, the resulting mixture was stirred at 25°C for 16 h under N₂. The mixture was partitioned between water (80 mL) and EtOAc (80 mL). The organic phase was separated, washed with water (20 mL × 2), dried over anhydrous sodium sulfate,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 3-3** (2.1 g, 67.8%). LCMS: 280.2 [M+H]⁺.

[00256] To a solution of **Compound 3-3** (2.1 g, 7.50 mmol) in EtOH (10 mL) was added LiOH (1.3 g, 30.02 mmol) in H₂O (10 mL) at 0°C. The mixture was stirred at 25°C for 3 hrs. The pH of the mixture was adjusted to 4 with HCl (1M). Then the mixture was extracted with Ethyl acetate (30 mL × 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude **Compound 3-4** (2 g, 100.3%). LCMS: 266.1 [M+H]⁺.

[00257] A solution of **Compound 3-4** (2 g, 7.52 mmol) in SOCl₂ (10 mL) was stirred at 80°C for 1 hr. The mixture was concentrated to give a residue, then DCM (10 mL) was added, the solution was added dropwise to ammonia in MeOH (7M, 20 mL). The resulting mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0-50% EtOAc/ PE @ 40 mL/min) to afford **Compound 3-5** (1.8 g, 90.3%). LCMS: 265.1 [M+H]⁺;

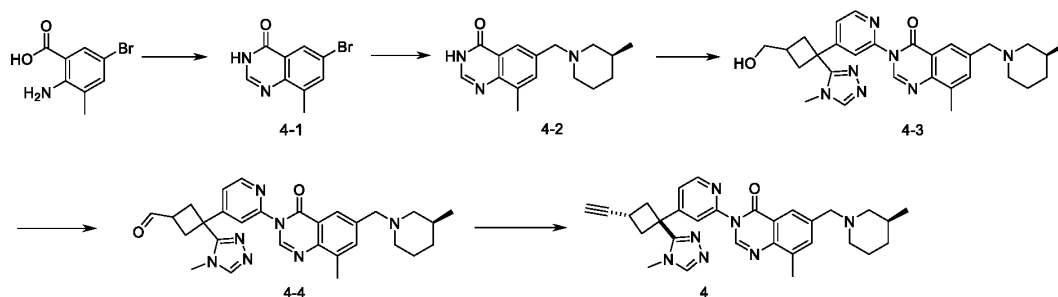
[00258] A solution of **Compound 3-5** (1.8 g, 6.79 mmol) in DMF-DMA (10 mL) was stirred at 100°C for 12 hrs under N₂. The reaction mixture was concentrated under reduced pressure to afford crude **Compound 3-6**. LCMS: 320.1 [M+H]⁺;

[00259] To a solution of **Compound 3-6** (1.8 g, 5.62 mmol) in AcOH (18 mL) was added hydrazine hydrate (18 mL, 370.06 mmol) at 0°C under N₂. The reaction mixture was stirred at 80°C for 3 hrs. The mixture was quenched with H₂O (60 mL) and extracted with EtOAc. The combined organic layers were washed brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase chromatography (Isolera-Biotage Column: Agela C18 40 g; Mobile Phase A: 10 mM aq. FA, Mobile Phase B: ACN; Flow rate: 40 mL/min; Gradient: 30% B to 40% B in 15 min; Detector: UV 210 nm) to afford **Compound 3-7**. LCMS: 289.1 [M+H]⁺;

[00260] To a solution of **Compound 3-7** (800 mg, 2.77 mmol) in DMF (10 mL) was added K₂CO₃ (765.7 mg, 5.54 mmol), chlorodifluoromethane was bubble into the mixture. The mixture stirred at 100°C for 16 hrs. The mixture was quenched by the addition of H₂O (60 mL) and extracted with EtOAc. The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase chromatography to afford **Compound 3-8**. LCMS: 339.0 [M+H]⁺;

[00261] **Compound 3** was synthesized according to the step of synthesis of Compound 1 in **Example 1** with **Compound 3-8** as the corresponding substrate. LCMS: 560.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.47 (s, 1H), 8.10 (s, 1H), 7.80 (d, *J* = 9.4 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.28 (m, 3H), 3.57 (s, 2H), 2.89 (td, *J* = 12.1, 3.8 Hz, 2H), 2.76 – 2.65 (m, 3H), 2.61 – 2.58 (m, 2H), 2.25 – 2.16 (m, 1H), 1.93 – 1.83 (m, 1H), 1.67 – 1.56 (m, 4H), 1.52 – 1.42 (m, 1H), 1.08 (d, *J* = 4.7 Hz, 3H), 1.01 – 0.96 (m, 4H), 0.88 – 0.77 (m, 4H).

Example 4



[00262] A solution of 2-amino-5-bromo-3-methylbenzoic acid (4.1 g, 17.82 mmol) in formamide (50 mL) was stirred at 170 °C for 4 h under N₂. The reaction mixture was cooled to room temperature and poured into water, the product was precipitated out. After filtration, the filter cake was dried to afford **Compound 4-1** (3.2 g, 75.1%). LCMS: 239.0/241.0 [M+H]⁺.

[00263] To a solution of potassium (S)-trifluoro[(3-methyl-1-piperidyl)methyl]borate (1.8 g, 8.365 mmol), **Compound 4-1** (1 g, 4.182 mmol) and K₂CO₃ (1.7 g, 12.547 mmol) in dioxane (10 mL) and water (2 mL) was added cataXciumA (0.3 g, 0.836 mmol) and Pd(OAc)₂ (0.1 g, 0.418 mmol). The mixture was stirred at 120 °C for 12 hrs under nitrogen atmosphere. The reaction mixture was partitioned between EtOAc (70 mL) and water (50 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 4-3** (870 mg, 76.6%). LCMS: 272.1 [M+H]⁺.

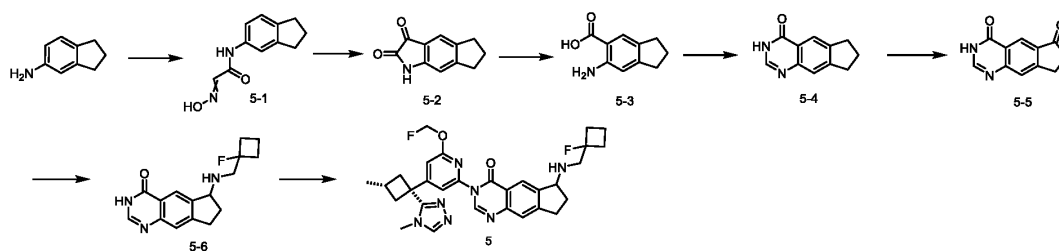
[00264] To a solution of **Compound 4-2** (500 mg, 1.84 mmol), (3-(2-bromopyridin-4-yl)-3-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)methanol (595.4 mg, 1.84 mmol) and K₂CO₃ (509.2 mg, 3.68 mmol) in 1, 4-dioxane (5 mL) was added CuI (351.0 mg, 1.84 mmol) and methyl[(1R,2R)-2-(methylamino)cyclohexyl]amine (523.9 mg, 3.68 mmol). The mixture was stirred at 90 °C for 1 h under N₂. The reaction mixture was partitioned between water (20 mL) and EtOAc (30 mL). The organic phase was separated, washed with water (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 4-3** (800 mg, 84.5%). LCMS: 514.3 [M+H]⁺.

[00265] To a solution of **Compound 4-3** (600 mg, 1.168 mmol) in DCM (10 mL) was added DMP (743.2 mg, 1.752 mmol). The mixture was stirred at 25 °C for 3 hrs. The reaction mixture was partitioned between Sodium thiosulfate (20 mL) and DCM (30 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 4-4** (500 mg, 83.7%, crude). LCMS: 512.4 [M+H]⁺.

[00266] To a solution of **Compound 4-4** (500 mg, 0.97 mmol) and K₂CO₃ (270.1 mg, 1.95 mmol) in MeOH (10 mL) was added (1Z)-1-(diazyn-1-iumyl)-1-[dimethoxy-(oxo)-λ⁵-phosphanyl]-prop-1-en-

2-olate (281.6 mg, 1.46 mmol). The mixture was stirred at 25°C for 3 hrs. The reaction mixture was partitioned between NH₄Cl (aq. sat. 20 mL) and EtOAc (30 mL). The organic phase was separated, washed with water (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford **Compound 4**. LCMS: 508.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.62 (d, *J* = 5.3 Hz, 1H), 8.55 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.71 – 7.65 (m, 2H), 7.35 (dd, *J* = 6.1, 0.8 Hz, 1H), 3.53 (s, 2H), 3.40 – 3.37 (m, 2H), 3.30 (s, 3H), 3.16 (d, *J* = 2.3 Hz, 1H), 3.10 – 3.05 (m, 1H), 2.79 – 2.70 (m, 4H), 2.57 (s, 3H), 1.91 – 1.84 (m, 1H), 1.67 – 1.55 (m, 4H), 1.52 – 1.44 (m, 1H), 0.88 – 0.79 (m, 4H).

Example 5



[00267] A mixture of 2,2,2-trichloroethane-1,1-diol (15 g, 90.689 mmol) and sodium sulfate (85 g, 598.592 mmol) in H₂O (500 mL) was heated to 40°C. To the stirred mixture was slowly added 2,3-dihydro-1H-inden-5-amine (10 g, 75.075 mmol). The reaction mixture was stirred for 1 hr, and the suspension of Hydroxylamine hydrochloride (21 g, 302.158 mmol) was rapidly added to the reaction mixture. The mixture was then stirred at 90°C for 5 hrs. The mixture was cooled to room temperature, filtered. The filter cake was washed with water (50 mL × 3) to afford **Compound 5-1** (12 g, 78.3%). LCMS: 205.3 [M+H]⁺.

[00268] A solution of **Compound 5-1** (10 g, 48.972 mmol) in H₂SO₄ (80 mL) was stirred at 80°C for 30 min. The mixture was poured into ice water (50 mL). The mixture was extracted with DCM : MeOH=10:1 (100 mL × 5). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated to afford **Compound 5-2** (6 g, 65.4%). LCMS: 188.1[M+H]⁺.

[00269] To a solution of **Compound 5-2** (6 g, 32.051 mmol) in 2M NaOH (60 mL, 120.000 mmol) were added dropwise hydrogen peroxide (7.8 mL, 100.659 mmol), and the reaction was stirred at room temperature for 3 hrs. To the reaction mixture was added 1N hydrochloric acid to adjust pH=5. The resulting mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers was washed with brine, dried, filtered and concentrated to afford **Compound 5-3** (4 g, 70.4%). LCMS: 178.0 [M+H]⁺.

[00270] The **compound 5-4** was synthesized according to step 1 in **Example 4** with **Compound 5-3** as the substrate. LCMS: 187.1 [M+H]⁺.

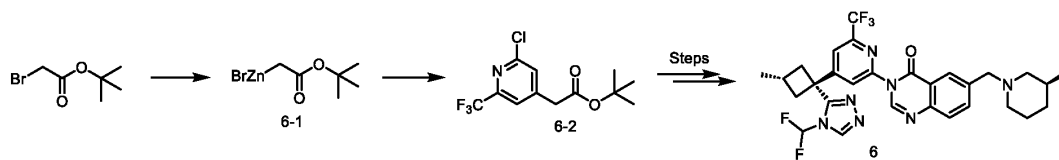
[00271] To a vigorously stirred suspension of trioxo-λ₆-chromium(VI) (53.7 mg, 0.537 mmol) in DCM (50 mL) was added dropwise tert-butyl hydroperoxide (11.1 mL, 80.559 mmol) at 0°C. The

mixture was allowed to warm to room temperature and stirred for another 30 min. **Compound 5-4** (1000.0 mg, 5.371 mmol) was slowly added and the mixture was stirred at room temperature for 12 hrs. The mixture was concentrated in vacuum to remove DCM. The residue was purified by flash silica gel chromatography to afford **Compound 5-5** (600 mg, 55.8%); LCMS: 201.1 [M+H]⁺.

[00272] A mixture of **Compound 5-5** (580 mg, 2.897 mmol), (1-fluorocyclobutyl) methanamine hydrochloride (606.7 mg, 4.346 mmol) in Titanium tetrakisopropanolate (6 mL, 20.267 mmol) was stirred at 80°C for 12 hrs in a sealed tube. After the addition of NaBH₄ (657.1 mg, 17.383 mmol) and THF (6 mL), the mixture was stirred at room temperature for 2 hrs. The reaction mixture was diluted with EtOAc (40 mL), quenched by addition of water (2 mL) and MeOH (20 mL) at 10°C. The mixture was washed with EtOAc (20 mL × 3). The combined organic layers was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HP to afford **Compound 5-6** (150 mg, 18.0%). LCMS: 288.1 [M+H]⁺.

[00273] **Compound 5** was synthesized according to the step 9 in **Example 1** with **Compound 5-6** as the corresponding substrate. LCMS: 562.4 [M+H]⁺.

Example 6



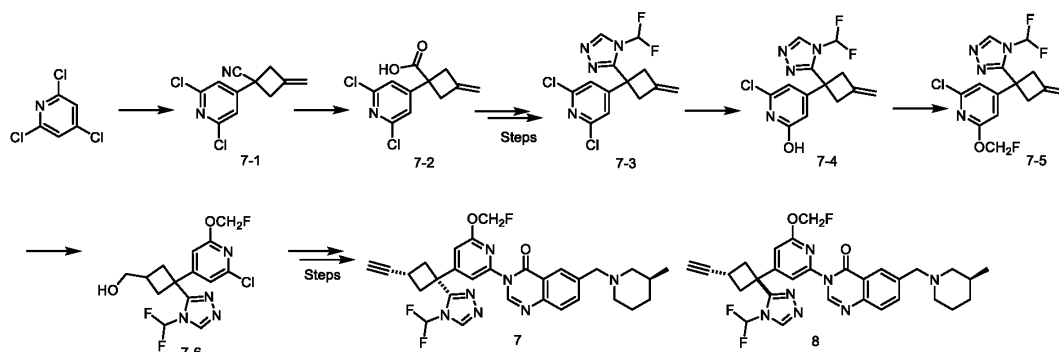
[00274] To a solution of Zn (4.0 g, 61.507 mmol) in dry THF (50 mL) at 25°C was added 1,2-dibromoethane (0.9 mL, 10.251 mmol). The reaction mixture was stirred at 70°C for 1 min and cooled down to 25°C. This procedure was repeated 3 times. Chlorotrimethylsilane (0.5 mL, 4.100 mmol) was added and the resulting suspension was stirred at 25°C for 15 min. It was then heated to 70°C. A solution of *tert*-butyl 2-bromoacetate (10 g, 51.256 mmol) in dry THF (10 mL) was then added while the mixture was refluxed. Upon completion of the addition, the reaction mixture was refluxed for an additional 20 min and cooled down to 25°C. The mixture was used directly for the next step.

[00275] To a solution of **Compound 6-1**, 2-chloro-4-iodo-6-(trifluoromethyl)pyridine (3000 mg, 9.759 mmol) and Pd₂(dba)₃ (553.4 mg, 0.976 mmol) in THF (30 mL) was added Qphos (693.6 mg, 0.976 mmol). The reaction mixture was stirred at 25°C for 2 hrs under nitrogen. The mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product. The crude product was purified by silica gel flash chromatography to give **Compound 6-2** (2 g, 69.3%). LCMS: 296.1 [M+H]⁺.

[00276] **Compound 6** was synthesized according to the **Example 3** with **Compound 6-2** as the corresponding substrate. LCMS: 629.5 [M+H+ACN]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.86 – 7.79 (m, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.52 (t, *J* = 58.6

Hz, 1H), 3.59 (s, 2H), 3.00 – 2.90 (m, 2H), 2.76 – 2.60 (m, 4H), 2.35 – 2.30 (m, 1H), 1.97 – 1.78 (m, 1H), 1.70 – 1.40 (m, 5H), 1.09 (d, $J = 5.9$ Hz, 3H), 0.91 – 0.75 (m, 4H).

Examples 7 & 8



[00277] To a solution of 3-methylenecyclobutane-1-carbonitrile (2.6 g, 27.41 mmol) in THF (20 mL) was added LiHMDS (27.4 mL, 27.41 mmol) at -78°C under N_2 . The mixture was stirred at -78°C for 1 h. Then 2,4,6-trichloropyridine (5 g, 27.41 mmol) was added at -78°C . The resulting mixture was stirred for 2 hours at -78°C under N_2 . The reaction mixture was partitioned between NH_4Cl (aq.) 100 mL and EtOAc (100 mL). The organic phase was separated, washed with sat. NH_4Cl (aq.) (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 7-1** (3.7 g, 56.5%). LCMS: 238.9 $[\text{M}+\text{H}]^+$.

[00278] To a solution of **Compound 7-1** (1 g, 4.18 mmol) in EtOH (10 mL) was added 1M NaOH (20.9 mL, 20.91 mmol). The reaction was stirred at 100°C for 16 hrs. The mixture was adjusted to pH 4 with HCl (3M), then extracted with Ethyl acetate (40 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by reverse phase chromatography to afford **Compound 7-2** (900 mg, 83.3%). LCMS: 258.0 $[\text{M}+\text{H}]^+$.

[00279] According to the procedure in **Example 3**, **Compound 7-3** was synthesized with **Compound 7-2** as the substrate. LCMS: 331.0 $[\text{M}+\text{H}]^+$.

[00280] To a solution of **Compound 7-3** (160 mg, 0.48 mmol) in DMSO (3 mL) was added ethanhydroxamic acid (108.9 mg, 1.45 mmol) and K_2CO_3 (200.4 mg, 1.45 mmol). The reaction mixture was stirred at 80°C for 16 hrs. The mixture was adjusted to pH 4 with HCl (1M), then extracted with Ethyl acetate (30 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 7-4** (100 mg, 66.2%). LCMS: 313.1 $[\text{M}+\text{H}]^+$.

[00281] To a solution of **Compound 7-4** (100 mg, 0.32 mmol) in DMF (2 mL) was added Cs_2CO_3 (104.2 mg, 0.32 mmol) and fluoromethyl 4-methylbenzenesulfonate (130.6 mg, 0.64 mmol). The

mixture stirred at 80°C for 16 hrs. The mixture was quenched by the addition of H₂O (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 7-5** (60 mg, 54.4%). LCMS: 344.8 [M+H]⁺.

[00282] To a solution of **Compound 7-5** (480 mg, 1.393 mmol) in THF (5 mL) was added borane-methyl sulfide complex (0.7 mL, 6.963 mmol) at -10°C under N₂ and the mixture was stirred at 25 °C for 4 h. A solution of sodium 1,3,2-dioxaboriran-2-olate (637.9 mg, 7.798 mmol) in H₂O (10 mL) and 1,4-dioxane (2 mL) was added. The reaction was stirred at 65°C for 6 h under N₂. The reaction mixture was partitioned between H₂O (20 mL) and EtOAc (100 mL). The organic phase was separated, washed with NH₄Cl (aq.) (30 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 7-6** (200 mg, 39.2%). LCMS: 363.0 [M+H]⁺.

[00283] **Compounds 7 & 8** were synthesized according to the previous procedures in **Example 4**.

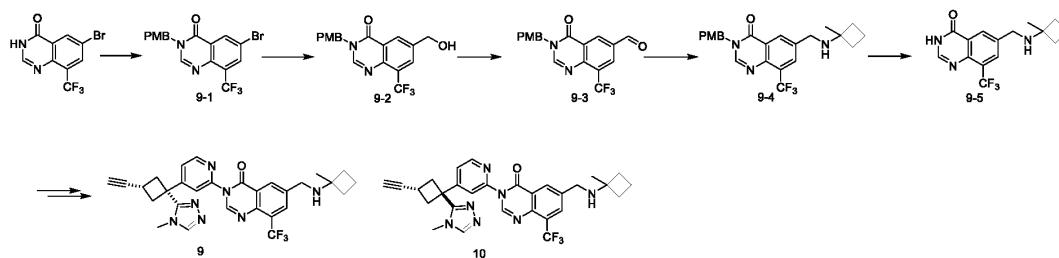
Compound 7:

[00284] LCMS: 578.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.56 (s, 1H), 8.10 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.66 – 7.33 (m, 2H), 7.11 (s, 1H), 6.13 (d, *J* = 52.1 Hz, 2H), 3.58 (s, 2H), 3.14 (d, *J* = 2.2 Hz, 1H), 3.13 – 3.02 (m, 4H), 2.74 – 2.67 (m, 2H), 1.93 – 1.84 (m, 1H), 1.69 – 1.55 (m, 4H), 1.52 – 1.43 (m, 1H), 1.33 – 1.24 (m, 1H), 0.87 – 0.77 (m, 4H).

Compound 8:

[00285] LCMS: 578.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.56 (d, *J* = 4.9 Hz, 1H), 8.11 (s, 1H), 7.84 – 7.78 (m, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.68 – 7.38 (m, 2H), 7.05 (s, 1H), 6.13 (d, *J* = 52.1 Hz, 2H), 3.58 (s, 2H), 3.18 – 3.16 (m, 1H), 3.16 – 3.11 (m, 1H), 2.86 – 2.78 (m, 2H), 2.77 – 2.65 (m, 3H), 1.90 (t, *J* = 10.4 Hz, 1H), 1.67 – 1.56 (m, 4H), 1.52 – 1.42 (m, 1H), 1.33 – 1.23 (m, 1H), 0.86 – 0.78 (m, 4H).

