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(54) Title: ISOINDOLINONE AND DIHYDROPYRROLOPRIDINONE COMPOUNDS AND USES THEREOF

(57) Abstract: Described herein are isoindolinone compounds and pharmaceutical compositions comprising said compounds. Additionally are described methods for the treatment of neurological disorders such as Huntington's disease (HD).



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# ISOINDOLINONE AND DIHYDROPYRROLOPRIDINONE COMPOUNDS AND USES THEREOF

## CROSS REFERENCE

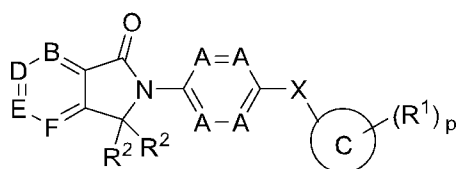
[0001] This application claims the benefit of International Application No. PCT/CN2023/098598, filed on June 6, 2023 and International Application No. PCT/CN2023/117262, filed on September 6, 2023 which are hereby incorporated by reference in their entirety.

## BACKGROUND OF THE INVENTION

[0002] Huntington's disease (HD) is a progressive, autosomal dominant neurodegenerative disorder of the brain, having symptoms characterized by involuntary movements, cognitive impairment, and mental deterioration. Death, typically caused by pneumonia or coronary artery disease, usually occurs 13 to 15 years after the onset of symptoms. The prevalence of HD is between three and seven individuals per 100,000 in populations of western European descent. In North America, an estimated 30,000 people have HD, while an additional 200,000 people are at risk of inheriting the disease from an affected parent. The disease is caused by an expansion of uninterrupted trinucleotide CAG repeats in the “mutant” huntingtin (Htt) gene, leading to production of HTT (Htt protein) with an expanded poly-glutamine (polyQ) stretch, also known as a “CAG repeat” sequence. There are no current small molecule therapies targeting the underlying cause of the disease, leaving a high unmet need for medications that can be used for treating or ameliorating HD. Consequently, there remains a need to identify and provide small molecule compounds for treating or ameliorating HD.

## SUMMARY OF THE INVENTION

[0003] Disclosed herein is a compound having the structure of Formula (I''), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I''),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is absent, -CH<sub>2</sub>-, -O-, -OCH<sub>2</sub>-, -S-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

or R<sup>3</sup> and one of R<sup>4</sup> are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -OCH<sub>2</sub>R<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

wherein at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

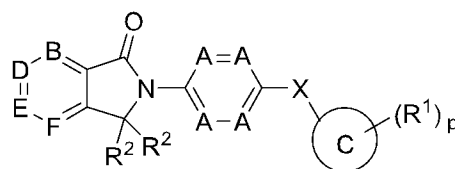
each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

[0004] In another aspect, disclosed herein is a compound having the structure of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

two R<sup>2</sup> are taken together to form an oxo;

X is absent, -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup> and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

one of R<sup>6</sup> or R<sup>7</sup> is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and the other of R<sup>6</sup> or R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; wherein R<sup>7</sup> is not pyridyl substituted with two methoxy groups;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>c</sup>; or two R<sup>10</sup> come together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -

C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

**[0005]** Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

**[0006]** Also disclosed herein is a method of treating a neurodegenerative disease or disorder in a patient in need thereof, the method comprising administering to the patient a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof.

**[0007]** In some embodiments, the neurodegenerative disease or disorder is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease (HD), Parkinson's disease, Prion disease, and spinocerebellar ataxias. In some embodiments, the neurodegenerative disease or disorder is Huntington's disease (HD).

**[0008]** Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

## DETAILED DESCRIPTION OF THE INVENTION

**[0009]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

**[0010]** 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.

**[0011]** 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.

**[0012]** The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0013] “oxo” refers to =O.

[0014] “Carboxyl” refers to -COOH.

[0015] “Cyano” refers to -CN.

[0016] “Alkyl” 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 “C<sub>1</sub>-C<sub>6</sub> alkyl” or “C<sub>1-6</sub>alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C<sub>1-10</sub>alkyl. In some embodiments, the alkyl is a C<sub>1-6</sub>alkyl. In some embodiments, the alkyl is a C<sub>1-5</sub>alkyl. In some embodiments, the alkyl is a C<sub>1-4</sub>alkyl. In some embodiments, the alkyl is a C<sub>1-3</sub>alkyl. Unless stated otherwise specifically in the specification, an alkyl 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 alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0017] “Alkenyl” 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* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH<sub>2</sub>), 1-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), isopropenyl [-C(CH<sub>3</sub>)=CH<sub>2</sub>], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C<sub>2</sub>-C<sub>6</sub> alkenyl” or “C<sub>2-6</sub>alkenyl”, 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 oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0018] “Alkynyl” 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-butylnyl,

1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C<sub>2</sub>-C<sub>6</sub> alkynyl” or “C<sub>2-6</sub>alkynyl”, 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 oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

**[0019]** “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene 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 alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

**[0020]** “Alkoxy” refers to a radical of the formula -OR<sub>a</sub> where R<sub>a</sub> is an alkyl radical as defined. 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, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

**[0021]** “Aryl” refers to a radical derived from an aromatic monocyclic or aromatic polycyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or aromatic polycyclic hydrocarbon ring system can contain only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2)  $\pi$ -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) 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 anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may

be optionally substituted, for example, with halogen, amino, nitrile, 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 halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

**[0022]** “Carbocycle” refers to a saturated, unsaturated, or aromatic rings in which each atom of the ring is carbon. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. An aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated, and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Unless stated otherwise specifically in the specification, a carbocycle may be optionally substituted.

**[0023]** “Cycloalkyl” refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C<sub>3</sub>-C<sub>15</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>15</sub> cycloalkenyl), from three to ten carbon atoms (e.g., C<sub>3</sub>-C<sub>10</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl), from three to eight carbon atoms (e.g., C<sub>3</sub>-C<sub>8</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkenyl), from three to six carbon atoms (e.g., C<sub>3</sub>-C<sub>6</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkenyl), from three to five carbon atoms (e.g., C<sub>3</sub>-C<sub>5</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>5</sub> cycloalkenyl), or three to four carbon atoms (e.g., C<sub>3</sub>-C<sub>4</sub> fully saturated cycloalkyl or C<sub>3</sub>-C<sub>4</sub> 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, decalyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, 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 oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a

cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

**[0024]** "Cycloalkenyl" refers to an unsaturated non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, preferably having from three to twelve carbon atoms and comprising at least one double bond. In certain embodiments, a cycloalkenyl comprises three to ten carbon atoms. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls includes, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

**[0025]** "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

**[0026]** As used herein, the term "haloalkyl" or "haloalkane" refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally further substituted. Examples of halogen substituted alkanes ("haloalkanes") include halomethane (*e.g.*, chloromethane, bromomethane, fluoromethane, iodomethane), di-and trihalomethane (*e.g.*, trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other suitable combinations of alkanes (or substituted alkanes) and halogens (*e.g.*, Cl, Br, F, I, etc.). When an alkyl group is substituted with more than one halogen radicals, each halogen may be independently selected *e.g.*, 1-chloro,2-fluoroethane.