Examples 9 & 10



[00286] To a solution of 6-bromo-8-(trifluoromethyl)quinazolin-4(3*H*)-one (10 g, 34.130 mmol) in DMF (100 mL) were added Cs₂CO₃ (33.4 g, 102.389 mmol) and 4-(chloromethyl)-1-methoxybenzene (23.1 mL, 170.648 mmol) at room temperature. The reaction mixture was stirred at 25°C for 18 hrs. The mixture was filtered and the filter cake was washed with EtOAc (100 mL × 2) to give the crude

product, which was further pulped with EtOAc at 25 °C for 30 min. The mixture was filtered and the filter cake was dried to give **Compound 9-1** (9.3 g, 65.9%). LCMS: 413.1/415.1 [M+H]⁺;

[00287] To a solution of **Compound 9-1** (5 g, 12.101 mmol) in dioxane (100 mL) was added (tributyl- λ^4 -stannanyl)methanol (7.8 g, 24.202 mmol) and XPhos Pd G₂ (1.0 g, 1.210 mmol). The mixture was stirred at 80 °C for 12 hrs under N₂. The reaction mixture was concentrated to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 9-2** (3.25 g, 73.7%). LCMS: 365.2 [M+H]⁺;

[00288] To a solution of **Compound 9-2** (1 g, 2.745 mmol) in DCM (20 mL) were added 1,1,1-triacetoxy-1,3-dihydro-1 λ^5 -benzo[d][1,2]iodoxol-3-one (1.7 g, 4.117 mmol) at 0 °C. The reaction was stirred at room temperature for 2 hrs. The reaction mixture was partitioned between DCM (30 mL) and NaHCO₃ (aq. sat. 25 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 9-3** (508 mg, 51.0%). LCMS: 363.2 [M+H]⁺;

[00289] To a solution of **Compound 9-3** (600 mg, 1.656 mmol) and 1-methylcyclobutan-1-amine hydrochloride (402.8 mg, 3.312 mmol) in MeOH (8 mL) was added triethylamine (0.5 mL, 3.312 mmol), the mixture was stirred at 100 °C for 2 min under M.W., then Sodium cyanoborohydride (208.0 mg, 3.312 mmol) was added, the mixture was stirred at 80 °C for 1 h under M.W.. The mixture was quenched by the addition of water (30 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography to afford **Compound 9-4** (550 mg, 77.0%). LCMS: 432.3 [M+H]⁺;

[00290] A solution of **Compound 9-4** (654 mg, 1.516 mmol) in TFA (7 mL) was stirred at 80 °C for 2 hrs under N₂. The mixture was quenched by the addition of water (30 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography to afford **Compound 9-5**. LCMS: 312.2 [M+H]⁺;

[00291] **Compound 9 & 10** were synthesized according to the previous procedures in **Example 4**.

Compound 9:

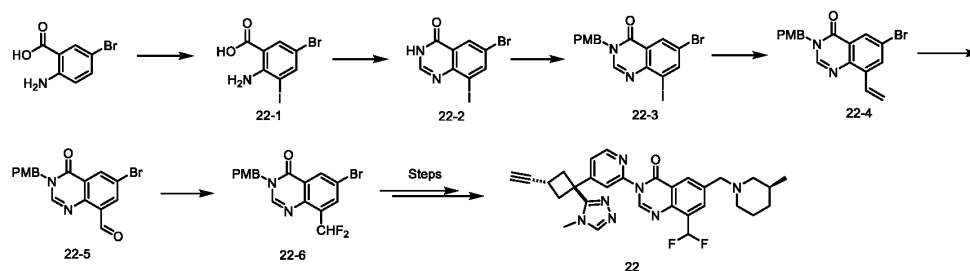
LCMS: 548.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 – 8.64 (m, 2H), 8.46 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 7.80 (s, 1H), 7.50 (dd, *J* = 5.3, 1.6 Hz, 1H), 3.84 (s, 2H), 3.32 – 3.28 (m, 2H), 3.26 (s, 3H), 3.14 (d, *J* = 2.3 Hz, 1H), 3.12 – 3.05 (m, 4H), 2.03 – 1.92 (m, 3H), 1.74 – 1.65 (m, 3H), 1.23 (s, 3H).

Compound 10:

LCMS: 548.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (d, *J* = 6.6 Hz, 2H), 8.47 (d, *J* = 6.4 Hz, 2H), 8.25 (s, 1H), 7.69 (s, 1H), 7.39 (dd, *J* = 5.3, 1.5 Hz, 1H), 3.84 (s, 2H), 3.31 – 3.27 (m, 5H), 3.16

(d, $J = 2.2$ Hz, 1H), 3.11 – 3.04 (m, 1H), 2.79 – 2.71 (m, 2H), 2.03 – 1.94 (m, 3H), 1.74 – 1.65 (m, 3H), 1.29 – 1.23 (m, 3H).

Example 22



[00292] To a solution of 2-amino-5-bromobenzoic acid (1 g, 4.63 mmol) in DCM (10 mL) was added NIS (1.04 g, 4.63 mmol). The mixture was stirred at 25 °C for 48 hrs under N₂. The reaction solution was poured into water (30 mL) and extracted with DCM (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with PE at 25 °C for 30 min. The mixture was filtered and the filter cake was concentrated to give **Compound 22-1** (1.2 g). LCMS: 341.8/343.8 [M+H]⁺;

[00293] A solution of **Compound 22-1** (1.2 g, 3.51 mmol) in formamide (10 mL) was stirred at 180 °C for 3 hrs under N₂. The reaction solution was poured into ice water (50 mL), and the product was precipitated under constant stirring. After filtration, the filter cake was washed with water and EtOAc/PE (1:1), and was spun dry to afford the crude **Compound 22-2** (750 mg). LCMS: 350.8/352.8 [M+H]⁺;

[00294] To a solution of **Compound 22-2** (27 g, 76.94 mmol) in DMF (270 mL) was added Cs₂CO₃ (75.2 g, 230.80 mmol) and PMBCl (24.1 g, 153.89 mmol). The mixture was stirred at 25 °C for 12 hrs under N₂. The reaction solution was poured into water (600 mL) and extracted with EtOAc (400 mL × 3). The combined organic phase was washed with water (300 mL × 2) and brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with EtOAc at 25 °C for 30 min. The mixture was filtered and the filtration was concentrated to give **Compound 22-3** (31 g). LCMS: 471.0/473.0 [M+H]⁺;

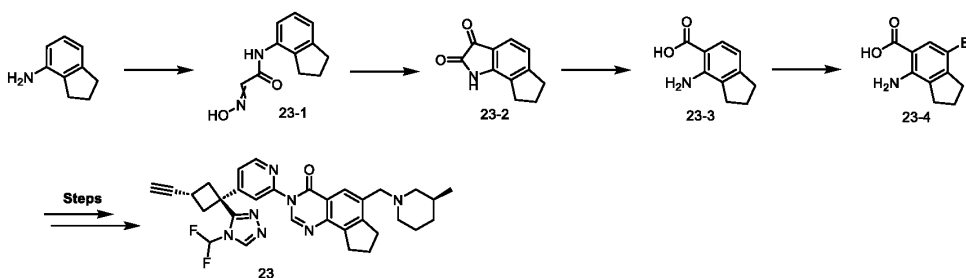
[00295] To a solution of **Compound 22-3** (5 g, 10.61 mmol) in dioxane (50 mL) was added Tributyl(vinyl)tin (3.4 g, 10.613 mmol), Caesium fluoride (3.2 g, 21.227 mmol) and bis(ethane) methane palladium chloride bis(triphenylphosphane) (0.8 g, 1.061 mmol). The mixture was stirred at 100 °C for 3 hrs under N₂. The reaction solution was poured into water (50 mL) and extracted with EtOAc (45 mL × 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude was purified by flash silica gel chromatography (Agela @: 40 g SepaFlash @-Silica Flash Column, Eluent of 0 - 20% PE/EtOAc gradient @:55 mL/min) to afford **Compound 22-4** (2.1 g, 53.3%). LCMS: 371.1/373.1 [M+H]⁺;

[00296] To a solution of **Compound 22-4** (2.21 g, 5.954 mmol), 2-hydroxypropane-1,2,3-tricarboxylic acid (1.5 g, 7.740 mmol) and NMO (0.9 g, 7.740 mmol) in Water (20 mL) were added dipotassium dioxidodioxo- λ 6-osmium(VI) dihydrate (0.2 g, 0.595 mmol) in tBuOH (20 mL). The mixture was stirred at 25°C for 2 hrs. Then sodium periodate (2.5 g, 11.907 mmol) was added and the mixture was stirred at 25°C for 3 hrs. The reaction solution was poured into water (50 mL) and extracted with EtOAc (45 mL $\times$ 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude was purified by flash silica gel chromatography (Agela @: 20 g SepaFlash @-Silica Flash Column, Eluent of 0-10% MeOH/DCM gradient @:40 mL/min) to afford **Compound 22-5** (1.77 g, 74.9%). LCMS: 373.0/375.0 [M+H]⁺;

[00297] To a solution of **Compound 22-5** (1.77 g, 4.743 mmol) in DCM (20 mL) was added DAST (1.3 mL, 9.486 mmol) at 0°C. The reaction mixture was stirred at 25°C for 3 hrs. The mixture was quenched by the addition of water 30 mL and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The crude was purified by flash silica gel chromatography (Agela @: 20 g SepaFlash @-Silica Flash Column, Eluent of 0-25% EtOAc/PE gradient @:40 mL/min) to afford **Compound 22-6** (1.5 g, 80.0%). LCMS: 394.8/396.8 [M+H]⁺;

[00298] The **compound 22** was synthesized according to the previous procedures in **Example 9** with **compound 22-6** as the substrate. LCMS: 544.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 – 8.61 (m, 2H), 8.47 (s, 1H), 8.27 (s, 1H), 8.05 (s, 1H), 7.71 (s, 1H), 7.63 (t, *J* = 55.1 Hz, 1H), 7.38 (dd, *J* = 5.3, 1.4 Hz, 1H), 3.64 (s, 2H), 3.40 – 3.39 (m, 1H), 3.30 (s, 3H), 3.16 (d, *J* = 2.3 Hz, 1H), 3.13 – 3.02 (m, 2H), 2.77 – 2.69 (m, 4H), 1.96 – 1.90 (m, 1H), 1.68 – 1.57 (m, 4H), 1.52 – 1.44 (m, 1H), 0.90 – 0.80 (m, 4H).

Example 23



[00299] To a solution of 2,2,2-trichloroethane-1,1-diol (22.35 g, 135 mmol) in H₂O (750 mL) was added Na₂SO₄ (128 g, 901 mmol). When the temperature reached 45°C, 2,3-dihydro-1*H*-inden-4-amine (15 g, 113 mmol) in HCl (45 mL, 90 mmol, 2 N) was added dropwise. The reaction mixture was stirred for 1 h, then the suspension of NH₂OH·HCl (31.3 g, 450 mmol) was rapidly added to the reaction mixture. The mixture was stirred at 80°C for 1 h. The mixture was cooled to room

temperature, filtered and the filter cake was washed with water (50 mL $\times$ 3). The filter cake was concentrated to afford **Compound 23-1** (22.5 g). LCMS: 205.1 [M+H]⁺;

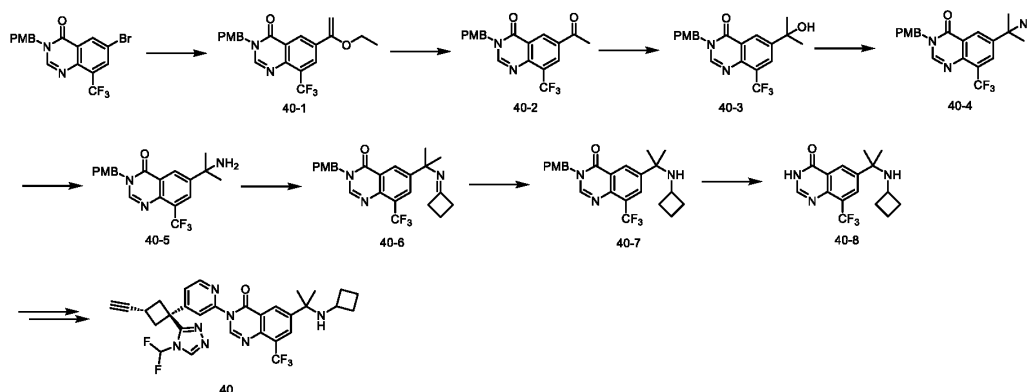
[00300] A solution of **Compound 23-1** (6 g, 29.383 mmol) in Methanesulfonic acid (25 mL, 29.383 mmol) was stirred at 80 °C for 30 min. The reaction was cooled to room temperature, poured into ice water and filtered. The filter cake was dissolved in warmed 1 N NaOH, and neutralized with acetic acid. After filtration, the filtrate was acidized with concentrated HCl. The mixture was filtered and the filter cake was washed with water. The solid was dried to yield the **Compound 23-2** (6.0 g). LCMS: 188.0 [M+H]⁺;

[00301] To a solution of **Compound 23-2** (6.6 g, 35.256 mmol) in NaOH (2 M in water, 70 mL, 140.000 mmol) was added hydrogen peroxide (3 mL, 26.471 mmol) at room temperature, the reaction was stirred at room temperature for 2 hrs. The mixture was adjusted to pH 4 with 1N HCl and was extracted with EtOAc (50 mL $\times$ 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude **Compound 23-3**. LCMS: 178.0 [M+H]⁺;

[00302] To a solution of **Compound 23-3** (5.5 g, 31.038 mmol) in AcOH (25 mL) was added NBS (8.3 g, 46.558 mmol) at room temperature, the reaction was stirred at room temperature for overnight. The reaction mixture was partitioned between water (100 mL) and EtOAc (200 mL). The organic phase was separated, washed with water (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO@; 80 g SepaFlash@ Silica Flash Column, Eluent of 0-60% EtOAc/PE gradient @ 50 mL/min) to afford **Compound 23-4** (2.3 g). LCMS: 256.0/258.0 [M+H]⁺;

[00303] The **compound 23** was synthesized according to the previous procedures in **Example 9** with **compound 23-4** as the substrate. LCMS: 570.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.62 (d, *J* = 5.3 Hz, 1H), 8.49 (s, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 7.64 – 7.34 (m, 2H), 3.50 (s, 2H), 3.22 – 3.10 (m, 5H), 3.10 – 3.03 (m, 2H), 2.86 – 2.66 (m, 5H), 2.15 (p, *J* = 7.6 Hz, 2H), 1.96 – 1.88 (m, 1H), 1.69 – 1.55 (m, 4H), 1.49 – 1.40 (m, 1H), 0.90 – 0.79 (m, 4H).

Example 40



[00304] To a solution of 6-bromo-3-(4-methoxybenzyl)-8-(trifluoromethyl)quinazolin-4(3*H*)-one (522 mg, 1.263 mmol) in dioxane (10 mL) was added Tributyl(1-ethoxyvinyl)stannane (912.6 mg, 2.527 mmol) and Pd(PPh₃)₄ (146.0 mg, 0.126 mmol) at room temperature. The reaction was stirred at 110°C for 12hrs under N₂. The mixture was quenched by the addition of KF (sat. aq. 30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed brine (30 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude **Compound 40-1** (522 mg). The crude product was used to the next step without further purification. LCMS: 405.1[M+H]⁺;

[00305] To a solution of **Compound 40-1** (18.1 g, 44.758 mmol) in THF (90 mL) was added HCl (100 mL, 100.000 mmol) at room temperature. The reaction was stirred at 25°C for 1h. The mixture was quenched by the addition of water (45 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed brine (50 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to afford **Compound 40-2** (12.5 g, 74.2%). The crude product was used to the next step without further purification. LCMS: 377.1[M+H]⁺;

[00306] To a solution of **Compound 40-2** (7 g, 18.602 mmol) in THF (100 mL) was added magnesium monobromide methanide (22.3 mL, 23.736 mmol) at room temperature. The reaction was stirred at 60°C for 12 hrs. The mixture was quenched by the addition of water (45 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (45 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (Agela @: 80 g SepaFlash @-Silica Flash Column, Eluent of 0 - 30% EtOAc/PE gradient @:70 mL/min) to afford **Compound 40-3** (4.07 g, 55.8%). LCMS: 393.5 [M+H]⁺;

[00307] To a solution of **Compound 40-3** (4 g, 10.194 mmol) in DCM (40 mL) were added azidotrimethylsilane (3.3 mL, 25.484 mmol) and ethoxyethane trifluoroborane (2.6 mL, 20.898 mmol) at room temperature. The reaction was stirred at 25°C for 2hrs. The mixture was quenched by the addition of water (40 mL) and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (Agela @: 40 g SepaFlash @-Silica Flash Column, Eluent of 0 - 20% EtOAc/PE gradient @:50 mL/min) to afford **Compound 40-4** (4.06 g, 95.4%). LCMS: 418.3 [M+H]⁺;

[00308] To a solution of **Compound 40-4** (4 g, 9.58 mmol) in AcOH (40 mL) was added zinc (1.253 g, 19.17 mmol). The mixture was stirred at 50°C for 2 hrs under N₂. The reaction mixture was filtered and the filtrate was concentrated. The crude was purified by reversed phase chromatography (Isolera-Biotage Column: Agela C18 80 g; Mobile Phase A: 0.1% FA/H₂O, Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 20% B to 40% B in 20 min; Detector: UV 210 nm) to afford **Compound 40-5** (2.55 g, 68.0 % yield).

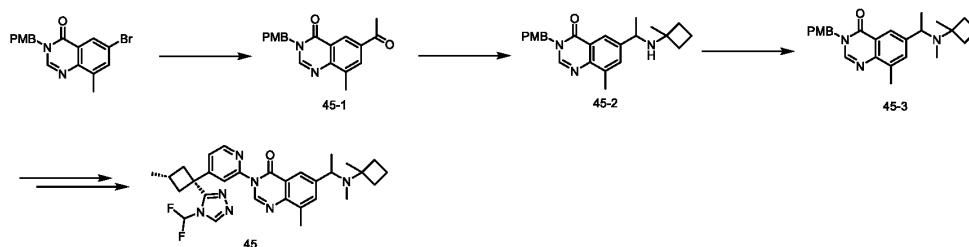
[00309] To a solution of **Compound 40-5** (1 g, 2.55 mmol) in Titanium tetrakisopropanolate (10 mL) was added cyclobutanone (0.269 g, 3.83 mmol). The mixture was stirred at 100°C for 36 hrs in a sealed tube. The reaction solution was used directly for the next step without purification.

[00310] To a solution of **Compound 40-6** (1 g, 2.255 mmol) in THF (10 mL) was added NaBH₄ (0.427 g, 11.27 mmol) at 0°C. The mixture was stirred at 25°C for 2 h under N₂. The reaction mixture was partitioned between water (30 mL) and EtOAc (35 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude. The crude product was purified by reverse phase chromatography (Column: Agilent C18, 40 g; Mobile Phase A: 0.1 % FA/H₂O, B: ACN; flow rate: 35 mL/min; gradient: 30-60 %; Retention Time: 30 min) to afford **Compound 40-7** (500mg, 49.8 % yield). LCMS: 446.1 [M+H]⁺;

[00311] To a solution of **Compound 40-7** (450 mg, 1.010 mmol) was added TFA (10 mL). The mixture was stirred at 80 °C for 2 hrs under N₂. The reaction solution was directly concentrated to obtain this crude product. The crude was purified by flash silica gel chromatography (Agela @: 4g SepaFlash @-Silica Flash Column, Eluent of 0-15% MeOH/DCM gradient @:20 mL/min) to afford **Compound 40-8**. LCMS: 326.1 [M+H]⁺;

[00312] According to the previous procedures in **Example 4**, the **compound 40** was synthesized with **Compound 40-8** as the substrate. LCMS: 598.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.67 – 8.62 (m, 2H), 8.46 (d, *J* = 1.9 Hz, 1H), 8.39 – 8.36 (m, 1H), 7.74 (s, 1H), 7.65 – 7.33 (m, 2H), 3.42 – 3.36 (m, 2H), 3.18 – 3.16 (m, 1H), 2.93 – 2.86 (m, 1H), 2.84 – 2.76 (m, 2H), 2.73 – 2.68 (m, 1H), 1.95 – 1.84 (m, 2H), 1.72 – 1.62 (m, 2H), 1.48 – 1.35 (m, 8H).

Example 45



[00313] **Compound 45-1** was synthesized according to the procedures of preparation of **40-2** with 6-bromo-3-(4-methoxybenzyl)-8-methylquinazolin-4(3*H*)-one as the substrate.

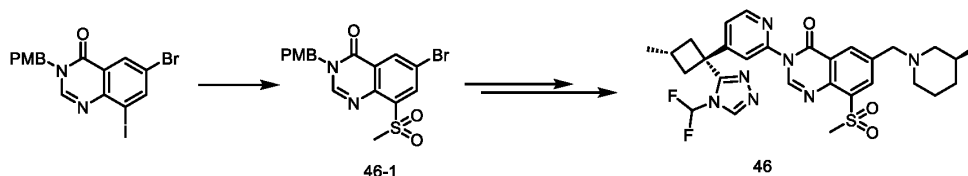
[00314] A solution of **Compound 45-1** (800 mg, 2.48 mmol) and 1-methylcyclobutan-1-amine (254 mg, 2.98 mmol) in Titanium tetrakisopropanolate (10 mL) was stirred at 100°C for 16 hrs. After cooled to 25°C, THF (5 mL) and sodium boranuide (563 mg, 14.89 mmol) was added. The resulting mixture was stirred at 25°C for 2 hrs. The reaction mixture was diluted with EtOAc (20 mL), quenched by addition of water (5 mL) and MeOH (5 mL) at 10°C. The suspension was filtered, a filter cake was washed with EtOAc (15 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase chromatography

(Isolera-Biotage Column: Agela C18 20 g; Mobile Phase A: 0.1% FA, Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 35% B to 45% B in 15 min; Detector: UV 210 nm) to afford **Compound 45-2** (300 mg, 30.9%). LCMS: 392.2 [M+H]⁺;

[00315] To a solution of **Compound 45-2** (300 mg, 0.76 mmol) in DCM (5 mL) was added Formaldehyde (0.021 mL, 0.76 mmol). The resulting mixture was stirred at 25 °C for 1 h. Then STAB (244 mg, 1.15 mmol) was added. The mixture was stirred at 25 °C for 16 hrs. The mixture was concentrated to get the residue. The residue was purified by flash silica gel chromatography (ISCO@; 12 g SepaFlash@ Silica Flash Column, Eluent of 0-100% EtOAc/PE @ 20 mL/min) to afford **Compound 45-3** (220 mg, 70.8%). LCMS: 406.0 [M+H]⁺;

[00316] According to the previous procedures in **Example 1**, the **compound 45** was synthesized with **Compound 45-3** as the substrate. LCMS: 548.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.62 (d, *J* = 5.3 Hz, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.76 (s, 1H), 7.45 (t, *J* = 58.6 Hz, 1H), 7.42 (dd, *J* = 5.2, 1.6 Hz, 1H), 3.85 – 3.75 (m, 1H), 2.92 – 2.84 (m, 2H), 2.67 – 2.58 (m, 6H), 2.13 (q, *J* = 9.4 Hz, 1H), 1.92 (s, 3H), 1.90 – 1.60 (m, 5H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.22 (s, 3H), 1.09 (d, *J* = 5.6 Hz, 3H).

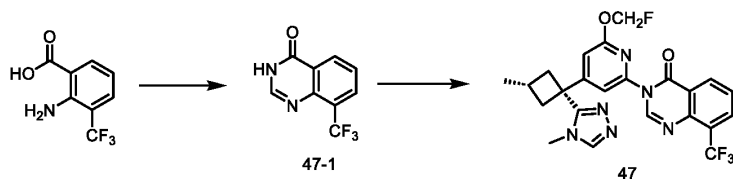
Example 46



[00317] To a solution of 6-bromo-8-iodo-3-(4-methoxybenzyl)quinazolin-4(3H)-one (3 g, 6.37 mmol), CuI (0.122 g, 0.637 mmol) and K₃PO₄ (1.352 g, 6.37 mmol) in DMSO (30 mL) was added Sodium methyl sulfinate (0.975 g, 9.55 mmol) and DMPHPC (0.149 g, 0.637 mmol). The mixture was stirred at 80 °C for 12 hrs under N₂. The reaction solution was directly concentrated to obtain a crude product. The crude product was purified by flash silica gel chromatography (Agela @: 80g SepaFlash @-Silica Flash Column, Eluent of 0-50% EtOAc/PE gradient @:70 mL/min) to afford **Compound 46-1** (330 mg, 12.24 % yield). LCMS: 422.8/424.8 [M+H]⁺;

[00318] According to the previous procedures in **Example 9**, the **compound 46** was synthesized with **Compound 46-1** as the substrate. LCMS: 598.3 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.74 (s, 1H), 8.64 (d, *J* = 5.3 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 7.86 (s, 1H), 7.48 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.45 (t, *J* = 58.7 Hz, 1H), 3.67 (s, 2H), 3.56 (s, 3H), 2.94 – 2.82 (m, 2H), 2.80 – 2.69 (m, 2H), 2.69 – 2.58 (m, 3H), 1.95 (t, *J* = 10.3 Hz, 1H), 1.71 – 1.56 (m, 4H), 1.55 – 1.42 (m, 1H), 1.09 (d, *J* = 5.7 Hz, 3H), 0.93 – 0.78 (m, 4H).

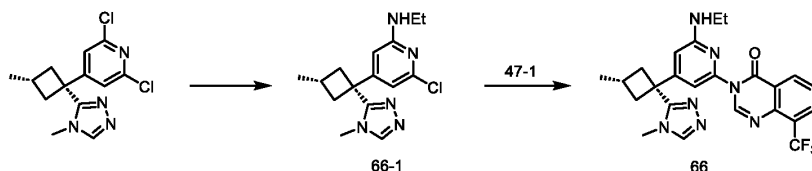
Example 47



[00319] A solution of 2-amino-3-(trifluoromethyl)benzoic acid (1 g, 4.87 mmol) in formamide (10 mL) was stirred at 170 °C for 4 hrs under N₂. The reaction solution was poured into ice water (50 mL), and the product was precipitated under constant stirring. The mixture was filtrated, the filter cake was washed with water, and was concentrated under reduced pressure to afford the crude **Compound 47-1** (730 mg, 69.93 % yield). LCMS: 215.1 [M+H]⁺;

[00320] To a solution of **Compound 47-1** (200 mg, 0.934 mmol), 2-chloro-6-(fluoromethoxy)-4-((*Is,3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridine (348 mg, 1.121 mmol) and K₂CO₃ (258 mg, 1.868 mmol) in Dioxane (5 mL) was added CuI (178 mg, 0.934 mmol) and (*IR,2R*)-*N,N'*-Dimethyl-1,2-cyclohexanediamine (266 mg, 1.868 mmol). The mixture was stirred at 120 °C for 1h under N₂. The reaction mixture was partitioned between ethyl acrylate (12 mL) and water (10 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Waters 3767/QDA, Column: XBridge XBridge C18, 19*250mm, 10 um; Mobile Phase A: 10 mmol/L NH₄HCO₃/H₂O, B: ACN; flow rate: 20 mL/min; gradient: 50-50%; Retention Time: 7.1-7.7min) to afford **Compound 47** as the major peak. LCMS: 489.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 8.50 (d, *J* = 7.3 Hz, 1H), 8.37 (s, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 1.1 Hz, 1H), 7.10 (d, *J* = 1.2 Hz, 1H), 6.14 (d, *J* = 52.1 Hz, 2H), 3.27 (s, 3H), 2.94 – 2.84 (m, 2H), 2.65 – 2.56 (m, 3H), 1.09 (d, *J* = 5.3 Hz, 3H).

Example 66

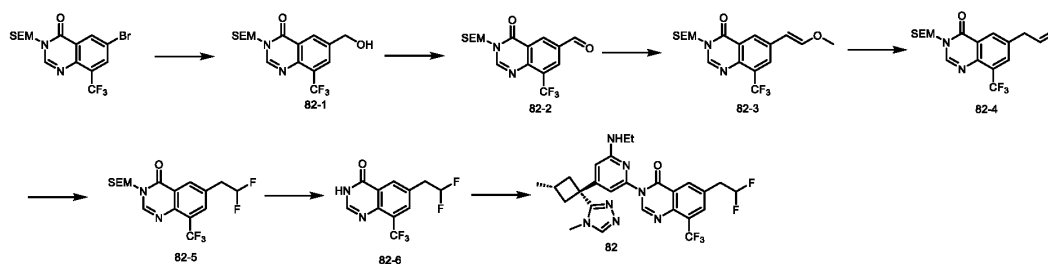


[00321] A solution of 2,6-dichloro-4-((*Is,3s*)-3-methyl-1-(4-methyl-4*H*-1,2,4-triazol-3-yl)cyclobutyl)pyridine (10 g, 33.6 mmol) in ethylamine (100 ml, 2M in THF) was stirred at 110°C for 72 hrs under N₂. The mixture was concentrated to give the residue. The residue was purified by flash silica gel chromatography (Agela @: 120g SepaFlash @-Silica Flash Column, Eluent of 0 - 5% DCM/MeOH gradient @:85 mL/min) to afford **Compound 66-1** (6 g, 58.3 % yield). LCMS: 306.1 [M+H]⁺;

[00322] To a solution of **Compound 66-1** (200 mg, 0.654 mmol), **47-1** (210 mg, 0.981 mmol) and K₂CO₃ (181 mg, 1.308 mmol) in 1,4-Dioxane (5 mL) was added CuI (125 mg, 0.654 mmol) and *rac*-(*IR,2R*)-*N1,N2*-dimethylcyclohexane-1,2-diamine (186 mg, 1.308 mmol). The mixture was stirred at

120 °C for 12 hrs under N₂. The mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed brine (30 mL × 2), dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by prep-HPLC (Gilson GX-281, Column: XSelect CHS C18, 19*250mm, 10 μm; Mobile Phase A: 10mmol NH₄HCO₃ B: ACN; flow rate: 20 l/min; gradient: 53-53% Retention Time: 8-9.5 min to afford **Compound 66** as the major peak. LCMS: 484.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.36 (s, 1H), 8.25 (d, *J* = 6.9 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 5.3 Hz, 1H), 6.87 (d, *J* = 1.2 Hz, 1H), 6.45 (d, *J* = 1.2 Hz, 1H), 3.28 (s, 3H), 3.26 – 3.19 (m, 2H), 2.82 – 2.71 (m, 2H), 2.62 – 2.52 (m, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 5.8 Hz, 3H).

Example 82



[00323] To a solution of 6-bromo-8-(trifluoromethyl)-3-((2-(trimethylsilyl)ethoxy)methyl)quinazolin-4(3H)-one (1 g, 2.362 mmol) in 1,4-Dioxane (10 mL) were added (tributylstannyl)methanol (1.517 g, 4.72 mmol) and XPhos Pd G₂ (0.186 g, 0.236 mmol) at room temperature. The reaction was stirred at 80 °C for 12hrs. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Agela @: 12g SepaFlash @-Silica Flash Column, Eluent of 0 - 15% MeOH / DCM gradient @:30 mL/min) to afford **Compound 82-1** (800 mg, 90 % yield). LCMS: 375.1 [M+H]⁺;

[00324] To a solution of **82-1** (932 mg, 2.489 mmol) in DCM (10 mL) was added DMP (1584 mg, 3.73 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hr under N₂. The reaction mixture was partitioned between water and DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (Agela: 12 g SepaFlash @-Silica Flash Column, Eluent of 0 - 20% EtOAc/PE gradient @:30 mL/min) to afford **Compound 82-2** (631 mg, 68.1 % yield). LCMS: 373.0 [M+H]⁺;

[00325] To a solution of Ph₃P(CH₂OMe)Br (911 mg, 2.352 mmol) in THF (10 mL) was added potassium tert-butoxide (2.352 mL, 2.352 mmol), the mixture was stirred at 0 °C for 30 min, then THF (10 mL) and **Compound 82-2** (730 mg, 1.960 mmol) was added, the mixture was stirred at 10 °C for 12 hrs. The reaction mixture was partitioned between water and DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Agela: 12 g SepaFlash @-Silica Flash

Column, Eluent of 0 - 20% EtOAc / PE gradient @:30 mL/min) to afford **Compound 82-3** (323 mg, 41.1 % yield). LCMS:401.0 [M+H]⁺;

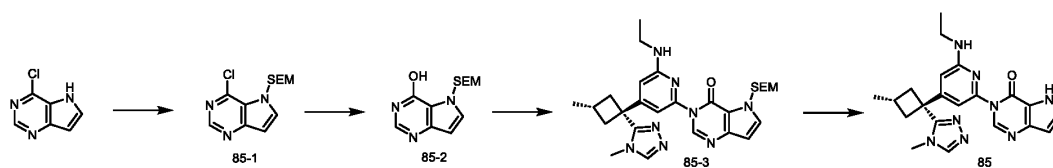
[00326] To a solution of **Compound 82-3** (323 mg, 0.807 mmol) in THF (5 mL) were added HCl (4 mL, 24.00 mmol). The mixture was stirred at 60°C for 1hr under N₂. The mixture was quenched by the addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (Agela @: 4g SepaFlash @-Silica Flash Column, Eluent of 0 - 25% EtOAc /PE gradient @:20 mL/min) to afford crude **Compound 82-4** (42 mg, 13.48 % yield). The crude was used to next step without further purification. LCMS: 387.0 [M+H]⁺;

[00327] To a solution of **Compound 82-4** (30 mg, 0.078 mmol) in DCM (3 mL) was added DAST (0.021 ml, 0.155 mmol) at 0°C. The reaction was stirred at 25°C for 3 hrs. The mixture was quenched by the addition of water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford **Compound 82-5** as a white solid. The crude product was used to the next step without further purification. LCMS: 409.1 [M+H]⁺;

[00328] To a solution of **Compound 82-5** (40 mg, 0.098 mmol) in THF (2 mL) were added HCl (2 mL, 12.00 mmol). The mixture was stirred at 70°C for 12hrs under N₂. The mixture was quenched by the addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (Agela @: 4 g SepaFlash @-Silica Flash Column, Eluent of 0 - 15% MeOH / DCM gradient @:20 mL/min) to afford crude **Compound 82-6**. The crude was used to next step without further purification. LCMS: 279.0 [M+H]⁺;

[00329] According to the previous procedure in **Example 66**, **Compound 82** was synthesized with **82-6** and 6-chloro-N-ethyl-4-(3-methyl-1-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-amine as the substrates. LCMS: 548.2 [M+H]⁺;

Example 85



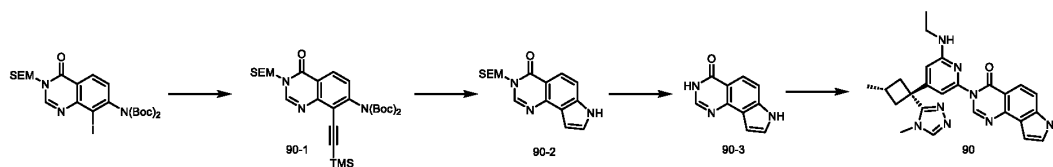
[00330] To a solution of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (1 g, 6.51 mmol) in DMF (15 mL) was added SEM-Cl (4.62 mL, 26.0 mmol) and Cs₂CO₃ (12.73 g, 39.1 mmol). The mixture was stirred at 20°C for 12h under N₂. The mixture was quenched by the addition of water (50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO@: 12 g SepaFlash@ Silica Flash Column, Eluent of 0-25%EtOAc/PE @ 30 mL/min) to afford **Compound 85-1** (470 mg, 25.4 % yield). LCMS: 283.9 [M+H]⁺;

[00331] To a solution of **Compound 85-1** (470 mg, 1.656 mmol) in DMSO (8 mL) was added N-hydroxyacetamide (373 mg, 4.97 mmol) and K_2CO_3 (687 mg, 4.97 mmol). The mixture was stirred at 80 °C for 2h under N_2 . The reaction mixture was partitioned between EtOAc (12 mL) and water (20 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-100% EtOAc/PE @ 30 mL/min) to afford **Compound 85-2** (320 mg, 72.8 % yield). LCMS: 266.1 [M+H]⁺;

[00332] According to the previous procedure in **Example 66**, **Compound 85-3** was synthesized with **Compound 85-2** and 6-chloro-N-ethyl-4-(3-methyl-1-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-amine as the substrates. LCMS: 535.4 [M+H]⁺;

[00333] To a solution of **Compound 85-3** (80 mg, 0.150 mmol) in THF (2 mL) was added TBAF (39.1 mg, 0.150 mmol). The mixture was stirred at 70 °C for 2 hrs. The reaction mixture was partitioned between EtOAc (12 mL) and NH_4Cl (sat. aq., 20 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Waters 3767QDA, Column: XBridge XBridge C18, 19*250mm, 10 μ m; Mobile Phase A: 10 mmol/L NH_4HCO_3/H_2O , B: ACN; flow rate: 20 mL/min; gradient: 28-28%; Retention Time: 6.7-7.8min) to afford **Compound 85**. LCMS: 404.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 7.45 (s, 1H), 6.91 (t, *J* = 4.8 Hz, 1H), 6.72 (s, 1H), 6.43 (d, *J* = 1.8 Hz, 1H), 6.40 (s, 1H), 3.29 (s, 3H), 3.21 – 3.28 (m, 2H), 2.83 – 2.71 (m, 2H), 2.53 (s, 3H), 1.14 – 1.08 (m, 3H), 1.07 (d, *J* = 5.5 Hz, 3H).

Example 90



[00334] To a solution of tert-butyl (tert-butoxycarbonyl)(8-iodo-4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydroquinazolin-7-yl)carbamate (1g, 1.619 mmol) in DMF (10 mL) were added (dibutyl(propyl)stannyl)ethynyltrimethylsilane (0.665 g, 1.781 mmol) and $Pd(PPh_3)_4$ (0.187 g, 0.162 mmol). The mixture was stirred at 90 °C for 12 hrs under N_2 . The reaction mixture was poured into water (30 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Agela: 12 g SepaFlash® -Silica Flash Column, Eluent of 0 - 20% EtOAc/PE gradient @:30 mL/min) to afford **Compound 90-1** (740 mg, 78 % yield). LCMS: 588.5 [M+H]⁺;

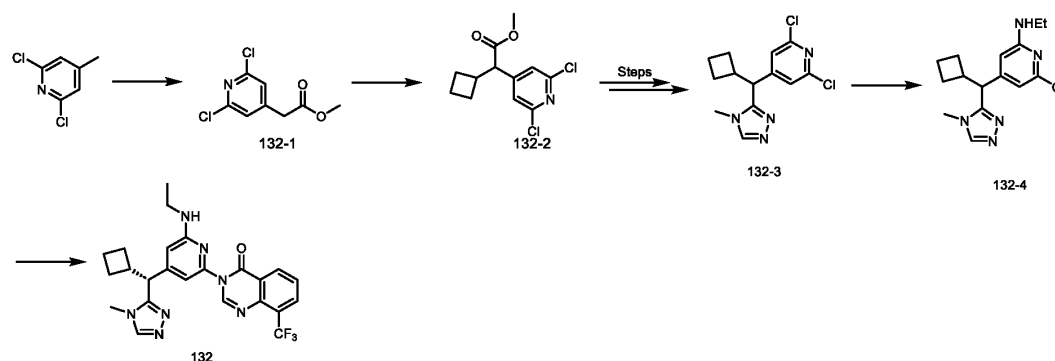
[00335] To a solution of **Compound 90-1** (500 mg, 0.851 mmol) in DMF (10 mL) was added Cs_2CO_3 (831 mg, 2.55 mmol), the mixture was stirred at 80 °C for 12 hrs under N_2 . The resulting

mixture was stirred at 120 °C for 2 hrs. The reaction mixture was poured into water (30 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Agela: 4 g SepaFlash @-Silica Flash Column, Eluent of 0 - 30% EtOAc / PE gradient @:20 mL/min) to afford **Compound 90-2**. LCMS: 316.2 [M+H]⁺;

[00336] To a solution of **Compound 90-2** (102 mg, 0.323 mmol) in THF (3 mL) were added TBAF (85 mg, 0.323 mmol). The mixture was stirred at 70 °C for 12hrs under nitrogen atmosphere. The reaction mixture was purified by reverse phase chromatography to afford **Compound 90-3**. The crude product was used into the next step without further purification. LCMS: 186.1 [M+H]⁺;

[00337] According to the previous procedure in **Example 66**, **Compound 90** was synthesized with **90-3** and 6-chloro-N-ethyl-4-(3-methyl-1-(4-methyl-4H-1,2,4-triazol-3-yl)cyclobutyl)pyridin-2-amine as the substrates. LCMS: 455.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.78 (s, 1H), 8.60 (s, 1H), 8.36 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.52 (m, 1H), 6.98 – 6.92 (m, 2H), 6.85 (d, *J* = 1.0 Hz, 1H), 6.41 (d, *J* = 1.0 Hz, 1H), 3.29 (s, 3H), 3.26 – 3.21 (m, 2H), 3.21 – 3.12 (m, 2H), 2.83 – 2.76 (m, 2H), 2.59 – 2.54 (m, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 5.9 Hz, 3H).

Example 132



[00338] To a solution of 2,6-dichloro-4-methylpyridine (10 g, 61.7 mmol) in THF (100 mL) was added LDA (61.7 mL, 123 mmol). The mixture was stirred at -78 °C for 30 min. Then dimethyl carbonate (15.57 g, 173 mmol) was added and stirred at 0 °C for 1 hr. The reaction mixture was poured into water (100 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO@; 120 g SepaFlash@ Silica Flash Column, Eluent of 0-25% EtOAc/ PE @ 80 mL/min) to afford crude **Compound 132-1** (8.8 g, 64.8 % yield). LCMS: 220.0 [M+H]⁺;

[00339] To a solution of **Compound 132-1** (7.76 g, 35.3 mmol) in DMF (70 mL) was added Cs₂CO₃ (11.49 g, 35.3 mmol). The mixture was stirred at 0 °C for 30 min. Then bromocyclobutane (33.2 mL, 353 mmol) was added into the solution and the mixture was stirred at 20 °C for 16 hr. The reaction mixture was poured into water (100 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a

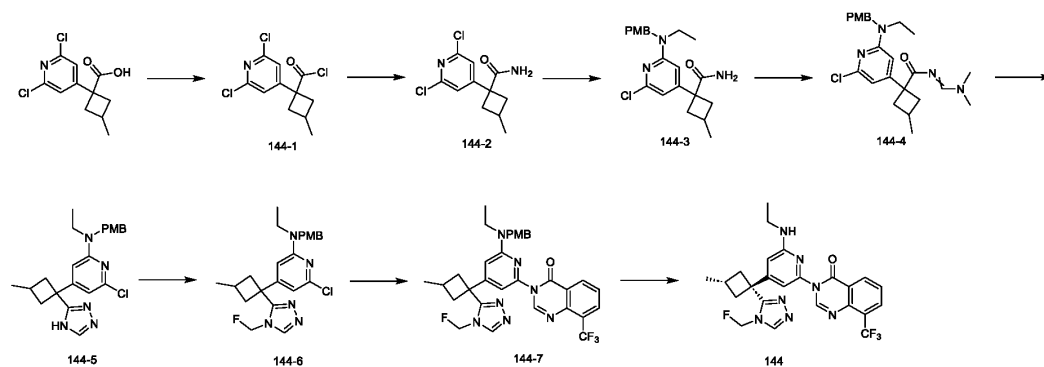
residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0-25% EtOAc/ PE @ 60 mL/min) to afford **Compound 132-2** (2.4 g, 24.83 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51 (s, 2H), 3.86 (s, 1H), 3.59 (s, 3H), 2.90 – 2.79 (m, 1H), 2.10 – 2.01 (m, 1H), 1.83 – 1.64 (m, 5H).

[00340] According to the previous procedures in **Example 3**, **Compound 132-3** was synthesized with **compound 132-2** as the substrate. LCMS: 297.1 [M+H]⁺;

[00341] A solution of **Compound 132-3** (819 mg, 2.76 mmol) in EtNH₂/THF (10mL, 10.00 mmol) was stirred at 110 °C for 96 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to afford **Compound 132-4**. LCMS: 306.2 [M+H]⁺;

[00342] According to the previous procedures in **Example 66**, **Compound 132** was synthesized with compound 132-4 as the substrate and further separated by SFC (Waters SFC 80 column: DAICELCHIRALPAK®AD 250mm*30mm,10 um; mobile phase A: Supercritical CO₂; mobile phase B: IPA (+0.1% 7.0 mol/l Ammonia in MeOH); A:B: 80:20, Flow rate: 50 mL/min, Cycle time: 5.3 min). LCMS: 484.2 [M+H]⁺; Chiral analytic conditions: Waters UPCC CA-185, column: DAICELCHIRALPAK®AD 100mm*3.0mm,3.0 um; mobile phase A: Supercritical CO₂; mobile phase B: IPA (+0.1% DEA), flow rate 15 mL/min. Retention time (as the second peak) = 2.017 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.48 (d, *J* = 7.1 Hz, 1H), 8.37 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 5.2 Hz, 1H), 6.80 (s, 1H), 6.39 (s, 1H), 4.18 (d, *J* = 10.5 Hz, 1H), 3.48 (s, 3H), 3.25 – 3.18 (m, 2H), 3.17 – 3.10 (m, 1H), 2.11 – 2.03 (m, 1H), 1.93 – 1.77 (m, 4H), 1.76 – 1.66 (m, 1H), 1.11 (t, *J* = 7.2 Hz, 3H).