**[0027]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

**[0028]** "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.

**[0029]** "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

**[0030]** "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<sub>1</sub>-C<sub>6</sub> 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<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH(CH<sub>3</sub>)OCH<sub>3</sub>, -CH<sub>2</sub>NHCH<sub>3</sub>, -CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>. 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<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

**[0031]** “Heterocycloalkyl” refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one 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, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), 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 (e.g., C<sub>2</sub>-C<sub>15</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>15</sub> heterocycloalkenyl), from two to ten carbon atoms (e.g., C<sub>2</sub>-C<sub>10</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>10</sub> heterocycloalkenyl), from two to eight carbon atoms (e.g., C<sub>2</sub>-C<sub>8</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>8</sub> heterocycloalkenyl), from two to seven carbon atoms (e.g., C<sub>2</sub>-C<sub>7</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>7</sub> heterocycloalkenyl), from two to six carbon atoms (e.g., C<sub>2</sub>-C<sub>6</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>6</sub> heterocycloalkenyl), from two to five carbon atoms (e.g., C<sub>2</sub>-C<sub>5</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>5</sub> heterocycloalkenyl), or two to four carbon atoms (e.g., C<sub>2</sub>-C<sub>4</sub> fully saturated heterocycloalkyl or C<sub>2</sub>-C<sub>4</sub> heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, 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-

thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term 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 oxo, halogen, amino, nitrile, 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 oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

**[0032]** “Heteroaryl” 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, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) 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, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, 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 halogen, amino, nitrile, 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 halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

**[0033]** The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH, of the structure. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched, and unbranched, carbocyclic, and heterocyclic, aromatic, and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

**[0034]** The term “one or more” when referring to an optional substituent means that 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.

**[0035]** The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

**[0036]** The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

**[0037]** The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

**[0038]** The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17)

isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

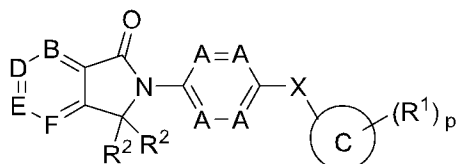
**[0039]** An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

**[0040]** The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

### Compounds of the disclosure

**[0041]** Described herein are compounds, or a pharmaceutically acceptable salts or solvates thereof useful in the treatment of neurodegenerative disorders.

**[0042]** In one aspect, the disclosure provides a compound represented by Formula (I’), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I’),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is absent, -CH<sub>2</sub>-, -O-, -OCH<sub>2</sub>-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each  $R^4$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

or  $R^3$  and one of  $R^4$  are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

$R^5$ ,  $R^6$ ,  $R^7$  or  $R^8$  are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

wherein at least one of  $R^5$ ,  $R^6$ ,  $R^7$  or  $R^8$  is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>c</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

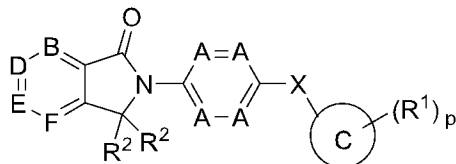
R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-

C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

**[0043]** In another aspect, the disclosure provides a compound represented by Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

two R<sup>2</sup> are taken together to form an oxo;

X is absent, -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-; wherein

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup> and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

one of R<sup>6</sup> or R<sup>7</sup> is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and the other of R<sup>6</sup> or R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; wherein R<sup>7</sup> is not pyridyl substituted with two methoxy groups;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>c</sup>; or two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

**[0044]** In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently halogen. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In

some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently -OH. In some embodiments of Formula (I''), (I'), or (I), each R<sup>2</sup> is independently hydrogen.

**[0045]** In some embodiments of Formula (I''), (I'), or (I), two R<sup>2</sup> together with the atom to which they are attached form an oxo.

**[0046]** In some embodiments of Formula (I''), (I'), or (I), D is CR<sup>6</sup>. In some embodiments of Formula (I''), (I'), or (I), D is N.

**[0047]** In some embodiments of Formula (I'') or (I'), R<sup>6</sup> is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of Formula (I''), (I'), or (I), R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of Formula (I''), (I'), or (I), R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>7</sup> is hydrogen.

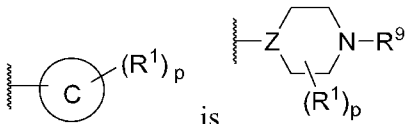
**[0048]** In some embodiments of Formula (I'') or (I'), R<sup>7</sup> is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R<sup>10</sup>; wherein R<sup>7</sup> is not pyridyl substituted with two methoxy groups; and R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of Formula (I''), (I'), or (I), R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R<sup>10</sup>; wherein R<sup>7</sup> is not pyridyl substituted with two methoxy groups; and R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of Formula (I''), (I'), or (I), R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>6</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>6</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), or (I), R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and R<sup>6</sup> is hydrogen.

**[0049]** In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 10-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 8-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 6-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 6-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 7-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 8-membered heterocycloalkenylene.

**[0050]** In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 10-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 5-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 6-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 7-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 8-membered heterocycloalkyl.

[0051] In some embodiments of Formula (I''), (I'), or (I), ring C is piperidine, piperazine, or morpholine. In some embodiments of Formula (I''), (I'), or (I), ring C is piperidine. In some embodiments of Formula (I''), (I'), or (I), ring C is piperazine. In some embodiments of Formula (I''), (I'), or (I), ring C is morpholine.

[0052] In some embodiments of Formula (I''), (I'), or (I),  is ,  
wherein,

Z is CH or N;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or  
two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

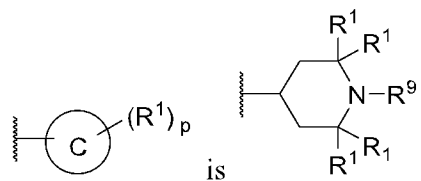
R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; and

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl.

[0053] In some embodiments of Formula (I''), (I'), or (I),



wherein,

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>e</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

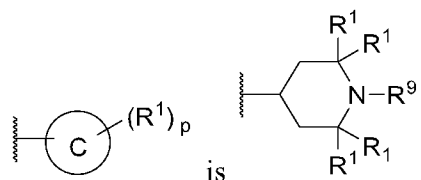
two  $R^1$  are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or two  $R^1$  are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>e</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; and

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl.



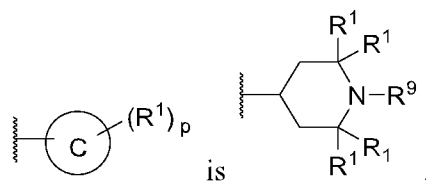
[0054] In some embodiments of Formula (I''), (I'), or (I),

wherein,

each  $R^1$  is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

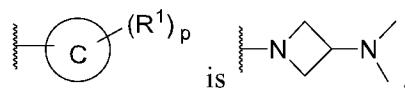
R<sup>9</sup> is hydrogen.

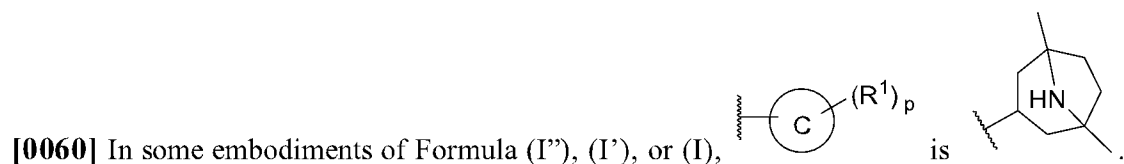
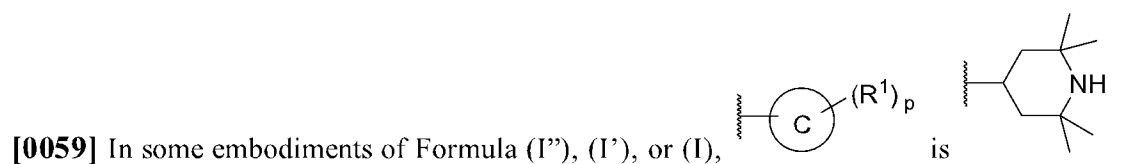
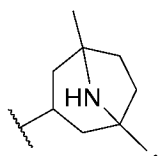
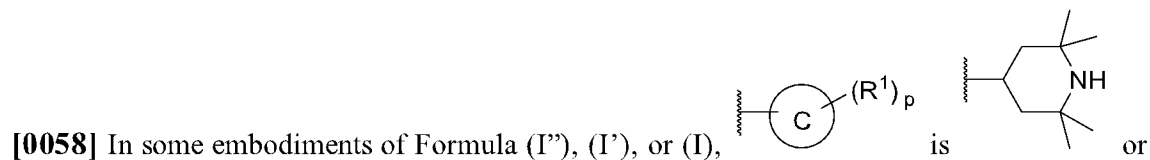
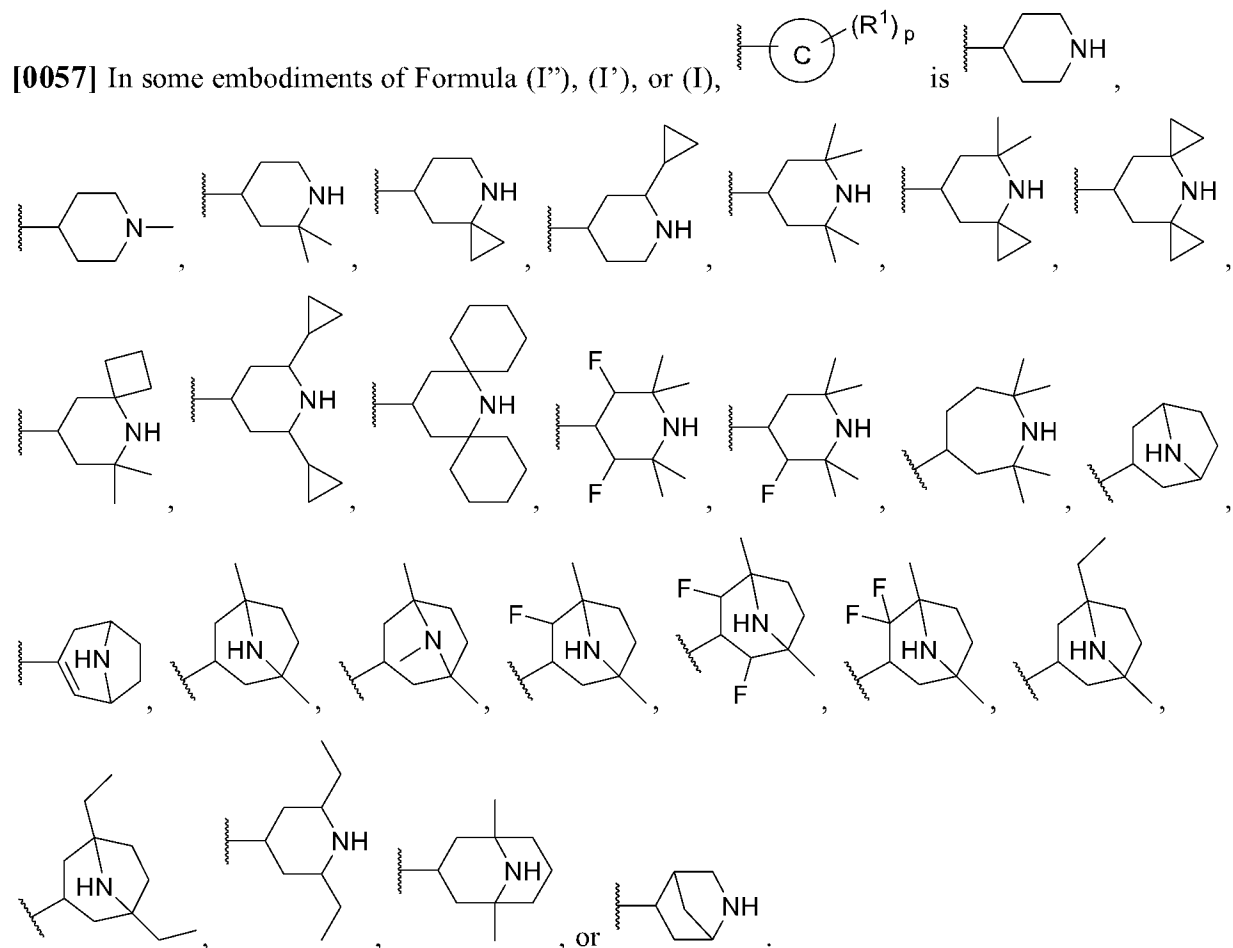


wherein,

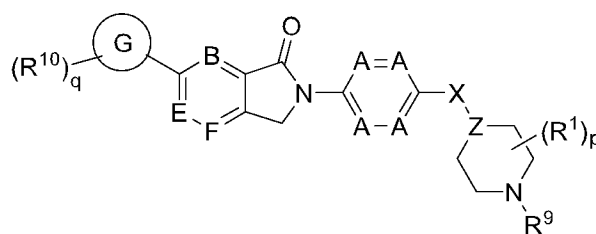
two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene; or

R<sup>9</sup> is hydrogen.





[0061] In another aspect, the disclosure provides a compound represented by Formula (II'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

X is bond, -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-, wherein

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

Z is CH or N, when X is -O-, -S-, or -NR<sup>3</sup>-, then Z is CH;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

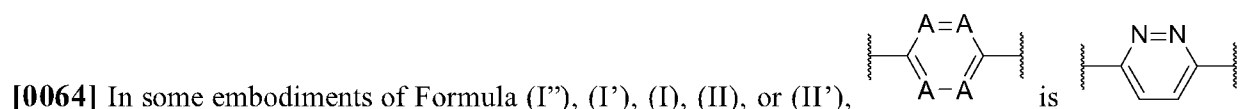
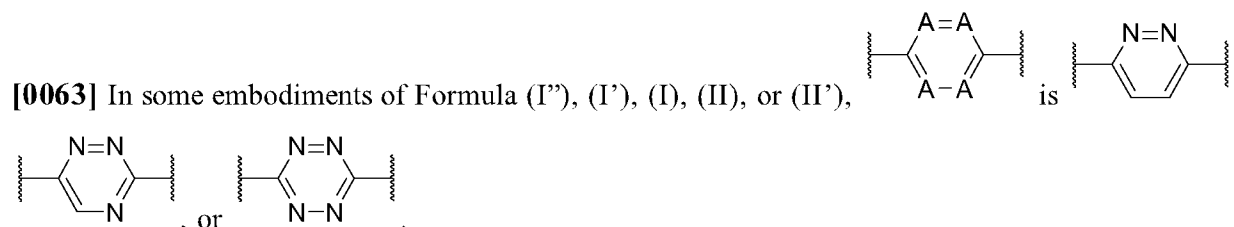
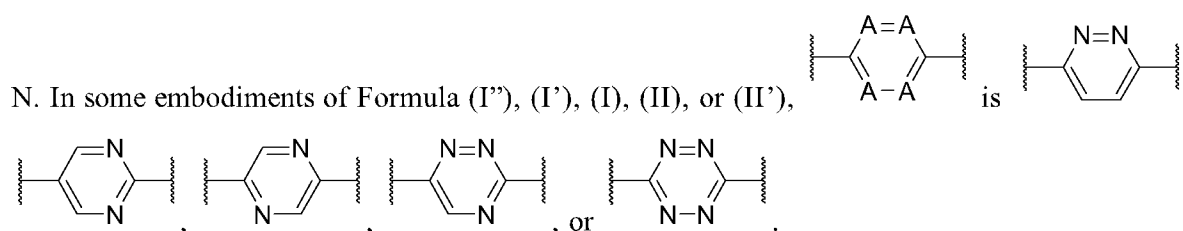
R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl;

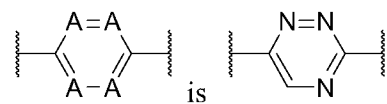
p is 8; and

q is 0, 1, 2, or 3.