Example 144



[00343] To a solution of 1-(2,6-dichloropyridin-4-yl)-3-methylcyclobutane-1-carboxylic acid (10 g, 38.4 mmol) in DCM (100 mL) was added oxalyl dichloride (5 mL, 57.7 mmol) and DMF (0.3 mL, 3.84 mmol). The reaction was stirred at 15 °C for 2 h. The mixture was concentrated under reduced pressure to give a crude. The crude product was used into the next step without further purification. LCMS: 274.2 [M+H]⁺ (as methyl ester)

[00344] A solution of **Compound 144-1** (10.7 g, 38.4 mmol) in DCM (40 mL) was added dropwise to the ammonia (7M in MeOH, 18.2 mL, 126.9 mmol). The mixture was stirred at 0°C for 1 hrs. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO@; 80 g SepaFlash@ Silica Flash Column, Eluent of 0-10% MeOH/DCM @ 80 mL/min) to afford **Compound 144-2** (6.3 g, 63.3 % yield). LCMS: 300.0 [M+H]⁺;

[00345] A solution of **Compound 144-2** (500 mg, 1.93 mmol), K₂CO₃ (800 mg, 5.79 mmol) and PMBNHEt (638 mg, 3.86 mmol) in DMF (10 mL) was stirred at 130 °C for 16 h. The mixture was quenched by the addition of H₂O (150 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO @; 40 g SepaFlash @ Silica Flash Column, Eluent of 0-100 % MeOH/DCM gradient @ 50 mL/min) to afford **Compound 144-3** (800 mg, 13.36% yield). LCMS: 388.2 [M+H]⁺;

[00346] A solution of **Compound 144-3** (60 mg, 0.155 mmol) in DMF-DMA (4 mL, 29.9 mmol) was stirred at 100°C for 16 hrs. The mixture was concentrated under reduced pressure to give a crude. The crude product was used into the next step without further purification. LCMS: 443.3 [M+H]⁺;

[00347] To a solution of **Compound 144-4** (50 mg, 0.113 mmol) in AcOH (2 mL) was added hydrazinium hydroxide (1mL, 0.113 mmol) at 0°C. The mixture was stirred at 80°C for 3 hr under nitrogen atmosphere. The mixture was quenched by the addition of H₂O (20 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO @; 4 g SepaFlash @ Silica Flash Column, Eluent of 0-15 % MeOH/ DCM gradient @ 15 mL/min) to afford **Compound 144-5** (40 mg, 86 % yield). LCMS: 412.4 [M+H]⁺;

[00348] To a solution of **Compound 144-5** (40 mg, 0.097 mmol) in THF (10 mL) was added NaH (8 mg, 0.194 mmol). The mixture was stirred at 0°C for 30 min, then fluoroiodomethane (24 mg, 0.146 mmol) was added at 0°C. The resulting mixture was stirred at 20°C for 16 hr. The mixture was quenched by the addition of H₂O (10 mL) and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO @; 4 g SepaFlash @ Silica Flash Column, Eluent of 0-100 % EtOAc/ PE gradient @ 18 mL/min) to afford **Compound 144-6**. The crude product was used into the next step without further purification. LCMS: 444.0 [M+H]⁺;

[00349] To a solution of **Compound 144-6** (10 mg, 0.023 mmol), 8-(trifluoromethyl)quinazolin-4(3H)-one (5.31 mg, 0.025 mmol) and K₂CO₃ (7 mg, 0.045 mmol) in 1,4-dioxane (4 mL) was added CuI (5 mg, 0.023 mmol) and methyl[(1R,2R)-2-(methylamino)cyclohexyl]amine (7 mg, 0.045 mmol). The mixture was stirred at 120°C for 16 hr under nitrogen atmosphere. The reaction mixture was poured into water (15 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The residue was

purified by flash silica gel chromatography to afford **Compound 144-7**. The crude product was used into the next step without further purification. LCMS: 622.3 [M+H]⁺.

[00350] To a solution of **144-7** (5 mg, 8.04 μ mol) in DCM (2 mL) was added TFA (2 mL, 26.0 mmol). The reaction was stirred at 20 °C for 3 hr. The reaction mixture was poured into NaHCO₃ (sat. aq. 15 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the residue. The mixture was filtered and the filtrate was purified by prep-HPLC (Waters 3767/QDA Column: Sunfire C18, 19*250mm, 10 μ m; Mobile Phase A: 0.1% NH₄HCO₃/H₂O, B: ACN; flow rate: 20 mL/min; gradient: 62-72 % Retention Time = 9.4-11.2 min as the major peak) to afford **Compound 144**. LCMS: 502.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.68 (s, 1H), 8.48 (d, *J* = 7.1 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 5.3 Hz, 1H), 6.93 (d, *J* = 1.1 Hz, 1H), 6.48 (d, *J* = 1.1 Hz, 1H), 5.74 (d, *J* = 51.3 Hz, 2H), 3.28 – 3.19 (m, 2H), 2.84 – 2.73 (m, 2H), 2.62 – 2.52 (m, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 5.5 Hz, 3H).

[00351] The following compounds were synthesized according to the previous similar procedures.

Example (compound) No.	¹ H NMR	LCMS
11	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 (d, <i>J</i> = 5.2 Hz, 1H), 8.48 (s, 1H), 8.41 (s, 1H), 8.18 (s, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 7.46 (d, <i>J</i> = 5.2 Hz, 1H), 7.38 (s, 1H), 3.94 (s, 3H), 3.79 – 3.65 (m, 2H), 3.32 – 3.29 (m, 1H), 3.27 (s, 3H), 3.14 – 3.06 (m, 5H), 2.80 – 2.72 (m, 2H), 1.95 (t, <i>J</i> = 10.6 Hz, 1H), 1.69 – 1.58 (m, 4H), 0.87 – 0.78 (m, 4H).	524.4 [M+H] ⁺
12	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.66 – 8.57 (m, 2H), 8.47 (d, <i>J</i> = 1.9 Hz, 1H), 8.09 (d, <i>J</i> = 7.3 Hz, 1H), 7.70 (s, 1H), 7.36 (d, <i>J</i> = 5.2 Hz, 1H), 3.60 (s, 2H), 3.29 (s, 3H), 3.15 (s, 1H), 3.12 – 3.03 (m, 2H), 2.81 – 2.70 (m, 5H), 2.47 (s, 3H), 1.97 – 1.89 (m, 1H), 1.68 – 1.55 (m, 4H), 1.51 – 1.40 (m, 1H), 0.89 – 0.77 (m, 4H).	526.4 [M+H] ⁺
13	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.63 (d, <i>J</i> = 5.3 Hz, 1H), 8.54 (s, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.69 (s, 1H), 7.48 (t, <i>J</i> = 58.9 Hz, 1H), 7.44 (d, <i>J</i> = 5.3 Hz, 1H), 3.56 (s, 2H), 3.18 – 3.00 (m, 6H), 2.84 – 2.66 (m, 2H), 2.57 (s, 3H), 1.98 – 1.82 (m, 1H), 1.70 – 1.55 (m, 4H), 1.53 – 1.42 (m, 1H), 0.93 – 0.77 (m, 4H).	544.4 [M+H] ⁺
14	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.63 (d, <i>J</i> = 5.3 Hz, 1H), 8.52 (s, 1H), 8.01 – 7.91 (m, 1H), 7.74 (d, <i>J</i> = 1.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.49 (t, <i>J</i> = 58.5 Hz, 1H), 7.38 (dd, <i>J</i> = 5.3, 1.7 Hz, 1H), 3.53 (s, 2H), 3.43 – 3.37 (m, 2H), 3.21 – 3.09 (m, 2H), 2.85 – 2.69 (m, 4H), 2.57 (s, 3H), 1.94 – 1.83 (m, 1H), 1.67 – 1.56 (m, 4H), 1.52 – 1.43 (m, 1H), 0.87 –	544.3 [M+H] ⁺

	0.78 (m, 4H).	
15	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.62 (d, <i>J</i> = 5.4 Hz, 1H), 8.55 (s, 1H), 7.99 – 7.94 (m, 1H), 7.86 (d, <i>J</i> = 1.2 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.45 (t, <i>J</i> = 58.6 Hz, 1H), 7.43 (dd, <i>J</i> = 5.3, 1.7 Hz, 1H), 3.53 (s, 2H), 2.94 – 2.83 (m, 2H), 2.79 – 2.69 (m, 2H), 2.69 – 2.59 (m, 3H), 2.57 (s, 3H), 1.95 – 1.83 (m, 1H), 1.69 – 1.42 (m, 5H), 1.09 (d, <i>J</i> = 5.7 Hz, 3H), 0.90 – 0.78 (m, 4H).	534.5 [M+H] ⁺
18	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.63 (d, <i>J</i> = 5.2 Hz, 1H), 8.51 (s, 1H), 8.06 – 8.03 (m, 1H), 7.75 – 7.70 (m, 2H), 7.65 – 7.33 (m, 2H), 3.72 (s, 2H), 3.20 – 3.06 (m, 4H), 2.84 – 2.77 (m, 3H), 2.56 (s, 3H), 2.00 – 1.96 (m, 2H), 1.74 – 1.66 (m, 4H), 1.23 (s, 3H).	530.2 [M+H] ⁺
19	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.62 (d, <i>J</i> = 5.2 Hz, 1H), 8.49 (s, 1H), 8.07 (s, 1H), 7.80 (s, 1H), 7.75 (s, 1H), 7.49 (t, <i>J</i> = 58.4 Hz, 1H), 7.37 (d, <i>J</i> = 4.4 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.18 – 3.13 (m, 3H), 2.84 – 2.78 (m, 2H), 2.56 (s, 3H), 2.36 – 2.27 (m, 1H), 1.92 – 1.67 (m, 4H), 1.57 – 1.49 (m, 2H), 1.45 – 1.40 (m, 1H), 1.26 (d, <i>J</i> = 6.5 Hz, 3H), 1.07 (s, 3H).	544.4 [M+H] ⁺
21	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.62 (d, <i>J</i> = 5.3 Hz, 1H), 8.52 (s, 1H), 8.07 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H), 7.44 (t, <i>J</i> = 58.6 Hz, 1H), 7.42 (dd, <i>J</i> = 5.3, 1.6 Hz, 1H), 3.98 – 3.92 (m, 1H), 2.92 – 2.85 (m, 2H), 2.65 – 2.59 (m, 3H), 2.57 (s, 3H), 2.34 – 2.24 (m, 1H), 1.91 – 1.76 (m, 2H), 1.70 (dt, <i>J</i> = 7.1, 3.0 Hz, 1H), 1.59 – 1.50 (m, 2H), 1.45 – 1.40 (m, 1H), 1.26 (d, <i>J</i> = 6.6 Hz, 3H), 1.09 (d, <i>J</i> = 5.4 Hz, 3H), 1.07 (s, 3H).	534.5 [M+H] ⁺
25	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.61 (d, <i>J</i> = 5.1 Hz, 1H), 8.51 (s, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.60 – 7.29 (m, 2H), 3.50 (s, 2H), 3.17 (t, <i>J</i> = 7.3 Hz, 2H), 3.07 (t, <i>J</i> = 7.2 Hz, 2H), 2.94 – 2.84 (m, 2H), 2.75 – 2.67 (m, 2H), 2.65 – 2.57 (m, 3H), 2.14 (p, <i>J</i> = 7.0 Hz, 2H), 1.92 (t, <i>J</i> = 10.7 Hz, 1H), 1.68 – 1.55 (m, 4H), 1.51 – 1.40 (m, 1H), 1.14 – 1.04 (m, 3H), 0.88 – 0.83 (m, 1H), 0.81 (d, <i>J</i> = 5.7 Hz, 3H).	560.4 [M+H] ⁺
34	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 – 8.63 (m, 2H), 8.47 (s, 1H), 8.40 – 8.35 (m, 1H), 8.16 (s, 1H), 7.71 – 7.62 (m, 1H), 7.48 (d, <i>J</i> = 4.0 Hz, 1H), 5.03 – 4.91 (m, 2H), 3.79 – 3.73 (m, 2H), 3.68 – 3.63 (m, 2H), 3.45 – 3.42 (m, 2H), 3.32 (s, 3H), 2.76 – 2.69 (m, 2H), 2.00 – 1.91 (m, 1H), 1.68 – 1.58 (m, 4H), 1.52 – 1.46 (m, 1H), 0.86 – 0.80 (m, 4H).	550.4 [M+H] ⁺
36	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.56 (s, 1H), 8.11 (s, 1H), 7.82 (d, <i>J</i> = 8.4 Hz, 1H), 7.70 (d, <i>J</i> = 8.2 Hz, 1H), 7.60 – 7.37 (m, 2H), 7.04 (s, 1H), 6.13 (d, <i>J</i> = 52.2 Hz, 2H), 4.99 (s, 2H), 3.82 – 3.72 (m, 2H),	566.0 [M+H] ⁺

	3.60 (s, 2H), 3.48 – 3.41 (m, 2H), 2.80 – 2.69 (m, 2H), 1.97 – 1.83 (m, 1H), 1.69 – 1.56 (m, 4H), 1.53 – 1.43 (m, 1H), 0.89 – 0.78 (m, 4H).	
37	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 – 8.65 (m, 2H), 8.49 (s, 1H), 8.40 (s, 1H), 8.18 (s, 1H), 7.71 – 7.67 (m, 1H), 7.49 (dd, <i>J</i> = 5.3, 1.6 Hz, 1H), 6.84 (d, <i>J</i> = 84.0 Hz, 1H), 3.83 – 3.70 (m, 4H), 3.52 – 3.46 (m, 2H), 3.33 (s, 3H), 2.88 – 2.71 (m, 2H), 2.11 – 1.91 (m, 1H), 1.78 – 1.57 (m, 4H), 1.54 – 1.42 (m, 1H), 0.91 – 0.79 (m, 4H).	568.3 [M+H] ⁺
41	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.63 (d, <i>J</i> = 5.3 Hz, 1H), 8.60 (s, 1H), 8.25 (d, <i>J</i> = 8.0 Hz, 1H), 7.82 (s, 1H), 7.61 – 7.29 (m, 2H), 3.77 (s, 2H), 2.93 – 2.84 (m, 2H), 2.62 (d, <i>J</i> = 8.4 Hz, 3H), 2.48 (d, <i>J</i> = 2.0 Hz, 3H), 2.33 (s, 1H), 1.98 (q, <i>J</i> = 8.4, 6.5 Hz, 2H), 1.78 – 1.63 (m, 4H), 1.25 (s, 3H), 1.09 (d, <i>J</i> = 5.5 Hz, 3H).	538.4 [M+H] ⁺
42	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.66 (s, 1H), 8.63 (d, <i>J</i> = 5.3 Hz, 1H), 8.51 – 8.48 (m, 1H), 8.37 (s, 1H), 8.35 – 8.32 (m, 1H), 7.87 – 7.84 (m, 1H), 7.45 (dd, <i>J</i> = 5.3, 1.5 Hz, 1H), 4.12 (q, <i>J</i> = 6.2 Hz, 1H), 3.25 (s, 3H), 2.91 – 2.83 (m, 2H), 2.69 – 2.55 (m, 4H), 1.91 – 1.83 (m, 1H), 1.82 – 1.70 (m, 2H), 1.58 – 1.50 (m, 2H), 1.46 – 1.40 (m, 1H), 1.29 (d, <i>J</i> = 6.7 Hz, 3H), 1.09 (d, <i>J</i> = 5.4 Hz, 3H), 1.06 (s, 3H).	552.3 [M+H] ⁺
44	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.63 (d, <i>J</i> = 5.2 Hz, 1H), 8.57 (s, 1H), 8.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.71 (s, 1H), 7.49 (t, <i>J</i> = 58.6 Hz, 1H), 7.39 (d, <i>J</i> = 5.2 Hz, 1H), 3.76 (s, 2H), 3.22 – 3.08 (m, 4H), 2.83 – 2.76 (m, 2H), 2.47 (s, 3H), 2.02 – 1.94 (m, 2H), 1.80 – 1.61 (m, 5H), 1.25 (s, 3H).	548.3 [M+H] ⁺
48	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.75 (s, 1H), 8.43 (d, <i>J</i> = 1.0 Hz, 1H), 8.37 (s, 1H), 8.18 (d, <i>J</i> = 1.6 Hz, 1H), 7.53 (d, <i>J</i> = 1.2 Hz, 1H), 7.10 (d, <i>J</i> = 1.2 Hz, 1H), 6.14 (d, <i>J</i> = 52.0 Hz, 2H), 5.62 (t, <i>J</i> = 5.8 Hz, 1H), 4.72 (d, <i>J</i> = 5.7 Hz, 2H), 3.28 (s, 3H), 2.93 – 2.85 (m, 2H), 2.63 – 2.56 (m, 3H), 1.09 (d, <i>J</i> = 5.2 Hz, 3H).	519.2 [M+H] ⁺
49	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.66 – 8.61 (m, 2H), 8.09 (d, <i>J</i> = 1.9 Hz, 1H), 7.95 (d, <i>J</i> = 1.8 Hz, 1H), 7.85 (s, 1H), 7.62 – 7.28 (m, 2H), 3.58 (s, 2H), 2.93 – 2.84 (m, 2H), 2.78 – 2.69 (m, 2H), 2.68 – 2.57 (m, 3H), 1.96 – 1.87 (m, 1H), 1.70 – 1.56 (m, 4H), 1.53 – 1.41 (m, 1H), 1.09 (d, <i>J</i> = 5.6 Hz, 3H), 0.86 – 0.77 (m, 4H).	554.2 [M+H] ⁺
50	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.65 – 8.62 (m, 2H), 8.20 (d, <i>J</i> = 1.9 Hz, 1H), 7.96 (d, <i>J</i> = 1.9 Hz, 1H), 7.87 (s, 1H), 7.60 – 7.29 (m, 2H), 6.03 (dd, <i>J</i> = 54.6, 2.6 Hz, 1H), 5.34 (dd, <i>J</i> = 20.4, 2.6 Hz, 1H), 3.61 (s, 2H), 2.91 – 2.84 (m, 2H), 2.78 – 2.69 (m, 2H), 2.68 – 2.65 (m, 1H),	564.4 [M+H] ⁺

	2.64 – 2.61 (m, 2H), 1.97 – 1.88 (m, 1H), 1.69 – 1.56 (m, 4H), 1.51 – 1.40 (m, 1H), 1.09 (d, $J = 5.6$ Hz, 3H), 0.88 – 0.79 (m, 4H).	
51	^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.62 (d, $J = 5.3$ Hz, 1H), 8.52 (s, 1H), 8.02 (s, 1H), 7.85 (s, 1H), 7.75 (s, 1H), 7.59 – 7.28 (m, 2H), 4.10 – 4.07 (m, 1H), 2.92 – 2.84 (m, 3H), 2.63 – 2.59 (m, 3H), 2.57 (s, 3H), 1.24 (d, $J = 6.6$ Hz, 3H), 1.11 (s, 3H), 1.09 (d, $J = 5.5$ Hz, 3H), 0.51 – 0.45 (m, 1H), 0.26 – 0.18 (m, 2H), 0.09 – 0.02 (m, 1H).	520.3 [M+H] ⁺
53	^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.62 (d, $J = 5.3$ Hz, 1H), 8.55 (s, 1H), 7.99 – 7.97 (m, 1H), 7.87 – 7.83 (m, 1H), 7.73 – 7.68 (m, 1H), 7.45 (t, $J = 58.6$ Hz, 1H), 7.43 (dd, $J = 5.3, 1.7$ Hz, 1H), 5.95 (td, $J = 56.6, 4.4$ Hz, 1H), 3.60 (s, 2H), 2.93 – 2.85 (m, 2H), 2.81 – 2.70 (m, 2H), 2.68 – 2.59 (m, 3H), 2.58 (s, 3H), 2.06 – 1.93 (m, 3H), 1.74 – 1.64 (m, 2H), 1.56 – 1.44 (m, 1H), 1.21 – 1.07 (m, 4H).	570.3 [M+H] ⁺
54	^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.62 (d, $J = 5.3$ Hz, 1H), 8.54 (s, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.69 (s, 1H), 7.60 – 7.27 (m, 2H), 5.91 (t, $J = 56.6$ Hz, 1H), 3.97 (d, $J = 6.9$ Hz, 2H), 3.11 – 3.04 (m, 1H), 2.93 – 2.83 (m, 2H), 2.66 – 2.58 (m, 3H), 2.56 (s, 3H), 1.09 (d, $J = 5.6$ Hz, 3H), 0.81 – 0.75 (m, 4H).	542.2 [M+H] ⁺
56	^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.65 (d, $J = 5.3$ Hz, 1H), 8.62 (d, $J = 1.1$ Hz, 1H), 8.41 – 8.37 (m, 1H), 8.17 – 8.14 (m, 1H), 7.91 (d, $J = 1.4$ Hz, 1H), 7.53 (dd, $J = 5.3, 1.7$ Hz, 1H), 3.66 (s, 2H), 3.28 – 3.21 (m, 1H), 3.12 (d, $J = 2.3$ Hz, 1H), 3.11 – 3.05 (m, 2H), 2.94 – 2.88 (m, 2H), 2.77 – 2.69 (m, 2H), 1.99 – 1.89 (m, 1H), 1.68 (s, 3H), 1.67 – 1.56 (m, 4H), 1.53 – 1.43 (m, 1H), 0.89 – 0.81 (m, 4H).	562.2 [M+H] ⁺
57	^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (s, 1H), 8.67 (d, $J = 1.1$ Hz, 1H), 8.63 (d, $J = 5.2$ Hz, 1H), 8.39 (d, $J = 1.4$ Hz, 1H), 8.16 (d, $J = 1.6$ Hz, 1H), 7.78 (d, $J = 1.1$ Hz, 1H), 7.41 (dd, $J = 5.3, 1.7$ Hz, 1H), 3.66 (s, 2H), 3.25 – 3.19 (m, 2H), 3.14 (d, $J = 2.2$ Hz, 1H), 3.12 – 3.05 (m, 1H), 2.75 – 2.68 (m, 4H), 2.03 – 1.97 (m, 1H), 1.70 (d, $J = 1.0$ Hz, 3H), 1.68 – 1.58 (m, 4H), 1.50 – 1.45 (m, 1H), 0.87 – 0.85 (m, 1H), 0.82 (d, $J = 6.2$ Hz, 3H).	562.2 [M+H] ⁺
58	^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.62 (d, $J = 5.3$ Hz, 1H), 8.58 (s, 1H), 8.38 (d, $J = 8.1$ Hz, 1H), 7.86 (s, 1H), 7.59 – 7.29 (m, 2H), 4.24 – 4.17 (m, 1H), 2.92 – 2.83 (m, 2H), 2.66 – 2.58 (m, 3H), 2.47 (d, $J = 2.0$ Hz, 3H), 2.43 – 2.34 (m, 1H), 1.93 – 1.78 (m, 2H), 1.76 – 1.68 (m, 1H), 1.60 – 1.46 (m, 3H), 1.29 (d, $J = 6.7$ Hz, 3H), 1.11 – 1.06 (m, 6H).	552.4 [M+H] ⁺
60	^1H NMR (400 MHz, DMSO- d_6) δ 8.87 (s, 1H), 8.84 (d, $J = 5.1$ Hz, 1H), 8.44 – 8.36 (m, 2H), 7.50 (s, 1H), 7.16 (s, 1H), 6.15 (d, $J = 52.1$ Hz, 2H),	490.1 [M+H] ⁺

	3.27 (s, 3H), 2.91 – 2.86 (m, 2H), 2.62 – 2.58 (m, 3H), 1.09 (d, $J = 5.0$ Hz, 3H).	
61	^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (s, 1H), 8.98 (s, 1H), 8.75 (s, 1H), 8.65 (d, $J = 5.3$ Hz, 1H), 8.53 (dd, $J = 7.6, 1.7$ Hz, 1H), 8.41 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.92 (s, 1H), 7.87 (d, $J = 1.2$ Hz, 1H), 7.71 (t, $J = 7.8$ Hz, 1H), 7.48 (dd, $J = 5.3, 1.7$ Hz, 1H), 7.46 (t, $J = 58.6$ Hz, 1H), 2.94 – 2.83 (m, 2H), 2.71 – 2.57 (m, 3H), 1.09 (d, $J = 5.7$ Hz, 3H).	452.1 [M+H] ⁺
62	^1H NMR (400 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.49 (d, $J = 7.8$ Hz, 1H), 8.36 (s, 1H), 8.27 (d, $J = 7.6$ Hz, 1H), 7.75 (t, $J = 7.9$ Hz, 1H), 7.31 (d, $J = 1.3$ Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H), 5.41 – 5.32 (m, 1H), 3.27 (s, 3H), 2.92 – 2.79 (m, 2H), 2.60 – 2.54 (m, 3H), 2.00 – 1.90 (m, 2H), 1.80 – 1.68 (m, 4H), 1.63 – 1.54 (m, 2H), 1.07 (d, $J = 5.5$ Hz, 3H).	525.2 [M+H] ⁺
63	^1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.49 (d, $J = 7.9$ Hz, 1H), 8.36 (s, 1H), 8.26 (d, $J = 7.4$ Hz, 1H), 7.75 (t, $J = 7.8$ Hz, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 5.17 (p, $J = 7.3$ Hz, 1H), 3.26 (s, 3H), 2.91 – 2.81 (m, 2H), 2.62 – 2.54 (m, 3H), 2.42 – 2.33 (m, 2H), 2.15 – 2.01 (m, 2H), 1.82 – 1.58 (m, 2H), 1.07 (d, $J = 5.2$ Hz, 3H).	511.1 [M+H] ⁺
64	^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.54 (d, $J = 6.7$ Hz, 1H), 8.37 (s, 1H), 8.24 (d, $J = 7.8$ Hz, 1H), 7.80 (t, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 1.2$ Hz, 1H), 7.09 (d, $J = 1.2$ Hz, 1H), 6.14 (d, $J = 52.1$ Hz, 2H), 3.27 (s, 3H), 2.95 – 2.80 (m, 2H), 2.62 – 2.56 (m, 3H), 1.08 (d, $J = 5.4$ Hz, 3H).	539.2 [M+H] ⁺
65	^1H NMR (400 MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.49 (d, $J = 7.7$ Hz, 1H), 8.37 (d, $J = 12.1$ Hz, 1H), 8.27 (d, $J = 6.8$ Hz, 1H), 7.82 – 7.71 (m, 1H), 7.35 (d, $J = 1.3$ Hz, 1H), 6.93 (d, $J = 1.2$ Hz, 1H), 3.91 (s, 3H), 3.26 (s, 3H), 2.91 – 2.80 (m, 2H), 2.62 – 2.56 (m, 3H), 1.08 (d, $J = 5.5$ Hz, 3H).	471.1 [M+H] ⁺
67	^1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.39 (s, 1H), 8.33 (d, $J = 1.8$ Hz, 1H), 8.14 (d, $J = 1.7$ Hz, 1H), 7.54 (s, 1H), 7.09 (s, 1H), 6.14 (d, $J = 52.1$ Hz, 2H), 3.27 (s, 3H), 3.20 (dt, $J = 13.7, 6.9$ Hz, 1H), 2.94 – 2.84 (m, 2H), 2.66 – 2.56 (m, 3H), 1.30 (d, $J = 6.9$ Hz, 6H), 1.08 (d, $J = 5.2$ Hz, 3H).	531.1 [M+H] ⁺
68	^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.62 (d, $J = 5.2$ Hz, 1H), 8.52 (s, 1H), 8.07 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H), 7.44 (t, $J = 58.6$ Hz, 1H), 7.42 (d, $J = 5.2$ Hz, 1H), 3.99 – 3.92 (m, 1H), 2.93 – 2.84 (m, 2H), 2.62 (d, $J = 7.5$ Hz, 3H), 2.57 (s, 3H), 2.41 – 2.25 (m, 1H), 1.90 – 1.76 (m, 2H), 1.73 – 1.66 (m, 1H), 1.57 – 1.49 (m, 2H), 1.46 – 1.40 (m, 1H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 5.2$ Hz, 3H), 1.07 (s, 3H).	534.5 [M+H] ⁺
70	^1H NMR (400 MHz, DMSO- d_6) δ 9.10 (s, 1H), 8.64 (d, $J = 5.3$ Hz, 1H),	580.4

	8.61 (s, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.75 – 7.72 (m, 1H), 7.63 (s, 1H), 7.52 – 7.29 (m, 2H), 3.65 (s, 2H), 3.19 – 3.10 (m, 3H), 2.85 – 2.66 (m, 5H), 1.97 – 1.89 (m, 1H), 1.68 – 1.57 (m, 4H), 1.52 – 1.43 (m, 1H), 0.88 – 0.79 (m, 4H).	[M+H] ⁺
71	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.64 (s, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 7.84 (s, 1H), 7.60 – 7.28 (m, 2H), 3.83 (s, 2H), 2.96 – 2.82 (m, 2H), 2.70 – 2.59 (m, 3H), 2.05 – 1.91 (m, 2H), 1.77 – 1.61 (m, 4H), 1.23 (s, 3H), 1.09 (d, <i>J</i> = 5.4 Hz, 3H).	574.2 [M+H] ⁺
72	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.98 (s, 1H), 8.68 – 8.61 (m, 2H), 8.28 (s, 1H), 8.05 (s, 1H), 7.86 (d, <i>J</i> = 1.2 Hz, 1H), 7.79 – 7.29 (m, 3H), 3.65 (s, 2H), 2.92 – 2.83 (m, 2H), 2.78 – 2.69 (m, 2H), 2.67 – 2.57 (m, 3H), 1.99 – 1.89 (m, 1H), 1.71 – 1.55 (m, 4H), 1.54 – 1.42 (m, 1H), 1.09 (d, <i>J</i> = 5.7 Hz, 3H), 0.93 – 0.84 (m, 1H), 0.82 (d, <i>J</i> = 6.0 Hz, 3H).	570.4 [M+H] ⁺
74	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.53 – 8.45 (m, 2H), 8.25 (d, <i>J</i> = 7.6 Hz, 1H), 7.73 (t, <i>J</i> = 7.8 Hz, 1H), 7.03 (t, <i>J</i> = 5.3 Hz, 1H), 6.75 (d, <i>J</i> = 1.1 Hz, 1H), 6.32 (d, <i>J</i> = 1.2 Hz, 1H), 3.32 (s, 3H), 3.27 – 3.19 (m, 4H), 3.14 (d, <i>J</i> = 2.3 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.67 – 2.62 (m, 2H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H).	494.1 [M+H] ⁺
75	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.57 (s, 1H), 9.24 (s, 1H), 8.92 (s, 1H), 8.36 (s, 1H), 7.03 (t, <i>J</i> = 5.2 Hz, 1H), 6.85 (d, <i>J</i> = 1.2 Hz, 1H), 6.48 (d, <i>J</i> = 1.2 Hz, 1H), 3.27 (s, 3H), 3.26 – 3.22 (m, 2H), 2.79 – 2.74 (m, 2H), 2.56 – 2.53 (m, 3H), 1.12 (t, <i>J</i> = 7.2 Hz, 3H), 1.08 (d, <i>J</i> = 5.8 Hz, 3H).	485.2 [M+H] ⁺
79	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.38 (s, 1H), 8.18 (d, <i>J</i> = 2.7 Hz, 1H), 8.09 (d, <i>J</i> = 2.6 Hz, 1H), 7.76 – 7.35 (m, 2H), 7.12 (s, 1H), 6.14 (d, <i>J</i> = 52.0 Hz, 2H), 3.27 (s, 3H), 2.92 – 2.85 (m, 2H), 2.63 – 2.58 (m, 3H), 1.08 (d, <i>J</i> = 5.2 Hz, 3H).	555.1 [M+H] ⁺
84	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 (s, 1H), 8.35 (s, 1H), 8.25 – 8.17 (m, 1H), 7.93 – 7.83 (m, 1H), 7.73 (d, <i>J</i> = 8.0 Hz, 1H), 7.66 – 7.56 (m, 1H), 6.95 (t, <i>J</i> = 5.2 Hz, 1H), 6.84 (s, 1H), 6.42 (s, 1H), 3.28 (s, 3H), 3.26 – 3.19 (m, 2H), 2.83 – 2.73 (m, 2H), 2.62 – 2.51 (m, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	416.1 [M+H] ⁺
86	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.56 (s, 1H), 8.35 (s, 1H), 8.16 (d, <i>J</i> = 8.2 Hz, 1H), 7.72 (d, <i>J</i> = 1.4 Hz, 1H), 7.58 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 6.96 (t, <i>J</i> = 5.3 Hz, 1H), 6.84 (d, <i>J</i> = 1.1 Hz, 1H), 6.42 (d, <i>J</i> = 1.1 Hz, 1H), 3.68 (s, 2H), 3.27 (s, 3H), 3.25 – 3.20 (m, 2H), 2.81 – 2.71 (m, 2H), 2.64 – 2.58 (m, 4H), 2.58 – 2.51 (m, 3H), 1.75 (dq, <i>J</i> = 6.4, 3.0 Hz, 4H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	523.5 [M+H] ⁺

88	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.00 (s, 1H), 8.35 (s, 1H), 8.34 (s, 1H), 8.01 (s, 1H), 6.95 (t, <i>J</i> = 5.3 Hz, 1H), 6.75 (d, <i>J</i> = 1.2 Hz, 1H), 6.43 (d, <i>J</i> = 1.2 Hz, 1H), 3.28 (s, 3H), 3.25 – 3.17 (m, 2H), 2.82 – 2.72 (m, 2H), 2.61 – 2.52 (m, 3H), 1.10 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.9 Hz, 3H).	473.1 [M+H] ⁺
92	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (s, 1H), 8.49 (d, <i>J</i> = 7.2 Hz, 1H), 8.38 (s, 1H), 8.26 (d, <i>J</i> = 7.1 Hz, 1H), 7.75 (t, <i>J</i> = 7.8 Hz, 1H), 7.32 (s, 1H), 6.90 (s, 1H), 4.35 (q, <i>J</i> = 7.0 Hz, 2H), 3.26 (s, 3H), 2.91 – 2.82 (m, 2H), 2.62 – 2.54 (m, 3H), 1.33 (t, <i>J</i> = 7.0 Hz, 3H), 1.08 (d, <i>J</i> = 5.1 Hz, 3H).	485.1 [M+H] ⁺
93	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.54 – 8.45 (m, 1H), 8.36 (s, 1H), 8.25 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (t, <i>J</i> = 7.8 Hz, 1H), 7.27 (d, <i>J</i> = 2.5 Hz, 1H), 6.96 (d, <i>J</i> = 1.2 Hz, 1H), 6.52 (s, 1H), 3.28 (s, 3H), 2.86 – 2.75 (m, 2H), 2.60 – 2.53 (m, 4H), 1.08 (d, <i>J</i> = 5.7 Hz, 3H), 0.72 – 0.61 (m, 2H), 0.46 – 0.32 (m, 2H).	496.1 [M+H] ⁺
94	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.74 (s, 1H), 8.48 (d, <i>J</i> = 8.1 Hz, 1H), 8.36 (s, 1H), 8.25 (d, <i>J</i> = 7.6 Hz, 1H), 7.73 (t, <i>J</i> = 7.8 Hz, 1H), 7.27 (t, <i>J</i> = 5.7 Hz, 1H), 6.93 (s, 1H), 6.57 (s, 1H), 4.60 (t, <i>J</i> = 5.0 Hz, 1H), 4.48 (t, <i>J</i> = 5.0 Hz, 1H), 3.59 (q, <i>J</i> = 5.6 Hz, 1H), 3.52 (q, <i>J</i> = 5.3 Hz, 1H), 3.28 (s, 3H), 2.81 – 2.75 (m, 2H), 2.57 – 2.53 (m, 3H), 1.07 (d, <i>J</i> = 5.4 Hz, 3H).	502.1 [M+H] ⁺
95	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.49 (d, <i>J</i> = 8.0 Hz, 1H), 8.36 (s, 1H), 8.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.74 (t, <i>J</i> = 7.8 Hz, 1H), 7.40 (s, 1H), 7.02 (s, 1H), 6.61 (s, 1H), 6.18 (t, <i>J</i> = 55.9 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.28 (s, 3H), 2.82 – 2.74 (m, 2H), 2.58 – 2.54 (m, 3H), 1.08 (d, <i>J</i> = 5.1 Hz, 3H).	520.2 [M+H] ⁺
97	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.73 (s, 1H), 8.41 (d, <i>J</i> = 8.7 Hz, 1H), 8.35 (s, 1H), 7.81 (d, <i>J</i> = 8.7 Hz, 1H), 7.00 (t, <i>J</i> = 5.2 Hz, 1H), 6.85 (s, 1H), 6.46 (s, 1H), 3.27 (s, 3H), 3.26 – 3.20 (m, 2H), 2.80 – 2.73 (m, 2H), 2.59 – 2.52 (m, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.6 Hz, 3H).	518.6 [M+H] ⁺
98	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.66 (s, 1H), 8.36 (s, 1H), 8.32 (d, <i>J</i> = 8.2 Hz, 1H), 7.59 (d, <i>J</i> = 8.3 Hz, 1H), 6.98 (t, <i>J</i> = 5.2 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.47 – 6.41 (m, 1H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 2.83 – 2.73 (m, 2H), 2.66 (q, <i>J</i> = 3.7 Hz, 3H), 2.55 (s, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	498.2 [M+H] ⁺
99	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.75 (s, 1H), 8.52 (dd, <i>J</i> = 9.1, 5.6 Hz, 1H), 8.36 (s, 1H), 7.64 (dd, <i>J</i> = 11.4, 9.3 Hz, 1H), 7.00 (t, <i>J</i> = 5.2 Hz, 1H), 6.85 (d, <i>J</i> = 1.2 Hz, 1H), 6.45 (d, <i>J</i> = 1.2 Hz, 1H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 2.80 – 2.73 (m, 2H), 2.58 – 2.52 (m, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H).	502.1 [M+H] ⁺

	3H), 1.07 (d, $J = 5.8$ Hz, 3H).	
100	^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.35 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 1H), 6.98 (t, $J = 5.2$ Hz, 1H), 6.85 (s, 1H), 6.44 (s, 1H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 2.81 – 2.70 (m, 2H), 2.58 – 2.52 (m, 3H), 2.17 (s, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.6$ Hz, 3H).	522.3 [M+H] ⁺
101	^1H NMR (400 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.44 (s, 1H), 8.36 (s, 1H), 8.24 (s, 1H), 7.00 (t, $J = 5.1$ Hz, 1H), 6.85 (s, 1H), 6.46 (s, 1H), 4.56 (s, 1H), 3.27 (s, 3H), 3.26 – 3.20 (m, 2H), 2.80 – 2.73 (m, 2H), 2.56 – 2.53 (m, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.6$ Hz, 3H).	508.2 [M+H] ⁺
102	^1H NMR (400 MHz, DMSO- d_6) δ 8.88 (d, $J = 1.7$ Hz, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 7.03 (t, $J = 5.2$ Hz, 1H), 6.85 (d, $J = 1.0$ Hz, 1H), 6.49 (d, $J = 1.1$ Hz, 1H), 3.27 (s, 3H), 3.26 – 3.20 (m, 2H), 2.82 – 2.70 (m, 2H), 2.63 – 2.52 (m, 3H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.08 (d, $J = 5.6$ Hz, 3H).	509.3 [M+H] ⁺
103	^1H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.59 (d, $J = 8.3$ Hz, 1H), 8.36 (s, 1H), 8.15 (d, $J = 8.3$ Hz, 1H), 7.02 (t, $J = 5.2$ Hz, 1H), 6.85 (s, 1H), 6.48 (s, 1H), 3.27 (s, 3H), 3.26 – 3.20 (m, 2H), 2.80 – 2.72 (m, 2H), 2.58 – 2.52 (m, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.5$ Hz, 3H).	509.3 [M+H] ⁺
104	^1H NMR (400 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.36 (s, 1H), 8.22 (td, $J = 8.4, 2.9$ Hz, 2H), 7.00 (t, $J = 5.3$ Hz, 1H), 6.86 (d, $J = 1.2$ Hz, 1H), 6.46 (d, $J = 1.2$ Hz, 1H), 3.27 (s, 3H), 3.26 – 3.20 (m, 2H), 2.80 – 2.73 (m, 2H), 2.59 – 2.53 (m, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.8$ Hz, 3H).	502.2 [M+H] ⁺
105	^1H NMR (400 MHz, DMSO- d_6) δ 8.61 (d, $J = 5.3$ Hz, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 8.09 – 8.05 (m, 1H), 7.84 – 7.79 (m, 2H), 7.41 (dd, $J = 5.2, 1.6$ Hz, 1H), 4.01 – 3.92 (m, 1H), 3.26 (s, 3H), 2.92 – 2.85 (m, 2H), 2.64 – 2.58 (m, 3H), 2.57 (s, 3H), 1.89 – 1.69 (m, 3H), 1.58 – 1.49 (m, 2H), 1.46 – 1.40 (m, 1H), 1.26 (d, $J = 6.7$ Hz, 3H), 1.11 – 1.06 (m, 6H).	498.4 [M+H] ⁺
106	^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.61 (s, 1H), 8.51 (dd, $J = 9.0, 5.6$ Hz, 1H), 7.64 (dd, $J = 11.4, 9.2$ Hz, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 3.56 (q, $J = 6.9$ Hz, 2H), 3.33 (s, 3H), 3.01 (s, 3H), 2.93 – 2.84 (m, 2H), 2.63 – 2.53 (m, 3H), 1.11 – 1.06 (m, 6H).	516.3 [M+H] ⁺
107	^1H NMR (400 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.58 (s, 1H), 8.51 (dd, $J = 9.0, 5.5$ Hz, 1H), 7.64 (dd, $J = 11.3, 9.3$ Hz, 1H), 6.99 (s, 1H), 6.86 (d, $J = 1.2$ Hz, 1H), 6.48 (d, $J = 1.1$ Hz, 1H), 3.31 (s, 3H), 2.83 – 2.73 (m, 5H), 2.55 (dt, $J = 8.3, 3.4$ Hz, 3H), 1.08 (d, $J = 5.7$ Hz, 3H).	488.1 [M+H] ⁺
108	^1H NMR (400 MHz, DMSO- d_6) δ 8.66 (s, 1H), 8.51 (dd, $J = 9.0, 5.6$ Hz, 1H), 8.36 (s, 1H), 7.64 (dd, $J = 11.3, 9.2$ Hz, 1H), 6.86 (d, $J = 1.2$ Hz, 1H),	474.0 [M+H] ⁺

	6.44 (d, $J = 1.2$ Hz, 1H), 6.42 (s, 2H), 3.27 (s, 3H), 2.81 – 2.72 (m, 2H), 2.62 – 2.52 (m, 3H), 1.07 (d, $J = 5.8$ Hz, 3H).	
110	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.88 (s, 1H), 8.54 (dd, $J = 9.0, 5.6$ Hz, 1H), 8.38 (s, 1H), 8.09 – 7.63 (m, 2H), 7.59 (s, 1H), 7.28 (s, 1H), 3.27 (s, 3H), 2.93 – 2.86 (m, 2H), 2.63 – 2.57 (m, 3H), 1.08 (d, $J = 5.1$ Hz, 3H).	525.1 [M+H] ⁺
111	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 (s, 1H), 8.35 (s, 1H), 8.10 (dd, $J = 8.8, 6.2$ Hz, 1H), 7.43 (t, $J = 9.0$ Hz, 1H), 6.96 (t, $J = 5.3$ Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H), 6.43 (d, $J = 1.2$ Hz, 1H), 3.28 (s, 3H), 3.26 – 3.19 (m, 2H), 2.81 – 2.72 (m, 2H), 2.59 – 2.52 (m, 3H), 2.47 (d, $J = 2.2$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.9$ Hz, 3H).	448.1 [M+H] ⁺
112	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.45 (d, $J = 7.5$ Hz, 1H), 8.34 (s, 1H), 8.21 (d, $J = 7.2$ Hz, 1H), 7.69 (t, $J = 7.8$ Hz, 1H), 7.57 (s, 1H), 6.62 (t, $J = 4.4$ Hz, 1H), 6.37 (s, 1H), 3.24 (s, 3H), 3.20 – 3.08 (m, 2H), 2.79 – 2.73 (m, 2H), 2.61 – 2.54 (m, 3H), 1.14 (t, $J = 7.1$ Hz, 3H), 1.08 (d, $J = 5.9$ Hz, 3H).	484.2 [M+H] ⁺
113	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.74 (s, 1H), 8.51 (dd, $J = 9.0, 5.5$ Hz, 1H), 8.36 (s, 1H), 7.64 (dd, $J = 11.3, 9.3$ Hz, 1H), 7.13 (t, $J = 5.4$ Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H), 6.53 (d, $J = 1.2$ Hz, 1H), 3.28 (s, 3H), 3.11 – 3.05 (m, 2H), 2.80 – 2.71 (m, 2H), 2.57 – 2.51 (m, 3H), 1.07 (d, $J = 5.9$ Hz, 3H), 1.06 – 0.98 (m, 1H), 0.46 – 0.40 (m, 2H), 0.20 – 0.15 (m, 2H).	528.2 [M+H] ⁺
114	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (s, 1H), 8.38 – 8.31 (m, 2H), 8.15 (s, 1H), 7.00 (t, $J = 5.1$ Hz, 1H), 6.84 (s, 1H), 6.46 (s, 1H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 2.81 – 2.72 (m, 2H), 2.60 – 2.52 (m, 3H), 2.12 (s, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.7$ Hz, 3H).	522.1 [M+H] ⁺
116	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.50 – 8.45 (m, 2H), 8.25 (d, $J = 6.9$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.09 (t, $J = 5.3$ Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H), 6.41 (d, $J = 1.3$ Hz, 1H), 3.77 – 3.66 (m, 2H), 3.37 (s, 3H), 3.30 – 3.27 (m, 2H), 3.26 – 3.21 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H).	506.1 [M+H] ⁺
117	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.50 (d, $J = 6.9$ Hz, 1H), 8.42 (s, 1H), 8.28 (d, $J = 7.7$ Hz, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 1.3$ Hz, 1H), 7.18 (d, $J = 1.3$ Hz, 1H), 6.27 – 5.97 (m, 3H), 3.30 (s, 3H), 3.07 – 2.99 (m, 3H), 2.88 – 2.82 (m, 2H).	525.2 [M+H] ⁺
120	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 1H), 8.35 (s, 1H), 8.09 (d, $J = 9.1$ Hz, 1H), 6.94 (t, $J = 5.1$ Hz, 1H), 6.86 – 6.75 (m, 2H), 6.41 (d, $J = 1.1$ Hz, 1H), 5.76 (d, $J = 6.0$ Hz, 1H), 4.60 – 4.51 (m, 1H), 4.40 – 4.32 (m, 2H), 3.93 – 3.82 (m, 2H), 3.27 (s, 3H), 3.25 – 3.20 (m, 2H), 2.80 – 2.71 (m, 2H), 2.56 – 2.52 (m, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.9$ Hz, 3H).	555.2 [M+H] ⁺