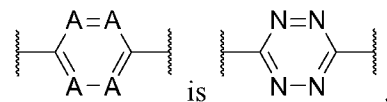
**[0062]** In some embodiments of Formula (I''), (I'), or (II'), two of A are N. In some embodiments of Formula (I''), (I'), or (II'), three of A are N. In some embodiments of Formula (I''), (I'), or (II'), each A is



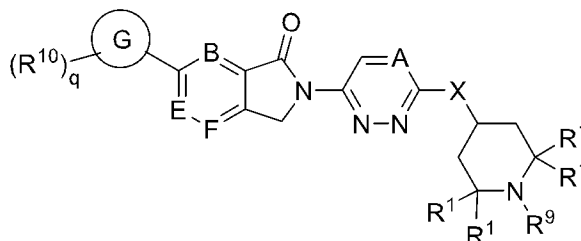
[0065] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),



[0066] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),



[0067] In some embodiments, the disclosure provides a compound represented by Formula (III'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

X is -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-; wherein

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

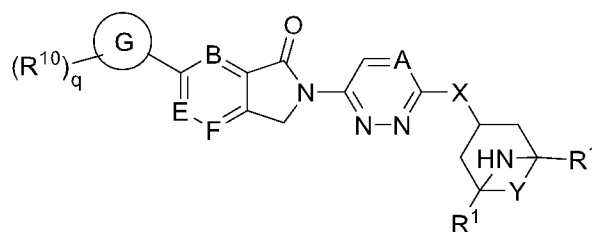
q is 0, 1, 2, or 3.

**[0068]** In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>. In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R<sup>9</sup> is hydrogen.

**[0069]** In some embodiments of Formula (II), (II), (III), or (III'), two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (II), (II), (III), or (III'), two R<sup>1</sup> are taken together to form a bond. In some embodiments of Formula (II),

(II'), (III), or (III'), two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene. In some embodiments of Formula (II), (II'), (III), or (III'), two R<sup>1</sup> are taken together to form or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene.

**[0070]** In some embodiments, the compound of Formula (III') has the structure of Formula (IIIa'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa'),

wherein,

Y is C<sub>1</sub>-C<sub>3</sub>alkylene

ring G is a 5 to 10-membered heteroaryl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

X is -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-, wherein

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each  $R^b$  is independently hydrogen,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

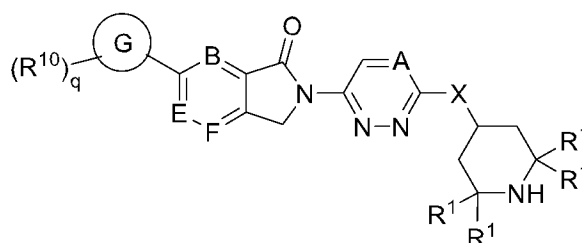
$R^c$  and  $R^d$  are each independently hydrogen,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

each  $R^e$  is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>,  $C_1$ - $C_6$ 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,  $C_3$ - $C_6$ cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

**[0071]** In some embodiments of Formula (IIIa'), Y is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-. In some embodiments of Formula (IIIa'), Y is -CH<sub>2</sub>CH<sub>2</sub>-. In some embodiments of Formula (IIIa'), Y is -CH<sub>2</sub>-.

**[0072]** In some embodiments, the compound of Formula (III') has the structure of Formula (IIIb'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl, or  $C_1$ - $C_6$ aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ; or

two  $R^1$  are taken together to form a  $C_3$ - $C_6$ cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

X is -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-, wherein

$R^3$  is hydrogen,  $C_1$ - $C_3$ alkyl,  $C_1$ - $C_3$ hydroxyalkyl,  $C_1$ - $C_3$ haloalkyl, or  $C_3$ - $C_6$  cycloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>c</sup>; or two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

**[0073]** In some embodiments of Formula (II'), when X is -O-, -S-, or -NR<sup>3</sup>-, then Z is CH. In some embodiments of Formula (II) or (II'), when X is bond, then Z is CH or N. In some embodiments of Formula (II) or (II'), when X is bond, then Z is N. In some embodiments of Formula (II) or (II'), when X

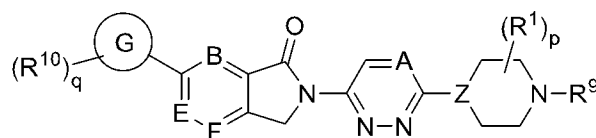
is  $-\text{CH}_2-$ , then Z is CH or N. In some embodiments of Formula (II) or (II'), when X is  $-\text{CH}_2-$ , then Z is CH. In some embodiments of Formula (II) or (II'), when X is  $-\text{CH}_2-$ , then Z is N.

**[0074]** In some embodiments of Formula (I''), (I'), or (II'), X is  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}^3-$ . In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is  $-\text{O}-$  or  $-\text{NR}^3-$ . In some embodiments of Formula (I''), (I'), or (II'), X is  $-\text{S}-$ . In some embodiments of Formula (I''), (I'), (I), (II), (II') (III), (III') (IIIa), (IIIa'), (IIIb), or (IIIb'), X is  $-\text{O}-$ . In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is  $-\text{NR}^3-$ . In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is  $-\text{NH}-$ . In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (II'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is  $-\text{NCH}_3-$ . In some embodiments of Formula (I'), (I), (II), (III), (IIIa), or (IIIb), X is  $-\text{CH}_2$ . In some embodiments of Formula (I''), X is  $-\text{OCH}_2-$ .

**[0075]** In some embodiments of Formula (I''), (I'), (I), (II), or (II'), X is absent.

**[0076]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is hydrogen,  $\text{C}_1$ - $\text{C}_3$ alkyl, or  $\text{C}_1$ - $\text{C}_3$ hydroxyalkyl. In some embodiments of Formula (I''), (I'), (II'), (IIIa'), or (IIIb),  $\text{R}^3$  is  $\text{C}_3$ - $\text{C}_6$ cycloalkyl. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), or (IIIb'),  $\text{R}^3$  is cyclopropyl or cyclobutyl. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), or (IIIb'),  $\text{R}^3$  is cyclopropyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is hydrogen or  $\text{C}_1$ - $\text{C}_3$ alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is  $\text{C}_1$ - $\text{C}_3$ hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is  $\text{C}_1$ - $\text{C}_3$ haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is  $\text{C}_1$ - $\text{C}_3$ alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is hydrogen or methyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is methyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'),  $\text{R}^3$  is hydrogen.

**[0077]** In another aspect, the disclosure provides a compound represented by Formula (IV'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each  $\text{R}^1$  is independently hydrogen, halogen,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{OH}$ ,  $-\text{OR}^a$ ,  $-\text{SH}$ ,  $-\text{SR}^a$ ,  $-\text{NR}^c\text{R}^d$ ,  $\text{C}_1$ - $\text{C}_6$ alkyl,

$\text{C}_1$ - $\text{C}_6$ haloalkyl,  $\text{C}_1$ - $\text{C}_6$ hydroxyalkyl, or  $\text{C}_1$ - $\text{C}_6$ aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from  $\text{R}^e$ ; or

two  $\text{R}^1$  are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

Z is CH or N;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl;

p is 8; and

q is 0, 1, 2, or 3.

**[0078]** In some embodiments of Formula (II), (II'), (IV), or (IV'), Z is N. In some embodiments of Formula (II), (II'), (IV), or (IV'), Z is CH.

**[0079]** In some embodiments of Formula (I''), (I'), (I), (II), or (II'), at least one of A is N.

**[0080]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is N. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is independently CR<sup>4</sup>.

**[0081]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is independently N or CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is CH.

**[0082]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV'), or (IV'), B is CR<sup>5</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), B is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), B is N.

**[0083]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is CR<sup>7</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is N.

**[0084]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is CR<sup>8</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is N.

**[0085]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl.

(IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -CF<sub>3</sub>, or -CHF<sub>2</sub>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen, -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, or -CH(CH<sub>3</sub>)<sub>2</sub>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently Cl, Br, or F. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently F. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>1</sup> is independently hydrogen.

**[0086]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a cyclopropyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a cyclobutyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a cyclopentyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form a cyclohexyl.

**[0087]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>1</sup> are taken together to form an oxo.

**[0088]** In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently hydrogen, halogen, -CN, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently halogen. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R<sup>4</sup> is independently hydrogen.

**[0089]** In some embodiments of Formula (I''), R<sup>3</sup> and one of R<sup>4</sup> are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene.

**[0090]** In some embodiments of Formula (I''), R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl;

wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; and wherein at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 8 membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>. In some embodiments of Formula (I''), R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl. In some embodiments of Formula (I''), R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> are independently hydrogen, halogen, -CN, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 5 to 10-membered heteroaryl.

**[0091]** In some embodiments of Formula (I''), R<sup>5</sup> is 5 to 10-membered heteroaryl; and R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), R<sup>6</sup> is 5 to 10-membered heteroaryl; and R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), R<sup>7</sup> is 5 to 10-membered heteroaryl; and R<sup>5</sup>, R<sup>6</sup> and R<sup>8</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), R<sup>8</sup> is 5 to 10-membered heteroaryl; and R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, halogen, -CN, -NO<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0092]** In some embodiments of Formula (I''), B is CR<sup>5</sup>, wherein R<sup>5</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; and F is N.

**[0093]** In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR<sup>6</sup>, wherein R<sup>6</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; and E is N. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR<sup>6</sup>, wherein R<sup>6</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; and F is N. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR<sup>6</sup>, wherein R<sup>6</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; B is N; and F is N. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR<sup>6</sup>, wherein R<sup>6</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; E is N; and F is N.

**[0094]** In some embodiments of Formula (I''), F is CR<sup>8</sup>, wherein R<sup>8</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl,

heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>e</sup>; and E is N.

**[0095]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is fluorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>5</sup> is chlorine.

**[0096]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'),

(IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>6</sup> is hydrogen.

**[0097]** In some embodiments of Formula (I'') (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is fluorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is chlorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>7</sup> is hydroxyl. In some embodiments of Formula (I'), (I), (II), (III), (IIIa), (IIIb), or (IV), R<sup>7</sup> is methoxy.

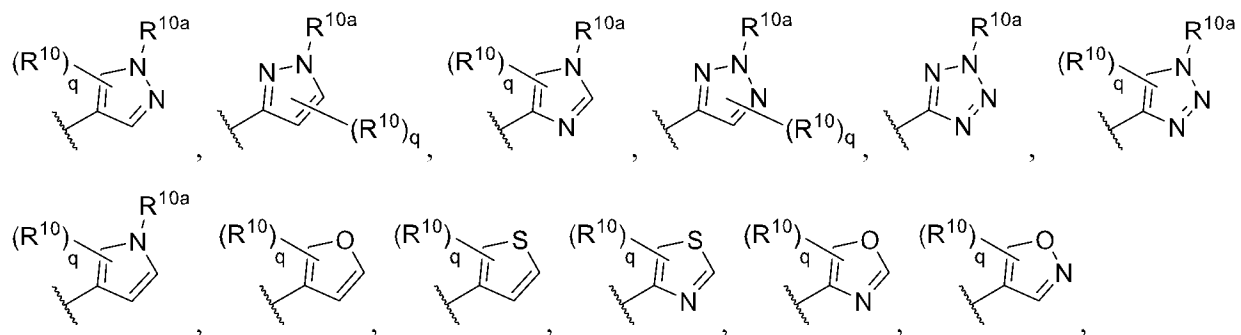
**[0098]** In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is C<sub>1</sub>-C<sub>6</sub>alkyl. In some

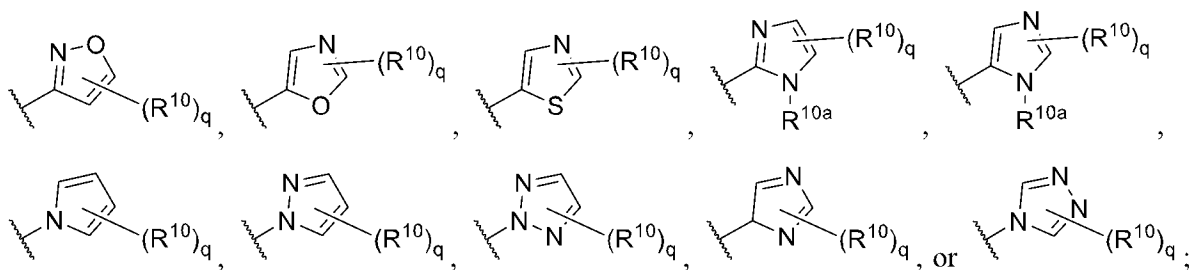
embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is flourine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R<sup>8</sup> is chlorine.

**[0099]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R<sup>10</sup>.

**[0100]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from R<sup>10</sup>. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, oxazole, triazole, thiazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, oxazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is imidazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is oxazole.

**[0101]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is:





wherein,

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl,

wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>;

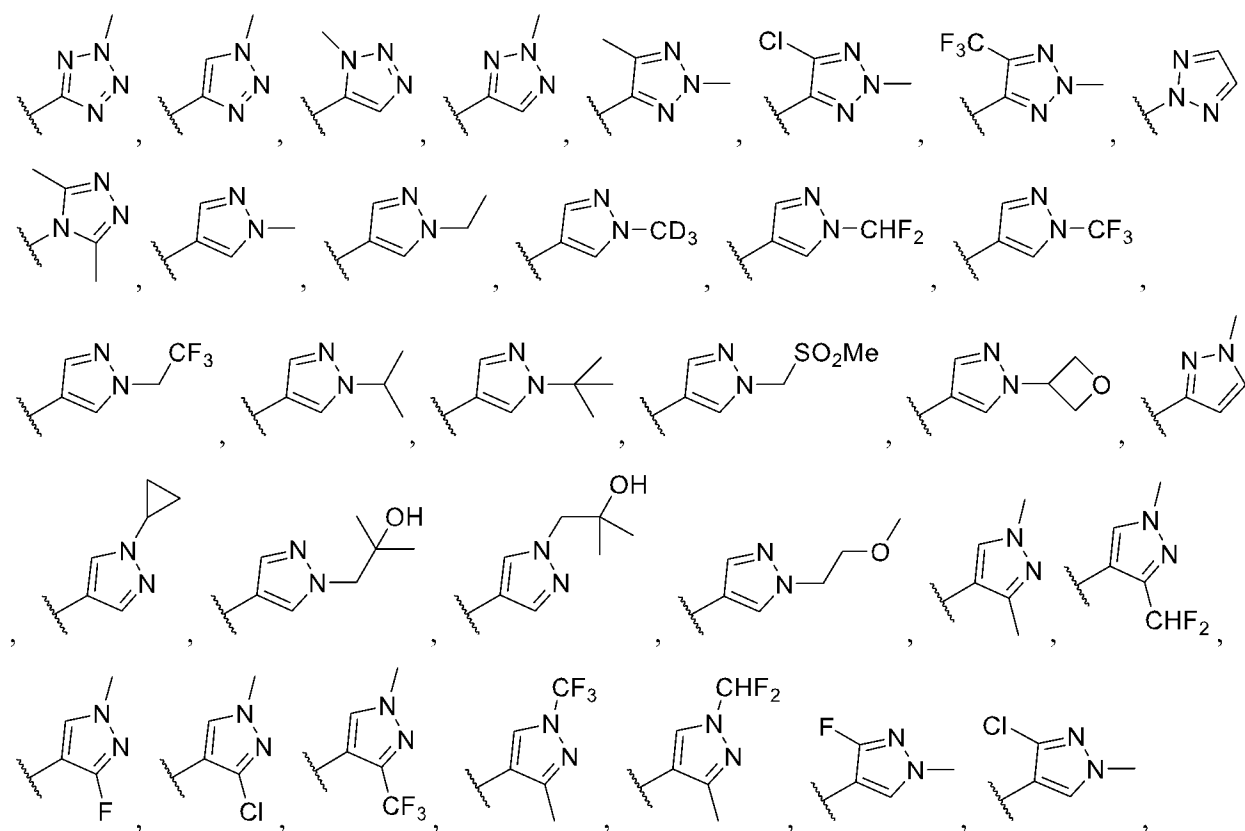
each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; and