	3H).	
121	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.37 (s, 1H), 8.22 (d, <i>J</i> = 9.0 Hz, 1H), 7.43 (d, <i>J</i> = 9.1 Hz, 1H), 6.95 (t, <i>J</i> = 5.1 Hz, 1H), 6.83 (d, <i>J</i> = 0.9 Hz, 1H), 6.42 (d, <i>J</i> = 1.1 Hz, 1H), 4.90 – 4.61 (m, 1H), 3.72 – 3.64 (m, 1H), 3.40 – 3.37 (m, 2H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 3.06 – 2.98 (m, 2H), 2.80 – 2.72 (m, 2H), 2.60 – 2.53 (m, 3H), 1.91 – 1.82 (m, 2H), 1.61 – 1.50 (m, 2H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	583.6 [M+H] ⁺
122	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.80 (s, 1H), 8.65 (s, 1H), 8.36 (s, 2H), 7.30 (t, <i>J</i> = 55.3 Hz, 1H), 7.01 (t, <i>J</i> = 5.1 Hz, 1H), 6.86 (d, <i>J</i> = 1.0 Hz, 1H), 6.50 – 6.45 (m, 1H), 3.28 (s, 3H), 3.26 – 3.20 (m, 2H), 2.82 – 2.72 (m, 2H), 2.58 – 2.53 (m, 3H), 1.12 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	534.4 [M+H] ⁺
123	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 – 8.79 (m, 2H), 8.36 (s, 1H), 7.02 (t, <i>J</i> = 5.3 Hz, 1H), 6.85 (s, 1H), 6.48 (s, 1H), 3.27 (s, 3H), 3.25 – 3.20 (m, 2H), 2.81 (q, <i>J</i> = 3.5 Hz, 3H), 2.79 – 2.72 (m, 2H), 2.57 – 2.53 (m, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.7 Hz, 3H).	523.3 [M+H] ⁺
125	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (s, 1H), 8.35 (s, 1H), 8.25 (d, <i>J</i> = 9.1 Hz, 1H), 7.43 (d, <i>J</i> = 9.1 Hz, 1H), 6.96 (t, <i>J</i> = 5.4 Hz, 1H), 6.83 (s, 1H), 6.42 (s, 1H), 3.27 (s, 3H), 3.25 – 3.22 (m, 2H), 3.20 – 3.17 (m, 4H), 2.79 – 2.74 (m, 2H), 2.62 – 2.53 (m, 7H), 2.24 (s, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.7 Hz, 3H).	582.5 [M+H] ⁺
127	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.50 (d, <i>J</i> = 9.5 Hz, 1H), 7.62 (d, <i>J</i> = 8.8 Hz, 1H), 6.98 (t, <i>J</i> = 4.4 Hz, 1H), 6.85 (s, 1H), 6.44 (s, 1H), 6.11 (d, <i>J</i> = 52.3 Hz, 2H), 3.27 (s, 3H), 3.25 – 3.22 (m, 2H), 2.80 – 2.73 (m, 2H), 2.57 – 2.54 (m, 3H), 1.11 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.6 Hz, 3H).	532.5 [M+H] ⁺
128	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.76 (s, 1H), 8.61 (d, <i>J</i> = 8.5 Hz, 1H), 8.36 (s, 1H), 8.00 (d, <i>J</i> = 8.6 Hz, 1H), 7.58 (t, <i>J</i> = 54.1 Hz, 1H), 7.01 (t, <i>J</i> = 5.2 Hz, 1H), 6.88 (d, <i>J</i> = 1.1 Hz, 1H), 6.47 (d, <i>J</i> = 1.0 Hz, 1H), 3.28 (s, 3H), 3.26 – 3.20 (m, 2H), 2.81 – 2.74 (m, 2H), 2.60 – 2.52 (m, 3H), 1.12 (t, <i>J</i> = 7.2 Hz, 3H), 1.08 (d, <i>J</i> = 5.7 Hz, 3H).	534.4 [M+H] ⁺
130	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (s, 1H), 8.36 (s, 1H), 8.32 (d, <i>J</i> = 8.3 Hz, 1H), 7.57 (d, <i>J</i> = 9.0 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.85 (s, 1H), 6.43 (s, 1H), 3.28 (s, 3H), 3.25 – 3.23 (m, 2H), 2.79 – 2.71 (m, 5H), 2.59 – 2.24 (m, 2H), 1.97 – 1.90 (m, 2H), 1.11 (t, <i>J</i> = 7.1 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	492.2 [M+H] ⁺
133	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (s, 1H), 8.50 – 8.43 (m, 2H), 8.25	500.6

	(d, $J = 7.6$ Hz, 1H), 7.73 (t, $J = 7.9$ Hz, 1H), 7.13 – 6.91 (m, 1H), 6.85 (d, $J = 1.4$ Hz, 1H), 6.55 (d, $J = 1.1$ Hz, 1H), 3.51 (t, $J = 6.1$ Hz, 2H), 3.33 – 3.31 (m, 2H), 3.30 (s, 3H), 2.84 – 2.71 (m, 2H), 2.59 – 2.52 (m, 3H), 1.08 (d, $J = 5.8$ Hz, 3H).	[M+H] ⁺
134	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (d, $J = 8.0$ Hz, 1H), 8.38 (s, 1H), 8.17 (d, $J = 7.5$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.70 (t, $J = 7.8$ Hz, 1H), 7.00 – 6.83 (m, 2H), 6.80 – 6.71 (m, 1H), 6.39 (s, 1H), 3.28 (s, 3H), 3.27 – 3.18 (m, 2H), 2.84 – 2.70 (m, 2H), 2.65 – 2.51 (m, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.8$ Hz, 3H).	483.3 [M+H] ⁺
138	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (s, 1H), 8.35 (s, 1H), 8.28 (d, $J = 9.0$ Hz, 1H), 7.44 (d, $J = 9.0$ Hz, 1H), 6.96 (t, $J = 5.0$ Hz, 1H), 6.83 (s, 1H), 6.43 (s, 1H), 3.79 – 3.72 (m, 4H), 3.27 (s, 3H), 3.25 – 3.21 (m, 2H), 3.19 – 3.14 (m, 4H), 2.80 – 2.73 (m, 2H), 2.58 – 2.51 (m, 3H), 1.11 (t, $J = 7.1$ Hz, 3H), 1.07 (d, $J = 5.3$ Hz, 3H).	569.5 [M+H] ⁺
139	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.58 (s, 1H), 8.35 (s, 1H), 8.23 (d, $J = 9.0$ Hz, 1H), 7.42 (d, $J = 9.1$ Hz, 1H), 6.95 (t, $J = 5.3$ Hz, 1H), 6.83 (d, $J = 1.2$ Hz, 1H), 6.42 (d, $J = 1.2$ Hz, 1H), 3.27 (s, 3H), 3.25 – 3.20 (m, 2H), 3.19 – 3.11 (m, 4H), 2.81 – 2.72 (m, 2H), 2.59 – 2.52 (m, 3H), 1.71 – 1.63 (m, 4H), 1.62 – 1.51 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.9$ Hz, 3H).	567.4 [M+H] ⁺
140	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (s, 1H), 8.35 (s, 1H), 8.25 (d, $J = 9.1$ Hz, 1H), 7.43 (d, $J = 9.2$ Hz, 1H), 6.96 (t, $J = 5.3$ Hz, 1H), 6.84 (s, 1H), 6.42 (s, 1H), 3.27 (s, 3H), 3.25 – 3.21 (m, 2H), 3.20 – 3.14 (m, 4H), 2.80 – 2.73 (m, 2H), 2.55 (d, $J = 12.1$ Hz, 3H), 2.48 – 2.42 (m, 4H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.8$ Hz, 3H).	585.5 [M+H] ⁺
141	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 (s, 1H), 8.35 (s, 1H), 8.09 (d, $J = 9.1$ Hz, 1H), 6.94 (t, $J = 5.2$ Hz, 1H), 6.83 – 6.78 (m, 2H), 6.41 (s, 1H), 4.16 (t, $J = 7.4$ Hz, 4H), 3.27 (s, 3H), 3.25 – 3.19 (m, 2H), 2.80 – 2.72 (m, 2H), 2.58 – 2.53 (m, 3H), 2.38 – 2.30 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.8$ Hz, 3H).	539.6 [M+H] ⁺
142	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 – 8.41 (m, 2H), 8.37 – 8.19 (m, 2H), 7.72 (t, $J = 7.6$ Hz, 1H), 6.76 (s, 1H), 6.54 (d, $J = 14.6$ Hz, 2H), 6.01 (s, 1H), 3.25 (s, 3H), 3.03 – 2.94 (m, 2H), 2.87 – 2.72 (m, 2H), 2.62 – 2.51 (m, 3H), 1.11 (dt, $J = 7.2, 3.5$ Hz, 5H), 1.06 (d, $J = 3.4$ Hz, 4H).	583.2 [M+H] ⁺
143	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 8.68 (s, 1H), 8.51 – 8.46 (m, 1H), 8.27 – 8.22 (m, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.39 (t, $J = 58.6$ Hz, 1H), 7.04 – 6.98 (m, 1H), 6.88 (d, $J = 1.3$ Hz, 1H), 6.45 (d, $J = 1.3$ Hz,	520.4 [M+H] ⁺

	¹ H, 3.28 – 3.20 (m, 2H), 2.84 – 2.74 (m, 2H), 2.64 – 2.53 (m, 3H), 1.12 (t, <i>J</i> = 7.2 Hz, 3H), 1.07 (d, <i>J</i> = 5.8 Hz, 3H).	
147	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.68 (s, 1H), 8.37 (s, 1H), 8.24 (d, <i>J</i> = 9.0 Hz, 1H), 7.52 (s, 1H), 7.45 (d, <i>J</i> = 9.1 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.14 (d, <i>J</i> = 52.1 Hz, 2H), 3.27 (s, 3H), 3.26 – 3.22 (m, 2H), 3.13 – 3.05 (m, 2H), 2.96 – 2.86 (m, 4H), 2.63 – 2.57 (m, 3H), 2.31 (s, 3H), 1.08 (d, <i>J</i> = 5.1 Hz, 3H), 0.68 – 0.62 (m, 2H), 0.49 – 0.43 (m, 2H).	613.6 [M+H] ⁺
148	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 8.37 (s, 1H), 8.21 (d, <i>J</i> = 9.1 Hz, 1H), 7.52 (d, <i>J</i> = 1.2 Hz, 1H), 7.07 (d, <i>J</i> = 1.2 Hz, 1H), 6.99 (d, <i>J</i> = 9.2 Hz, 1H), 6.20 (s, 1H), 6.07 (s, 1H), 4.64 – 4.56 (m, 4H), 3.27 (s, 3H), 2.92 – 2.86 (m, 2H), 2.68 – 2.61 (m, 1H), 2.60 – 2.58 (m, 2H), 1.08 (d, <i>J</i> = 5.3 Hz, 3H).	580.3 [M+H] ⁺
149	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (s, 1H), 8.38 (s, 1H), 8.06 (d, <i>J</i> = 9.3 Hz, 1H), 7.50 (s, 1H), 7.24 (d, <i>J</i> = 9.4 Hz, 1H), 7.04 (s, 1H), 6.13 (d, <i>J</i> = 52.1 Hz, 2H), 4.52 – 4.47 (m, 1H), 3.67 – 3.61 (m, 1H), 3.45 – 3.41 (m, 1H), 3.27 (s, 3H), 3.25 – 3.20 (m, 1H), 2.93 – 2.82 (m, 3H), 2.64 – 2.56 (m, 4H), 2.23 (s, 3H), 1.95 – 1.90 (m, 1H), 1.83 – 1.77 (m, 1H), 1.08 (d, <i>J</i> = 5.1 Hz, 3H).	599.3 [M+H] ⁺
150	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (s, 1H), 8.36 (s, 1H), 8.06 (d, <i>J</i> = 9.4 Hz, 1H), 7.50 (d, <i>J</i> = 1.2 Hz, 1H), 7.24 (d, <i>J</i> = 9.3 Hz, 1H), 7.04 (s, 1H), 6.13 (d, <i>J</i> = 52.1 Hz, 2H), 4.49 (s, 1H), 3.67 – 3.61 (m, 1H), 3.45 – 3.42 (m, 1H), 3.26 (s, 3H), 3.25 – 3.20 (m, 1H), 2.92 – 2.82 (m, 3H), 2.62 – 2.56 (m, 4H), 2.22 (s, 3H), 1.96 – 1.90 (m, 1H), 1.84 – 1.76 (m, 1H), 1.08 (d, <i>J</i> = 5.2 Hz, 3H).	599.3 [M+H] ⁺
151	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (s, 1H), 8.42 (s, 1H), 8.12 (d, <i>J</i> = 9.2 Hz, 1H), 7.52 (s, 1H), 7.05 (s, 1H), 6.85 (d, <i>J</i> = 9.2 Hz, 1H), 6.13 (d, <i>J</i> = 52.1 Hz, 2H), 4.26 – 4.21 (m, 4H), 3.28 (s, 3H), 2.96 – 2.85 (m, 2H), 2.59 (q, <i>J</i> = 7.0 Hz, 3H), 1.08 (d, <i>J</i> = 5.2 Hz, 3H), 0.73 – 0.68 (m, 4H).	570.2 [M+H] ⁺
152	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 8.51 (d, <i>J</i> = 7.6 Hz, 1H), 8.39 (s, 1H), 8.29 (d, <i>J</i> = 7.9 Hz, 1H), 8.06 (s, 1H), 7.77 (t, <i>J</i> = 7.6 Hz, 1H), 7.70 (s, 1H), 7.06 (t, <i>J</i> = 54.3 Hz, 1H), 3.27 (s, 3H), 2.96 – 2.88 (m, 2H), 2.67 – 2.62 (m, 3H), 1.10 (d, <i>J</i> = 5.8 Hz, 3H).	491.4 [M+H] ⁺
153	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.77 (s, 1H), 8.50 (d, <i>J</i> = 7.7 Hz, 1H), 8.37 (s, 1H), 8.28 (d, <i>J</i> = 8.4 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.53 (s, 1H), 6.68 – 6.51 (m, 1H), 3.48 – 3.46 (m, 2H), 3.25 (s, 3H), 2.89 – 2.85 (m, 2H), 2.64 – 2.60 (m, 3H), 1.09 (d, <i>J</i> = 5.5 Hz, 3H).	505.4 [M+H] ⁺
154	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (s, 1H), 8.36 (s, 1H), 8.14 (d, <i>J</i> =	562.4

	9.1 Hz, 1H), 7.51 (s, 1H), 7.05 (s, 1H), 6.89 (d, $J = 9.2$ Hz, 1H), 6.13 (d, $J = 52.1$ Hz, 2H), 5.47 (ddt, $J = 58.5, 5.8, 3.0$ Hz, 1H), 4.46 (dtd, $J = 19.3, 9.7, 8.5, 4.4$ Hz, 2H), 4.31 – 4.19 (m, 2H), 3.26 (s, 3H), 2.93 – 2.84 (m, 2H), 2.63 – 2.55 (m, 3H), 1.08 (d, $J = 5.1$ Hz, 3H).	[M+H] ⁺
155	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 (s, 1H), 8.37 (s, 1H), 8.09 (d, $J = 9.3$ Hz, 1H), 7.50 (s, 1H), 7.32 (d, $J = 9.4$ Hz, 1H), 7.05 (s, 1H), 6.13 (d, $J = 52.1$ Hz, 2H), 4.74 (s, 1H), 4.64 (s, 1H), 3.79 (dt, $J = 17.9, 8.6$ Hz, 3H), 3.27 (s, 3H), 3.11 (d, $J = 9.9$ Hz, 1H), 2.94 – 2.84 (m, 2H), 2.64 – 2.54 (m, 3H), 2.02 – 1.89 (m, 2H), 1.08 (d, $J = 5.2$ Hz, 3H).	586.5 [M+H] ⁺
156	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (s, 1H), 8.73 (s, 1H), 8.56 – 8.46 (m, 1H), 8.27 (d, $J = 7.1$ Hz, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 1.1$ Hz, 1H), 7.15 (d, $J = 1.1$ Hz, 1H), 6.14 (d, $J = 52.1$ Hz, 2H), 5.77 (d, $J = 51.3$ Hz, 2H), 2.99 – 2.87 (m, 2H), 2.66 – 2.54 (m, 3H), 1.08 (d, $J = 5.6$ Hz, 3H).	507.4 [M+H] ⁺
157	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 8.65 (s, 1H), 8.43 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.6$ Hz, 1H), 6.99 (t, $J = 5.1$ Hz, 1H), 6.92 (s, 1H), 6.47 (s, 1H), 5.73 (d, $J = 51.3$ Hz, 2H), 4.16 – 4.01 (m, 1H), 3.73 – 3.61 (m, 2H), 3.27 – 3.21 (m, 2H), 3.21 – 3.13 (m, 2H), 2.84 – 2.72 (m, 2H), 2.57 – 2.53 (m, 3H), 2.24 (s, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 5.5$ Hz, 3H).	507.4 [M+H] ⁺
158	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.73 (s, 1H), 8.68 (s, 1H), 8.49 (d, $J = 7.9$ Hz, 1H), 8.24 (d, $J = 7.5$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 5.2$ Hz, 1H), 6.89 (s, 1H), 6.49 (s, 1H), 6.12 (ddd, $J = 62.1, 51.3, 8.9$ Hz, 2H), 4.31 (d, $J = 10.5$ Hz, 1H), 3.26 – 3.18 (m, 2H), 3.17 – 3.08 (m, 1H), 2.03 – 1.95 (m, 1H), 1.94 – 1.77 (m, 4H), 1.72 – 1.62 (m, 1H), 1.11 (t, $J = 7.2$ Hz, 3H).	502.4 [M+H] ⁺
159	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.75 (s, 1H), 8.51 (d, $J = 7.1$ Hz, 1H), 8.27 (d, $J = 7.1$ Hz, 1H), 7.76 (t, $J = 7.8$ Hz, 1H), 7.68 (s, 1H), 7.16 (s, 1H), 6.32 – 6.03 (m, 4H), 4.61 (d, $J = 10.6$ Hz, 1H), 3.24 – 3.16 (m, 1H), 2.04 – 1.95 (m, 1H), 1.91 – 1.78 (m, 4H), 1.75 – 1.66 (m, 1H).	507.1 [M+H] ⁺

Biological Assay

[00352] Example A. HTRF based binding assay

[00353] Assay:

[00354] An HTRF based binding assay was applied to assess the affinity of candidate compounds to Cbl-b protein. CBL-B (GST-Tag) was purchased from BPS (Cat# 80415). A fluorescence labeled

Cbl-b binding probe was made in-house. Anti GST-Tb cryptate monoclonal antibody was from Cisbio (61GSTTLB). In brief, compounds were diluted and transferred to opti-384F black plate (PE, 6007279) by echo. 1x Assay Buffer (HEPES pH 7.5 50 mM, NaCl 50 mM, MgCl₂ 5 mM, TCEP 1 mM, Tween-20 0.01%), 2x Protein mix (10 nM), and 2x Probe mix (120 nM) were prepared. 10 µL 2x Protein mix (or 1x Assay buffer, as no protein control) was added to assay plate. After 30 min incubation 25°C, 10 µL 2x Probe mix was added for another 2 h incubation at 25°C. Data were collected by Envision reading using Ex340/Em495/520. IC₅₀ is calculated by XLFit excel add-in version 4.3.1 with the equation:

4 Parameter Logistic Model or Sigmoidal Dose-Response Model

$$\text{fit} = (A + ((B - A) / (1 + ((C/x)^D))))$$

$$\text{inv} = (C / (((B - A) / (y - A)) - 1)^{(1/D)})$$

$$\text{res} = (y - \text{fit})$$

[00355] Results:

[00356] The data for exemplary compounds are shown in Table 4.

Table 4

Compound No.	CBL-B HTRF IC ₅₀ (nM) ^a	Compound No.	CBL-B HTRF IC ₅₀ (nM) ^a	Compound No.	CBL-B HTRF IC ₅₀ (nM) ^a
1.	A	3.	A	4.	A
5.	B	6.	B	7.	A
8.	A	9.	A	10.	A
11.	B	12.	A	13.	B
14.	A	15.	A	18.	A
19.	A	21.	B	22.	A
23.	A	34.	A	36.	A
37.	B	40.	B	42.	A
43.	A	44.	B	45.	B
46.	B	47.	A	48.	A
49.	A	50.	B	51.	A
52.	B	53.	A	54.	D
55.	A	56.	A	57.	A
58.	A	59.	B	60.	B
61.	D	62.	D	63.	B
64.	A	65.	B	66.	A
67.	B	68.	A	70.	A

71.	A	72.	A		
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^a: A: < 20 nM; B: 20 ~ 200 nM; C: 200 ~ 500 nM; D: > 500 nM.

[00357] Other compounds of disclosed herein also show Cbl-b inhibitory activity.

[00358] **Example B.** ELISA based phosphorylated-CBLB assay

[00359] Assays:

[00360] The 384-well ELISA plate (781074, Greiner) is coated with 25 μ L E2 (UbcH5b) at final concentration of 20 μ g/ml, and centrifuge at 1000 rpm for 1 min, and incubate at 37°C for 90 min. After the protein coating is completed, wash the ELISA plate, and the solution in the plate is discarded and dried, and add 100 μ L PBST, standing for 5 min, and repeat three times. Transfer 100 μ L blocking buffer to each well. Incubate at 25°C for 90 min and wash the plate to wait for reaction. Incubate the compound with CBL-B and Src-Zap70. Serially dilute the compound using DMSO in a 384 PP Plate, and transfer 0.3 μ L of diluted compound using ECHO to the 384-well reaction plate (6007290, PE), and add 15 μ L CBL-B, and incubate at 25 °C for 10 min. Then add 15 μ L Src-Zap70&ATP, and incubate at 25 °C for 120 min, ensuring a final DMSO content of 1% (double duplication) (Final concentration: 50 mM Hepes (pH7.0), 5 mM MgCl₂, 100 mM NaCl, 0.01% TritonX-100, 0.01% BSA, 1 mM DTT, 1.5 nM CBL-B, 10 nM Src-Zap70 and 1 mM ATP). Transfer 20 μ L of the reaction mixture above from the 384 well reaction plate to the ELISA plate, and incubate at 25°C for 120 min. After washing the plate, transfer 25 μ L SA-HRP (16000X) to the ELISA plate and incubate at 25°C for 60 min, and then wash the plate. Transfer 25 μ L ECL Plus WB Substrate (A and B solution at a ratio of 1:1) to ELISA plate and incubate at 25°C for 5 min. Read the luminescence signal on BMG microplate reader (PHERAstar FSX). The wells of coated E2 and DMSO are used as high control, and the wells of coated E2 and the first concentration of the reference are used as low control. Calculate the inhibition rate of the compounds wells (% inh) = 100 * (high control-cpd well) / (high control-low control). The IC₅₀ values of the nonlinear regression equation is fitted and determined by XLfit 5.5.0.