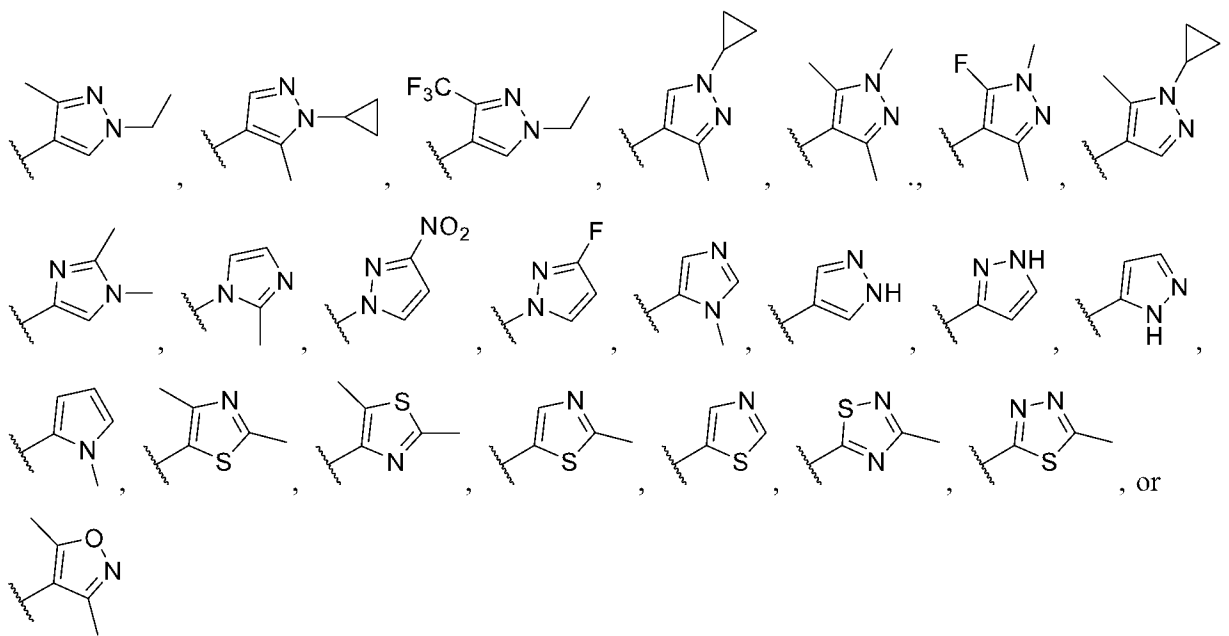
q is 0, 1, 2, or 3.

**[0102]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'): each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and p is 0, 1, or 2.

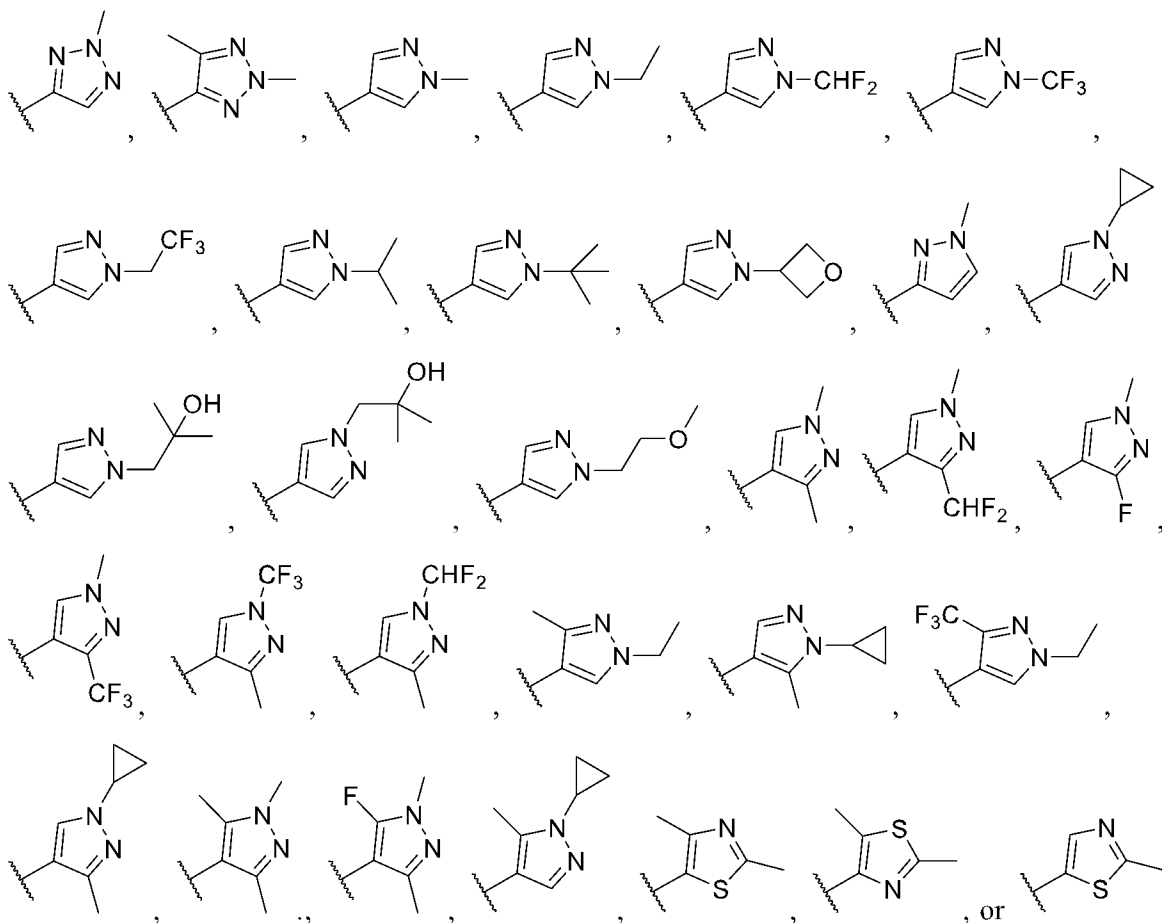
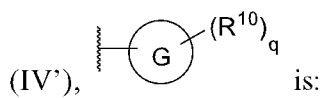
**[0103]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or

(IV'),  $\text{---G---}(R^{10})_q$  is:

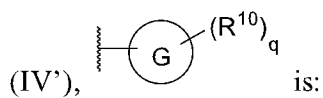


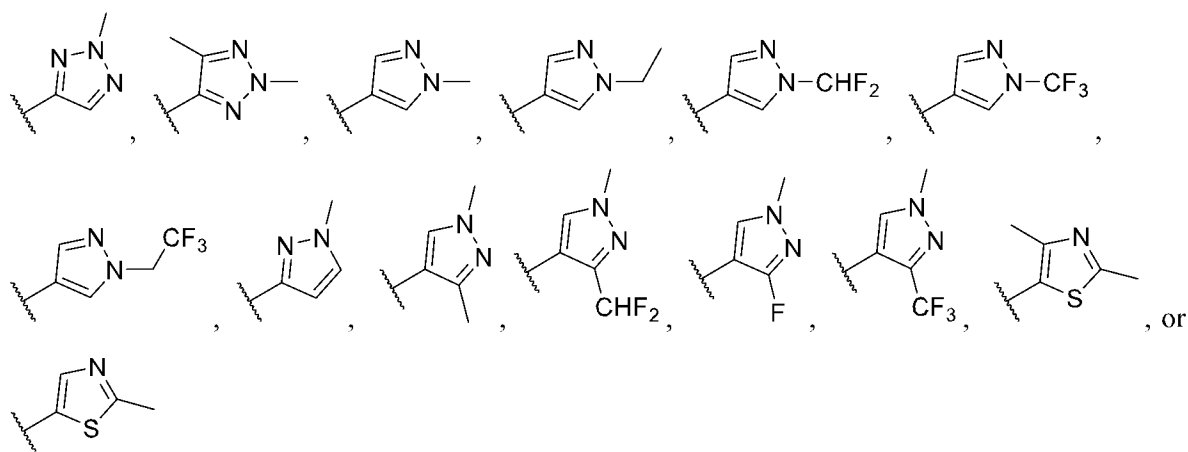


[0104] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or

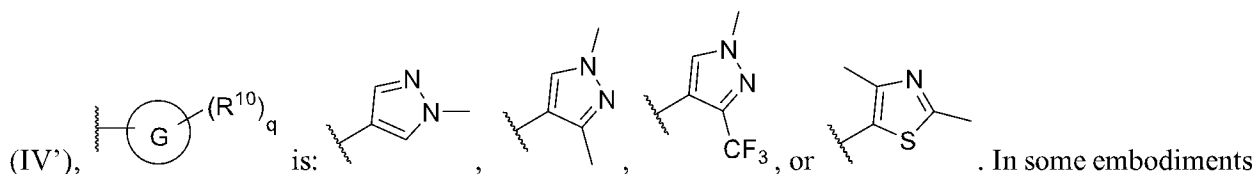


[0105] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or

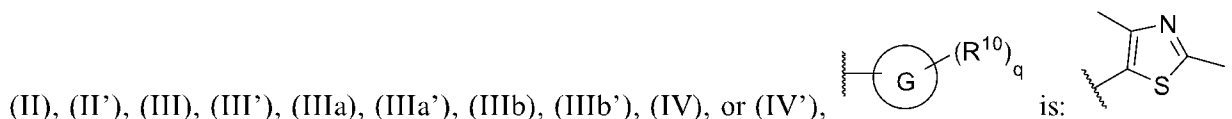
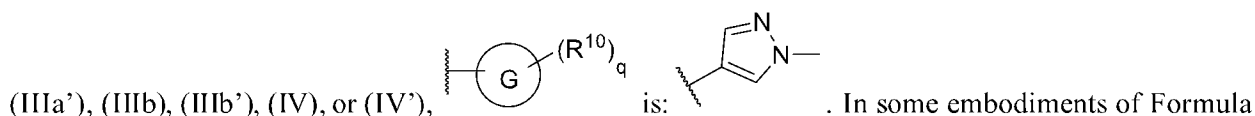
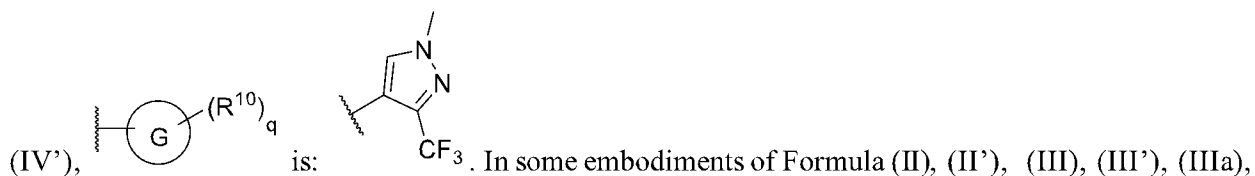
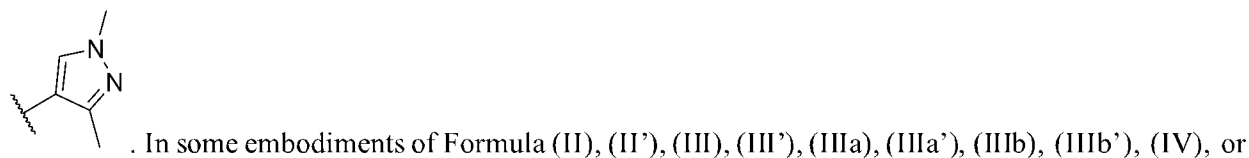




**[0106]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



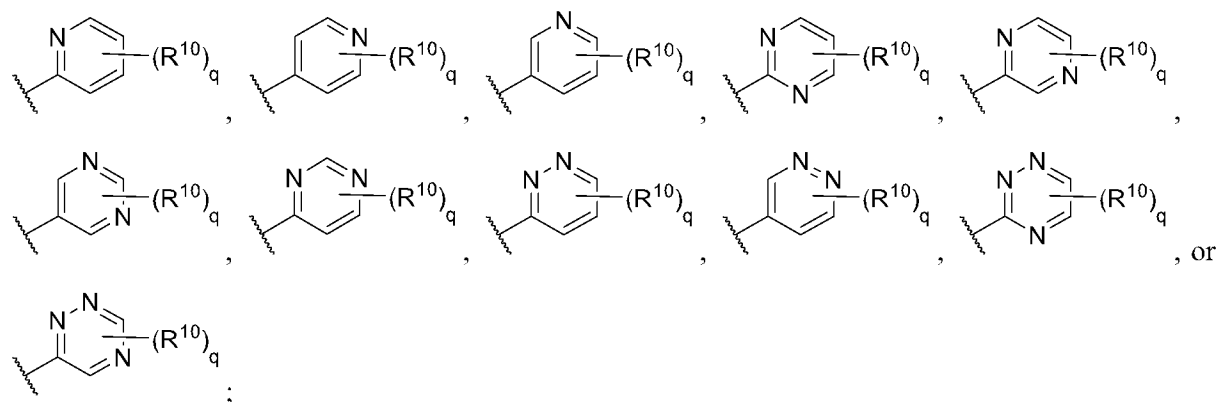
of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), is:



**[0107]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R<sup>10</sup>.

**[0108]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyridine, pyrimidine, or triazine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyridine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrimidine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is triazine.

**[0109]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is:



wherein,

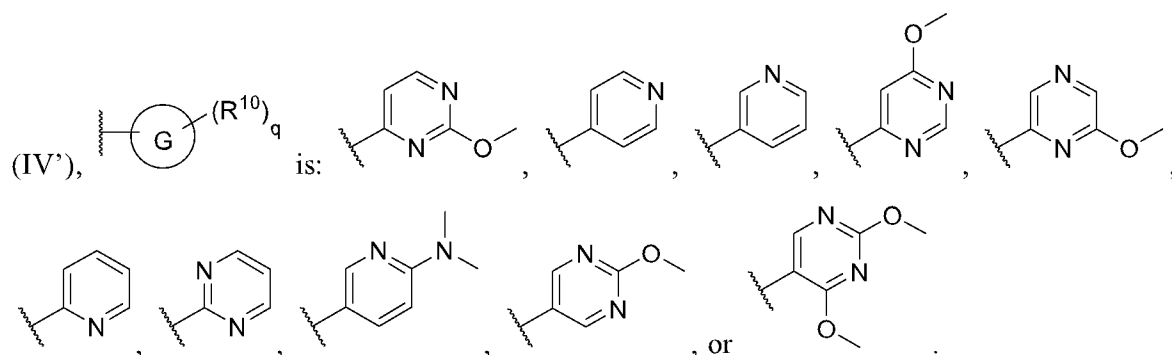
each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl,

wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>c</sup>; and

q is 0, 1, 2, or 3.