[00361] Result:

[00362] The data for exemplary compounds are shown in Table 5.

Table 5

Compound No.	IC ₅₀ (nM) ^a	Compound No.	IC ₅₀ (nM) ^a	Compound No.	IC ₅₀ (nM) ^a
47	B	52	C	55	B
60	B	64	B	65	D
66	A	67	D	74	A
75	A	78	A	79	D

80	B	82	A	84	D
85	C	86	D	88	B
92	C	93	D	94	A
95	A	96	D	97	A
98	A	99	A	101	A
102	A	103	A	104	A
105	A	106	B	107	B
108	D	109	B	110	D
111	B	112	A	113	B
114	A	130	B	116	B
117	D	120	A	121	A
122	A	123	A	125	A
126	A	127	A	128	A
132	A	133	C	134	B
136a	A	136b	B	138	A
139	A	140	A	141	A
142	B	143	A	144	A
146	D	147	A	148	B
149	A	150	A	151	B
152	D	153	D	154	A
155	A	156	B	157	A
158	A	159	A		

^a: A: < 100 nM; B: 100 ~ 500 nM; C: 500 ~ 1000 nM; D: > 1000 nM.

[00363] Example C. IL-2 secretion assay

[00364] Assays:

[00365] Human Cryopreserved PBMCs were thawed by pre-warmed complete medium containing 10% FBS and 1% PS. After resting for 30 min at 37°C & 5%CO₂, Human Pan T cells were isolated from PBMCs according to the instruction of isolation kit (Stemcell, 17951). The T cells were recovered overnight at 37°C & 5%CO₂, and the next day T cells were harvested and cell suspension at a desired density was prepared using complete medium containing 10% FBS, 1% PS and 55 µM beta mercaptoethanol, then seeded 1×10⁵/200 µL cells per well into the 96-well plate, which was pre-coated with 5 µg/mL anti-human CD3 antibody (eBioscience, 16-0037-38). The tested compounds were serially diluted by 3-fold in 100% DMSO and the intermediate dilutions was prepared in complete medium. Then the compounds at various concentrations were added into the 96-well cell culture plate. after 24 hours incubation, the IL-2 secretion in cell culture supernatant was measured by

Elisa (4A bio, CHE0003), according to the manufacturer's instruction. The standard curve was fitted using nonlinear fitting formula:

$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / [1 + 10^{-(\text{LogIC}_{50} - X) \times \text{HillSlope}}]$, Y means OD₄₅₀ data and X means the Log value of the standard samples' concentration.

And the IL2 concentration in compound treatment samples was calculated by returning to the standard curve. Wells containing cells and 1% DMSO served as low control, and the activation% was calculated using the formula: Fold change = IL-2 concentration_{Compound treated} / IL-2 concentration_{Low control}. Then the EC₅₀ curve of compounds was Fitted by non-linear regression equation:

$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{-(\text{LogIC}_{50} - X) \times \text{HillSlope}})$, Y means activation and X means the Log value of compound concentration.

[00366] Results:

[00367] The data for exemplary compounds are shown in Table 6.

Table 6

Compound No.	EC ₅₀ (nM) ^a	Fold Change ^b	Compound No.	EC ₅₀ (nM) ^a	Fold Change ^b
1	A	C	12	A	A
14	A	A	15	A	A
19	A	B	21	A	A
22	A	A	23	B	B
25	B	B	34	A	A
36	A	A	41	A	C
42	A	A	43	A	A
46	C	B	47	B	A
48	A	B	51	B	C
52	B	C	55	D	C
64	D	A	66	A	A
68	A	A	69	A	A
70	B	A	71	A	B
72	A	B	73	A	A
74	A	A	75	B	A
94	A	B	95	A	B
99	A	A	101	A	A
102	A	A	103	A	A
104	A	A	112	A	B
120	A	A	121	A	A
122	A	A	125	A	A

126	A	A	127	A	A
128	A	A	130	B	A
132	A	A	140	A	A
141	A	A	144	A	A
147	A	A	148	A	A
150	A	A	157	A	A
158	A	A	159	A	A

^a: A: < 500 nM; B: 500 ~ 1000 nM; C: 1000 ~ 2000 nM; D: > 2000 nM.

^b: A: > 15-fold; B: 10 ~ 15 fold; C: 5 ~ 10 fold; D: < 5 fold

[00368] Example D: Metabolic stability in liver microsomes

[00369] Assays:

[00370] Microsomes (final concentration 0.5 mg/mL), 100 mM phosphate buffer pH 7.4, and compound (final concentration 1 μ M) were added to the assay plate and allowed to preincubate for 10 min at 37 °C. The reaction was initiated by the addition of NADPH (final concentration 1 mM), and the plate was constantly shaken at 37 °C. After 0, 5-, 15-, 30-, 45-, and 60-min aliquots were taken, and the reaction was quenched using cold acetonitrile. The samples were shaken for 10 min, then centrifuged at 4000 rpm for 20 min at 4 °C and analyzed by LC-MS/MS. The *in vitro* intrinsic clearance was calculated from the rate of compound disappearance. Compound A (Example 85 in WO2024015863) and NX1607 (Example 23 in WO2020264398) was synthesized according to the corresponding patent.

[00371] Result:

[00372] The data for exemplary compounds are shown in Table 7, demonstrating the compounds disclosed in this disclosure exhibit improved liver microsome metabolic stability than NX1607.

Table 7

	CL _{liver} (ml/min/kg)			
	Human	Mouse	Rat	Dog
NX-1607	14.8	75.7	43.8	23.2
Compound A	18.7	72.9	-	-
Compound 47	6.6	<26.7	<13.2	<9.5
Compound 66	9.5	70.8	21.1	9.8
Compound 102	7.9	<26.7	<13.2	-
Compound 144	11.4	60.4	-	9.5

[00373] Example E: Metabolic stability in hepatocytes

[00374] Assays:

[00375] Cell viability was tested by trypan blue exclusion after thawing. 10 mM test compounds and 30 mM positive control compounds were diluted to 1 mM and 3 mM with DMSO in 96-well plates. 1 mM test compounds and 3 mM positive control compounds were then diluted to 100 μ M and 300 μ M dosing solutions with acetonitrile. Cryopreserved cells were thawed, isolated, and suspended in Incubation Medium (Williams' Medium E (no phenol red) containing 2 mM L-Glutamine and 25 mM HEPES), then diluted with pre-warmed Incubation Medium to 0.5×10^6 cells/mL. 198 μ L of pre-warmed cell suspensions were added to 96-well plates. 125 μ L of stop solution (acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards) was transferred to a set of pre-labeled 96-well plates. 2 μ L dosing solution was spiked into each well of 96-well plates in duplicates. For T0 Samples, 25 μ L of each sample homogenous suspension was immediately into well containing 125 μ L of ice-cold stop solution. All plates were incubated at 37 °C in a 95% humidified incubator at 5% CO₂ to start the reactions with constant shaking at 650 rpm. At 15, 30, 60 and 90 min, samples were mixed and then 25 μ L of each sample at each time point was transferred to a well containing 125 μ L of ice-cold stop solution. Medium Control (MC) sample plates (labeled as T0-MC and T90-MC) were prepared at T0 and T90 by adding the same components to each well except cell suspensions. The plates were immediately added to a plate shaker at 600 rpm for 10 minutes and centrifuged at 3220 x g for 20 min at 4°C. After centrifugation, 80 μ L/well of supernatant in the sample plates were transferred to another set of pre-labeled 96-well plates which containing 240 μ L of ultrapure water according to the plate map. Analytical plates are sealed and store at 4 °C until LC-MS/MS analysis.

[00376] Result:

[00377] The data for exemplary compounds are shown in Table 8, demonstrating the compounds disclosed in this disclosure exhibit improved hepatocyte metabolic stability than NX1607.

Table 8

	CL _{hep} (ml/min/kg)			
	Human	Mouse	Rat	Dog
NX-1607	16.2	86.7	49.2	26.4
Compound 66	-	-	33.6	-
Compound 47	<9.6	45.7	-	-
Compound 102	-	-	<19.4	-
Compound 144	12.8	-	-	-

[00378] **Example F: *In Vivo* Pharmacokinetic Studies**

[00379] Assays:

[00380] Male C57 mice (n = 3), male SD rats (n = 3) and beagle dogs (n = 2) received either a single intravenous (bolus) injection or single oral administration (by gavage) of the compound in a cocktail preparation. Doses of 1 mg/kg (per compound, intravenous administration) and 10 mg/kg (per

compound, perorally) for mice or rats, or 1 mg/kg (per compound, intravenous administration) and 5 mg/kg (per compound, perorally) for dogs were given as solutions in different formulations as needed. The blood samples were taken via cephalic vein 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, with 30 μ L collected per time point. Blood samples were placed in tubes containing K2-EDTA and stored on ice until centrifuged. The blood samples were centrifuged at 6800 g for 6 minutes at 2-8°C within 1 h after collected and stored frozen at approximately -80 °C. An aliquot of 20 μ L plasma samples were protein precipitated with 400 μ L MeOH in which contains 100 ng/mL Verapamil (IS). The mixture was vortexed for 1 min and centrifuged at 18000 x g for 10 min. 400 μ L of supernatant was transferred to 96 well plates. An aliquot of 5 μ L supernatant was injected for LC-MS/MS analysis by LC-MS/MS-27 (TQ6500+) instrument. 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 ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$), elimination half-life ($T_{1/2}$), maximum plasma concentration (C_{max}), oral bioavailability (F) will be calculated using noncompartmental analysis modules in FDA certified pharmacokinetic program Phoenix WinNonlin 7.0 (Pharsight, USA).

[00381] Result:

[00382] The data for exemplary compounds are shown in Table 9/10/11, demonstrating the compounds disclosed in this disclosure exhibit improved pharmacokinetic profile across the preclinical species than NX1607.

[00383]

Table 9 Mouse Pk

Compound ID		NX1607	Cpd. A	Cpd.47	Cpd.66	Cpd.102	Cpd.144
Mouse IV/PO 1/10 mpk	CL, mL/min/kg	69.9	40.1	16.3	27.7	6.6	10.0
	F%	28	48	97	68	146	101
	DNAUC,0-t (ng*h/mL) (PO)	66.2	198	995	415	3658	1652

Table 10 Rat Pk

Compound ID		NX1607	Cpd. A	Cpd.47	Cpd.66
Rat IV/PO 1/10 mpk	CL, mL/min/kg	110	51.6	13.1	19.7
	F%	4.7	5.8	45	47
	DNAUC,0-t (ng*h/mL) (PO)	7.1	18.4	608	391

Table 11 Dog Pk

Compound ID		NX1607	Cpd.66	Cpd.102
Dog IV/PO 1/5 mpk	CL, mL/min/kg	28.4	4.7	5.4
	F%	10.4	14.1	36
	DNAUC,0-t (ng*h/mL) (PO)	61.5	502	1032

[00384] **Example G: CT26 Efficacy Model**

[00385] Assays:

[00386] Cell Culture

[00387] The CT26.WT tumor cells (ATCC, Cat # CRL-2638™) were maintained in vitro with RPMI 1640 medium supplemented with 10% heat inactivated fetal bovine serum, at 37°C in an atmosphere of 5% CO₂ in air. The tumor cells were routinely subcultured twice weekly by trypsin-EDTA treatment. The cells growing to a confluency around 70% - 80% were harvested and counted for tumor inoculation.

[00388] Tumor Inoculation

[00389] Each mouse was inoculated subcutaneously in the right flank with CT26.WT tumor cells (3×10^5 /mouse) in 0.05 mL of serum-free RPMI-1640.

[00390] Randomization

[00391] The animals with tumors ranging at $\sim 46.88\text{mm}^3$ (40mm^3 - 54mm^3) were enrolled and grouped for efficacy study using stratified randomization based upon their tumor volumes. In total, 64 mice were enrolled in the study and randomly allocated into 8 groups, with 8 mice per group. The date of randomization was defined as day0.

[00392] Observation and Data Collection

[00393] After tumor inoculation, the animals were checked daily for morbidity and mortality. At the time of routine monitoring, the animals were checked for any effects of tumor growth and treatments on normal behavior such as mobility, body weight gain/loss (body weights will be measured twice weekly or every Monday/Wednesday/Friday), eye/hair matting and any other abnormal effect. Mortality and observed clinical signs were recorded for individual animals in detail.

[00394] Tumor sizes were measured every Monday/Wednesday/Friday) in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: $V = 0.5 \times a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. TGI was calculated accordingly.

[00395] Result:

[00396] The data for exemplary compounds are shown in Table 12, demonstrating the representative compounds in this disclosure (such as **Compound 66**) show improved *in vivo* efficacy in CT26 model than NX1607.

Table 12

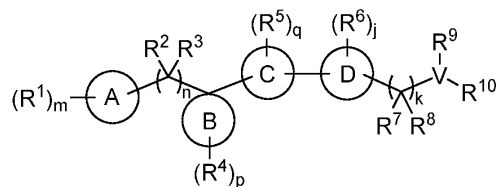
Group No.	Dose	TGI
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1	Vehicle	-
2	PD-1, 3 mpk, ip, BIW	58%
3	NX1607, 30 mpk, QD + PD-1, 3 mpk, ip, BIW	88%
4	Compound 66, 10 mpk, QD + PD-1, 3 mpk, ip, BIW	89%

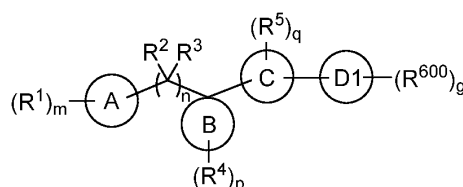
CLAIMS

WHAT IS CLAIMED IS:

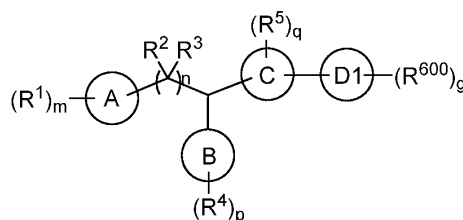
1. A compound of Formula (I), Formula (II), Formula (III) or Formula (IV):



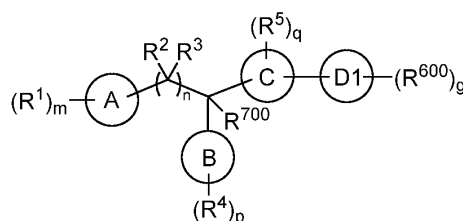
Formula (I),



Formula (II),



Formula (III),



Formula (IV),

or a pharmaceutically acceptable salt thereof,

wherein:

each R¹ is independently selected from halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more R;

Ring A is cycloalkyl, heterocyclyl, aryl or heteroaryl;

each of R^2 and R^3 is independently selected from hydrogen, halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more R;

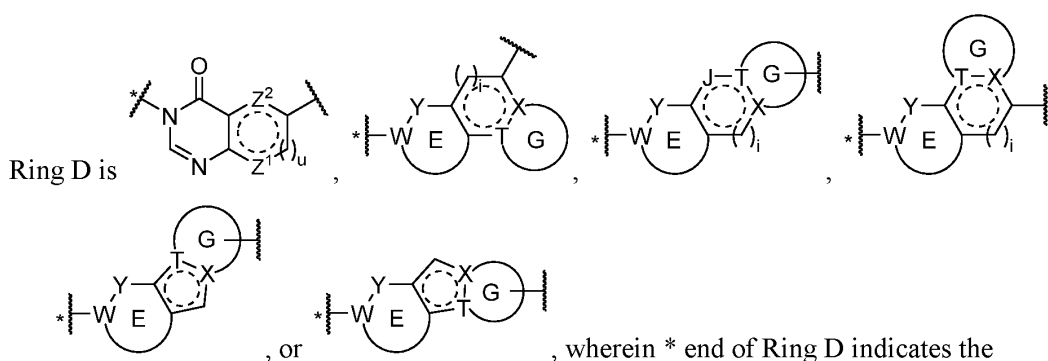
Ring B is cycloalkyl or heterocyclyl;

each R^4 is independently selected from hydrogen, halogen, cyano, oxo, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, or haloalkyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, and haloalkyl are optionally substituted with one or more R; or

two R^4 together with the same atom to which they are both attached form a C_2 - C_6 alkylidenyl optionally substituted with one or more R;

Ring C is aryl or heteroaryl;

each R^5 is independently selected from halogen, cyano, $-OR^a$, $-SR^a$, $-NR^bR^c$, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl are optionally substituted with one or more R;



Z^1 is $C(H)_{1-2}$ or $N(H)_{0-1}$;

Z^2 is $C(H)_{1-2}$, $N(H)_{0-1}$, O, or S;

W is $C(H)_{0-1}$ or N;

Y is $N(H)_{0-1}$, O, S, $C(O)$, $S(O)_{1-2}$ or $P(O)_{1-2}$;

J is $C(H)_{0-1}$ or N;

X is $C(H)_{0-1}$ or N;

T is $C(H)_{0-1}$ or N;

Ring E is heterocyclyl or heteroaryl;

Ring G is cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with one or more R;

each R⁶ is independently selected from halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl and heterocyclyl are optionally substituted with one or more R;

each of R⁷ and R⁸ is independently selected from hydrogen, deuterium, halogen, cyano, -OR^a, -SR^a, -NR^bR^c, alkyl, haloalkyl or cycloalkyl;

V is CH or N;

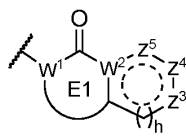
each of R⁹ and R¹⁰ is independently selected from hydrogen, deuterium, alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, or heterocyclylalkyl, wherein the cycloalkyl, heterocyclyl, cycloalkylalkyl, and heterocyclylalkyl are optionally substituted with one or more R; or

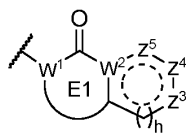
R⁹ and R¹⁰ together with the atom to which they are attached form a cycloalkyl or heterocyclyl, wherein the cycloalkyl and heterocyclyl is optionally substituted with one or more R;

R^a is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are independently optionally substituted with one or more R;

each of R^b and R^c is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are independently optionally substituted with one or more R; or

R^b and R^c taken together with the atom to which they are attached form a heterocyclyl optionally substituted with one or more R;



Ring D1 is , wherein == indicates a single bond or a double bond;

Ring E1 is a 6-membered heteroaryl or a 6-membered heterocyclyl;

Z³ is C(H)₁₋₂ or N(H)₀₋₁;

Z⁴ is C(H)₁₋₂, N(H)₀₋₁, O, or S;

Z⁵ is C(H)₁₋₂, N(H)₀₋₁, O, or S;

W¹ is C(H)₀₋₁ or N;

W² is C(H)₀₋₁ or N;

each R⁶⁰⁰ is independently selected from halogen, cyano, heterocyclyl, -SR^a, -NH₂, -N(alkyl)₂, -NH(cycloalkyl), -C(O)NH₂, -C(O)NH(alkyl), unsubstituted alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, hydroxylalkyl, haloalkoxy, -alkynyl-N(alkyl)₂, haloalkynyl, -alkynyl-heterocyclyl, or cycloalkyl, wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R'; or

two R⁶⁰⁰ taken together with the atom(s) to which they are attached form a cycloalkyl,

heterocyclyl or heteroaryl optionally substituted with one or more R;

R⁷⁰⁰ is halogen, alkyl, haloalkyl, cycloalkyl or heterocyclyl, wherein the alkyl, haloalkyl, cycloalkyl and heterocyclyl are independently optionally substituted with one or more R;

each of R and R' is independently halogen, cyano, oxo, -OH, -S(=O)(alkyl), -S(=O)₂(alkyl), -S(=O)₂N(alkyl)₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, -NH₂, -N(alkyl)₂, -NH(alkyl), -C(=O)(alkyl), -C(=O)OH, -C(=O)O(alkyl), alkyl, alkoxy, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, cycloalkyl, or heterocyclyl;

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

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

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

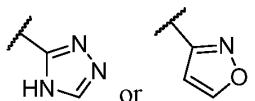
k is 0, 1, 2 or 3;

u is 0, 1 or 2;

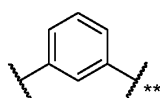
h is 0 or 1; and

i is 0, 1 or 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is heteroaryl.
3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is triazolyl, isoxazolyl, pyrrolyl, thienyl, furyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, or dihydropyrrolotriazolyl.
4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein Ring A is

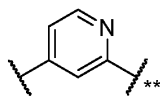


5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Ring B is a cycloalkyl.
6. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein Ring B is a cyclobutanyl.
7. The compound of any of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein Ring C is an aryl.
8. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein Ring C is phenyl.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein Ring C is



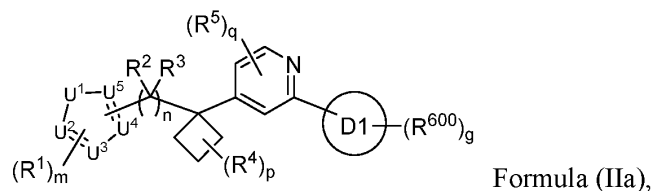
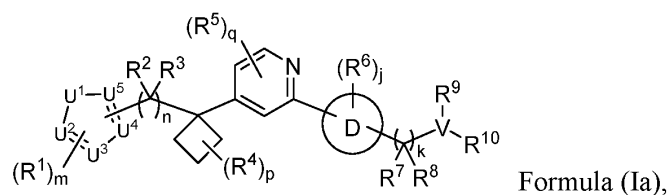
, and ** end of Ring C indicates the attachment point of Ring C to Ring D.

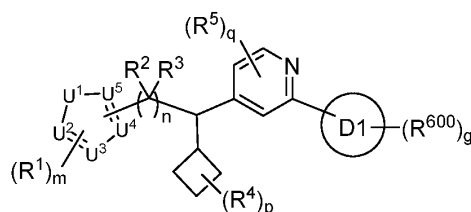
10. The compound of any of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein Ring C is a heteroaryl.
11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein Ring C is pyridinyl.
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein Ring C is



, and ** end of Ring C indicates the attachment point of Ring C to Ring D.

13. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound has a Formula (Ia), Formula (IIa) or Formula (IIIa):





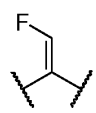
Formula (IIIa),

U^1 is O, S, NH or CH_2 ; and

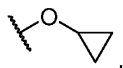
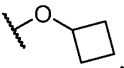
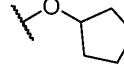
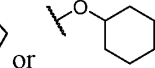
each of U^2 , U^3 , U^4 and U^5 is independently N or CH.

14. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein m is 1, and R^1 is alkyl or haloalkyl.
15. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_3$, $-CHF_2$ or $-CH_2F$.
16. The compound of any of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein n is 0.
17. The compound of any of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein n is 1, and both R^2 and R^3 are hydrogen.
18. The compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein p is 1, and R^4 is alkyl or alkynyl.
19. The compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^4 is alkyl.
20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl.
21. The compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^4 is alkynyl.
22. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein R^4 is ethynyl.
23. The compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein p is 2, and two R^4 together with the same atom to which they are both attached form a  optionally substituted with one or more halogen.

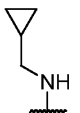
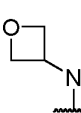
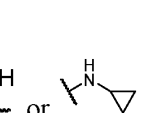
24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein two R^4

together with the same atom to which they are both attached form a  or .

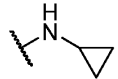
25. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein q is 0.
26. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein q is 1, and R^5 is $-OR^a$.
27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^a is alkyl, haloalkyl or cycloalkyl.
28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein R^5 is

selected from $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, , ,  or .

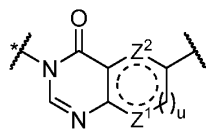
29. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein q is 1, and R^5 is cycloalkyl.
30. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein R^5 is cyclopropyl.
31. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein q is 1, and R^5 is $-NR^bR^c$.
32. The compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein R^b is hydrogen, and R^c is alkyl, haloalkyl, cycloalkyl, or heterocyclyl, wherein the alkyl, cycloalkyl, and heterocyclyl are independently optionally substituted with one or more R .
33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^b is hydrogen, and R^c is alkyl, haloalkyl or cycloalkyl.
34. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from NH_2 , $-NHCH_2CH_3$, $-N(CH_3)CH_2CH_3$, $-NHCH_2CH_2F$, $-NHCH_2CHF_2$, -

$NHCH_2CH_2OH$, ,  or .

35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein R^5 is

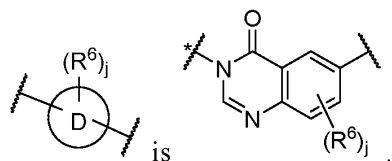
selected from $-NHCH_2CH_3$, $-NHCH_2CH_2F$, $-NHCH_2CHF_2$, or .

36. The compound of any of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein



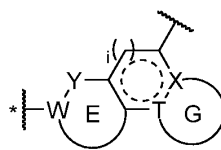
the compound has a Formula (I), and Ring D is

37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein



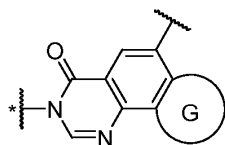
38. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein R^6 is independently -F, -CH₃, -CHF₂, -CF₃ or -OCH₃.

39. The compound of any of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein

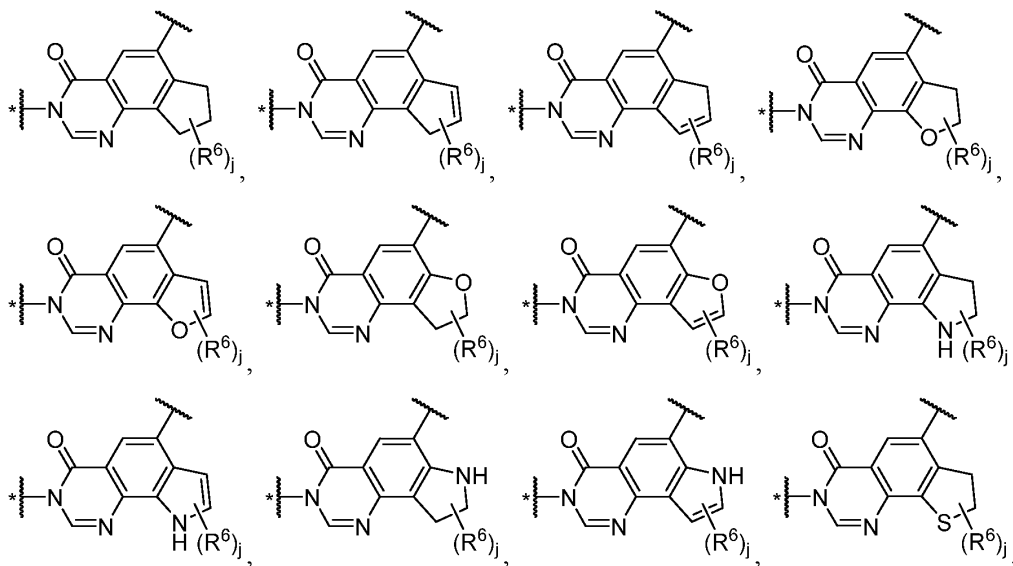
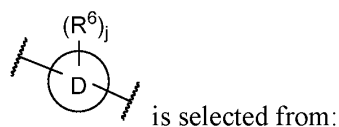


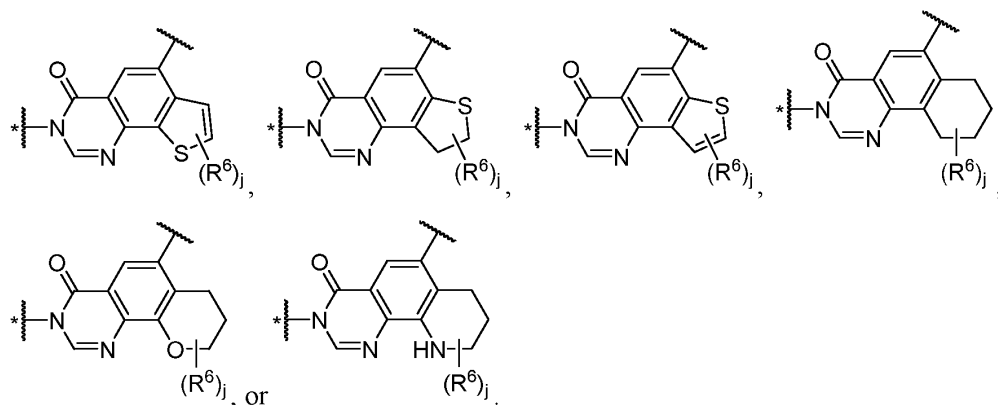
the compound has a Formula (I), and Ring D is

40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein Ring D is

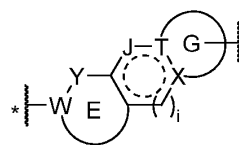


41. The compound of claims 39 or 40, or a pharmaceutically acceptable salt thereof, wherein



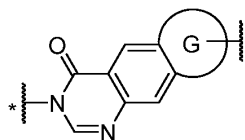


42. The compound of any of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein

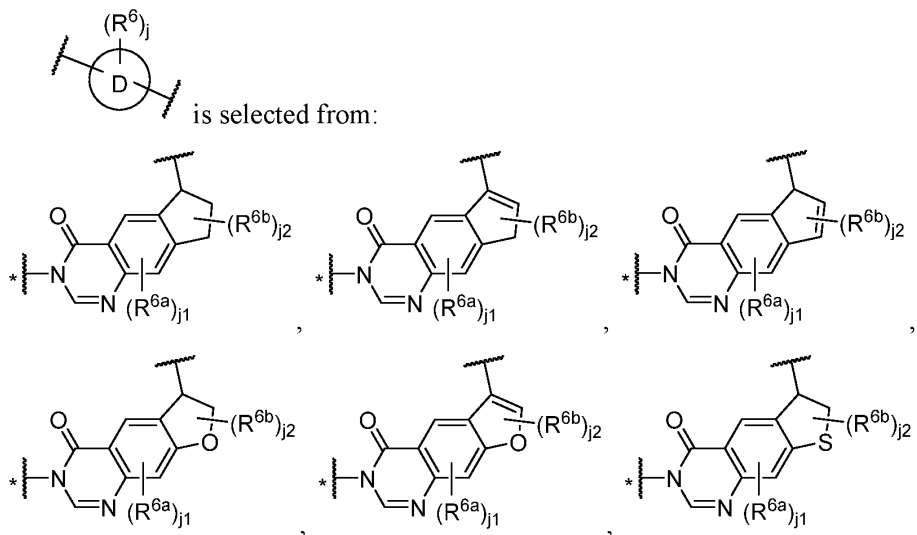


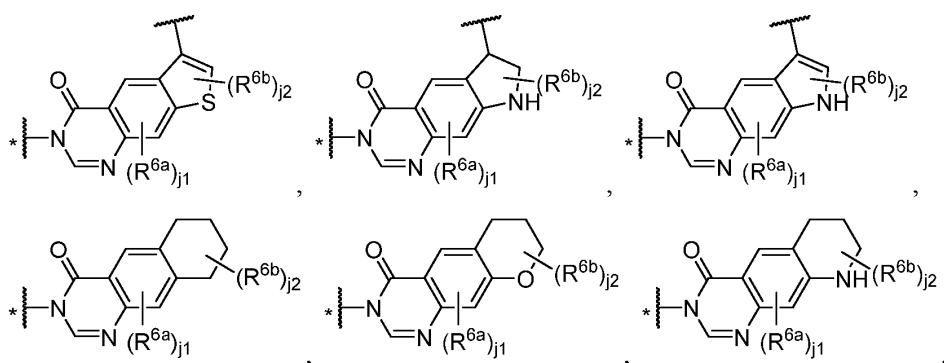
the compound has a Formula (I), and Ring D is

43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein Ring D is



44. The compound of claims 42 or 43, or a pharmaceutically acceptable salt thereof, wherein



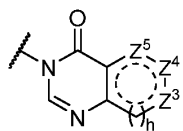


each of R^{6a} and R^{6b} is independently R^6 ;

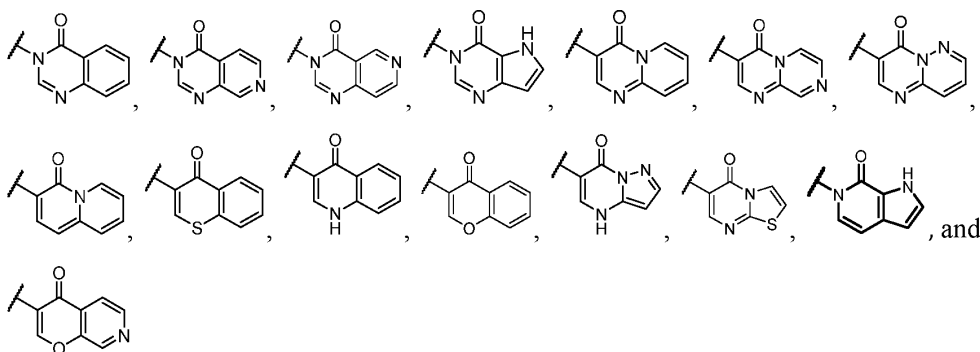
j_1 is 0, 1, or 2; and

j_2 is 0, 1, 2, 3 or 4.

45. The compound of any of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein the compound has a Formula (I), and V is N.
46. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen, and R^{10} is cycloalkylalkyl or cycloalkyl, each optionally substituted with one or more R, and each R is independently selected from halogen, alkyl or haloalkyl.
47. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein the compound has a Formula (II), (IIa), (III), (IIIa), or (IV), and Ring D1 is



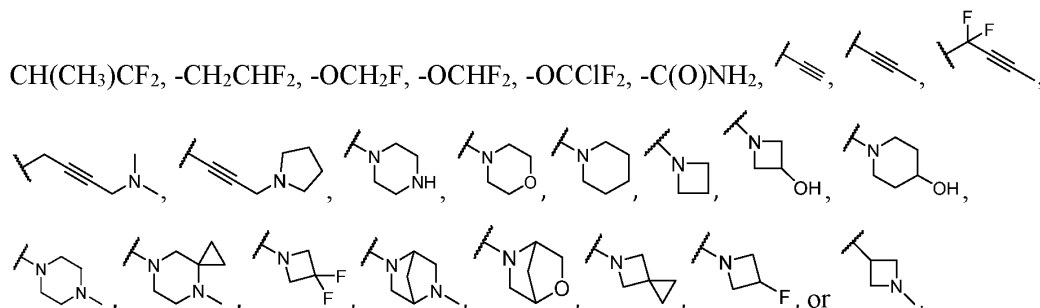
48. The compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein Ring D1 is selected from the group consisting of:



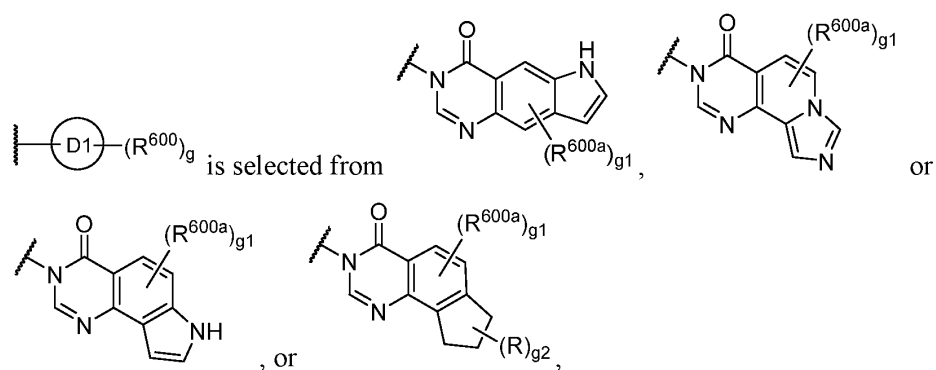
49. The compound of any one of claims 1-35 and 47-48, or a pharmaceutically acceptable salt thereof, wherein the compounds has a Formula (II), (IIa), (III), (IIIa), or (IV), and each R^{600} is independently selected from halogen, cyano, heterocyclyl, $-C(O)NH_2$, unsubstituted alkyl,

alkynyl, haloalkyl, hydroxylalkyl, haloalkoxyl, -alkynyl-N(alkyl)₂, haloalkynyl, -alkynyl-heterocyclyl or cycloalkyl, wherein the heterocyclyl and cycloalkyl are optionally substituted with one or more R'.

50. The compound of claim 49, or a pharmaceutically acceptable salt thereof, wherein each R⁶⁰⁰ is independently selected from -Cl, -F, -CN, -CH₃, -CH(CH₃)₂, -CH₂OH, -CF₃, -CF₂CF₃, -



51. The compound of any one of claims 1-35 and 47-48, or a pharmaceutically acceptable salt thereof, wherein the compounds has a Formula (II) , (IIa), (III), (IIIa), or (IV), and two R⁶⁰⁰ taken together with the atom to which they are attached form a cycloalkyl, heterocyclyl or heteroaryl, each optionally substituted with one or more R.
52. The compound of claim 51, or a pharmaceutically acceptable salt thereof, wherein

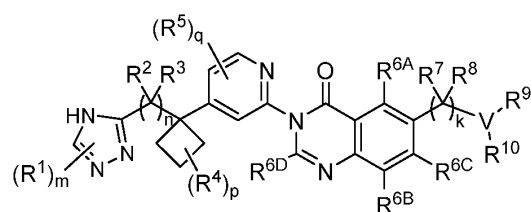


each R^{600a} is independently R^{600} ;

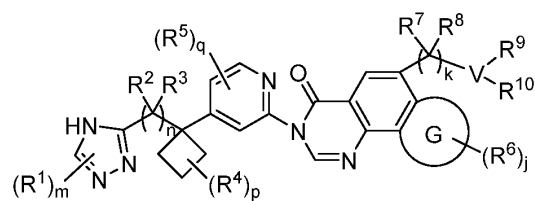
g1 is 0, 1, or 2; and

g2 is 0, 1, 2, 3, or 4.

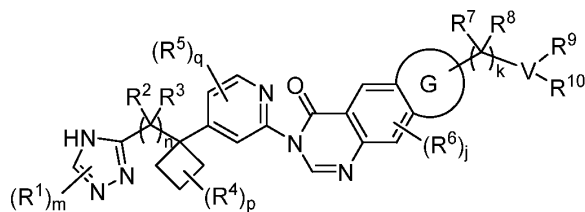
53. The compound of claim 1, having a formula selected from:



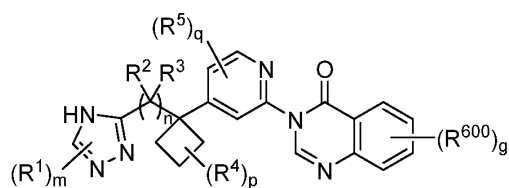
Formula (Ib),



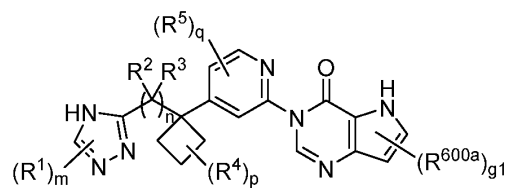
Formula (Ic),



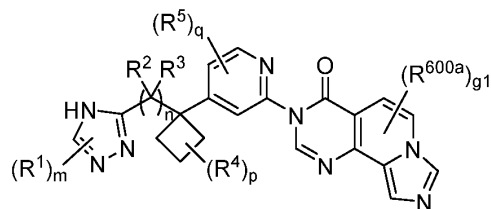
Formula (Id),



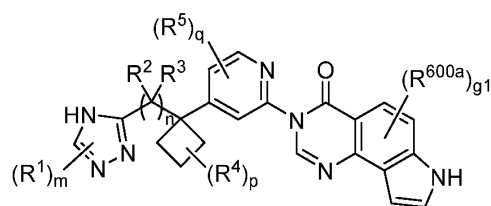
Formula (IIb),



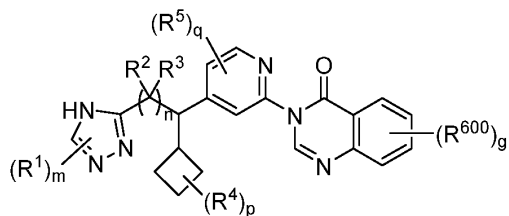
Formula (IIc),



Formula (IId),



Formula (IIe),



Formula (IIIb),

or a pharmaceutically acceptable salt thereof,

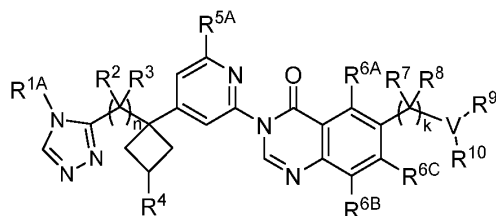
wherein each R^{6A} , R^{6B} , R^{6C} and R^{6D} is independently selected from hydrogen or R^6 ;

each R^{600a} is independently R^{600} ;

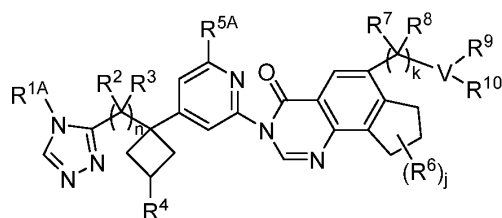
g is 0, 1, 2, 3, or 4; and

$g1$ is 0, 1, or 2.

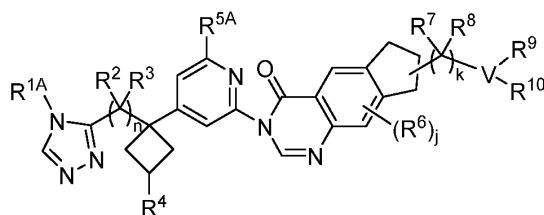
54. The compound of claim 53, having a formula selected from:



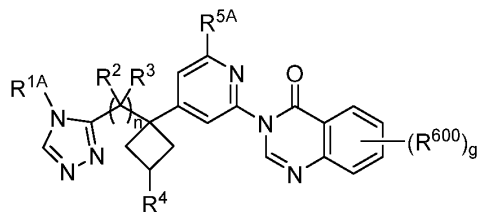
Formula (Ib-1),



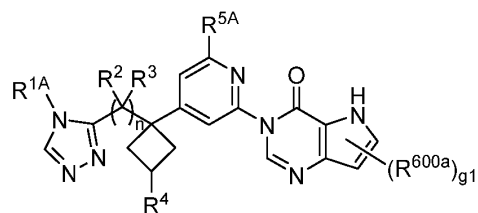
Formula (Ic-1),



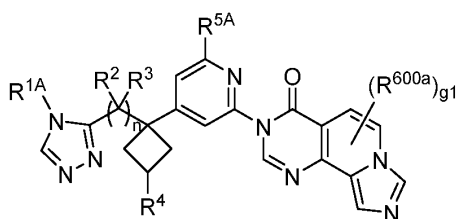
Formula (Id-1),



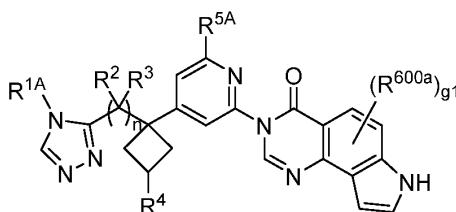
Formula (IIb-1),



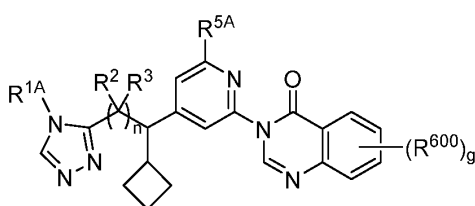
Formula (IIc-1),



Formula (IIId-1),



Formula (IIe-1),



Formula (IIIb-1),

or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from hydrogen or R^1 , each R^{5A} is independently selected from hydrogen or R^5 , each R^{6A} , R^{6B} , R^{6C} and R^{6D} is independently selected from hydrogen or R^6 .

55. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from any compound set forth in Table 1, Table 2 or Table 3.
56. A pharmaceutical composition comprising a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
57. A method of modulating activity of an immune cell, the method comprising contacting the immune cell with an effective amount of a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 56.
58. A method of treating a cancer, the method comprising administering an effective amount of a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 56 to the subject in need thereof.
59. A method of treating a cancer responsive to inhibition of Cbl-b activity, the method comprising administering an effective amount of a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 56 to the subject in need thereof.