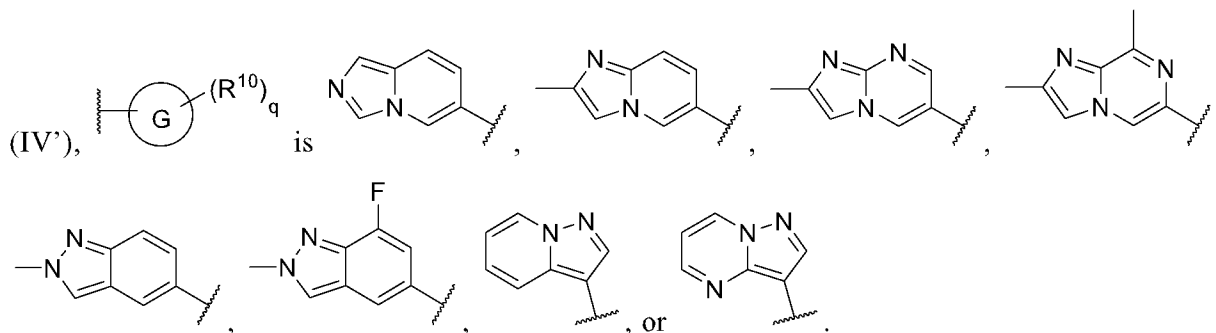
**[0110]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



**[0111]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8 to 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>10</sup>. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>10</sup>. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>10</sup>. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R<sup>10</sup>.

**[0112]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, pyrazolo[1,5-a]pyridine, pyrazolo[1,5-a]pyrimidine, or 2-methyl-2H-indazole.

**[0113]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



**[0114]** In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, or -NR<sup>c</sup>R<sup>d</sup>. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -OH or -OR<sup>a</sup>. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -OH or -OMe. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>CF<sub>3</sub>, or -CH<sub>2</sub>CHF<sub>2</sub>. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -CF<sub>3</sub> or -CHF<sub>2</sub>. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently methyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently halogen. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently fluorine or chlorine. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently fluorine. In some embodiments of

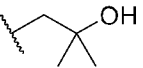
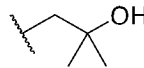
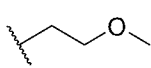
Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently chlorine.

**[0115]** In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -F, -Cl, -CN, methyl, ethyl, -OCH<sub>3</sub>, -CF<sub>3</sub>, -CHF<sub>2</sub>, or -CH<sub>2</sub>F. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10</sup> is independently -F, -Cl, methyl, -CF<sub>3</sub>, or -CHF<sub>2</sub>.

**[0116]** In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), two R<sup>10</sup> are taken together to form an oxo.

**[0117]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently C<sub>3</sub>-C<sub>6</sub>cycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently cyclopropyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently cyclopropyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently 4-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently 5-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently oxatanyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>CF<sub>3</sub>, or -CH<sub>2</sub>CHF<sub>2</sub>. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently methyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently hydrogen.

**[0118]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R<sup>10a</sup> is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, -CD<sub>3</sub>, -CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F,

-CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, cyclopropyl, oxetanyl, , , or .

**[0119]** In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-9. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-8. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-4. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, or 4. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, or 3. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1 or 2. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 2. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1.

**[0120]** In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1, 2, or 3. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 3. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1 or 2. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 2. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 0.

**[0121]** In some embodiments of the compound disclosed herein each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of a compound disclosed herein, each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound disclosed herein, each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>a</sup> is independently methyl, ethyl, isopropyl, tert-butyl, -OCH<sub>3</sub>, -CF<sub>3</sub>, or -CHF<sub>2</sub>. In some embodiments of a compound disclosed herein, each R<sup>a</sup> is independently methyl, ethyl, isopropyl or tertbutyl.

**[0122]** In some embodiments of the compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-

C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is hydrogen. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, -OCH<sub>3</sub>, -CF<sub>3</sub>, or -CHF<sub>2</sub>. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen, methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of a compound disclosed herein, each R<sup>b</sup> is independently hydrogen or methyl.

**[0123]** In some embodiments of the compound disclosed herein, R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl or C<sub>1</sub>-C<sub>6</sub>haloalkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are hydrogen. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently C<sub>1</sub>-C<sub>6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen methyl, ethyl, isopropyl, tert-butyl, -OCH<sub>3</sub>, -CF<sub>3</sub>, or -CHF<sub>2</sub>. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen, methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are independently hydrogen or methyl. In some embodiments of a compound disclosed herein, each R<sup>c</sup> and R<sup>d</sup> are methyl.

**[0124]** In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)C<sub>1</sub>-C<sub>6</sub>alkyl, -S(=O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHC<sub>1</sub>-C<sub>6</sub>alkyl, -S(=O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -NH<sub>2</sub>, -NHC<sub>1</sub>-C<sub>6</sub>alkyl, -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -

C(=O)C<sub>1-6</sub>alkyl, -C(=O)OH, -C(=O)OC<sub>1-6</sub>alkyl, -NHC(=O)C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>hydroxyalkyl, C<sub>1-6</sub>aminoalkyl, C<sub>1-6</sub>heteroalkyl, or C<sub>3-6</sub>cycloalkyl. In some embodiments, R<sup>e</sup> is -NHC(=O)C<sub>1-3</sub>alkyl such as -NHC(=O)CH<sub>3</sub>. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, -CN, -OH, or C<sub>1-6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, -OH, or C<sub>1-6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen or C<sub>1-6</sub>alkyl. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently -Cl or -F. In some embodiments of a compound disclosed herein, each R<sup>e</sup> is independently halogen, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>hydroxyalkyl, C<sub>3-6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments, each R<sup>e</sup> is independently -F, -Cl, -OH, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, methyl, ethyl, isopropyl, tertbutyl, -OCH<sub>3</sub>, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or azetidine, oxytane, piperidine, piperazine, or morpholine. In some embodiments, each R<sup>e</sup> is independently -F, -OH, -CF<sub>3</sub>, -CHF<sub>2</sub>, -OCH<sub>3</sub>, or methyl. In some embodiments, each R<sup>e</sup> is independently -F, -CF<sub>3</sub>, -CHF<sub>2</sub>, or methyl. In some embodiments, each R<sup>e</sup> is methyl.

**[0125]** In some embodiments of a compound disclosed herein, one or more of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>10a</sup>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, and R<sup>e</sup> groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

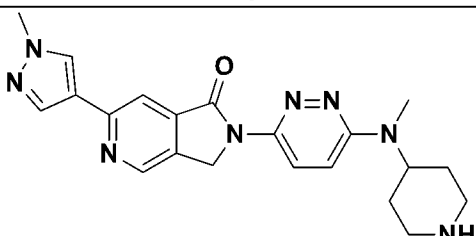
**[0126]** In some embodiments of a compound disclosed herein, one or more <sup>1</sup>H are replaced with one or more deuteriums in one or more of the following groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>10a</sup>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, and R<sup>e</sup>.

**[0127]** In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>10a</sup>, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, and R<sup>e</sup> 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.

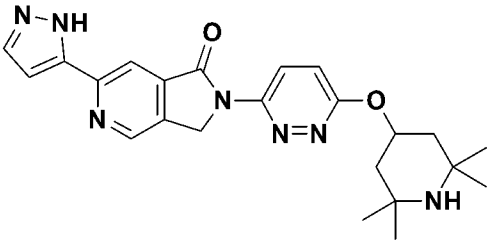
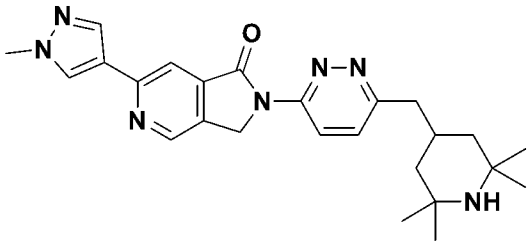
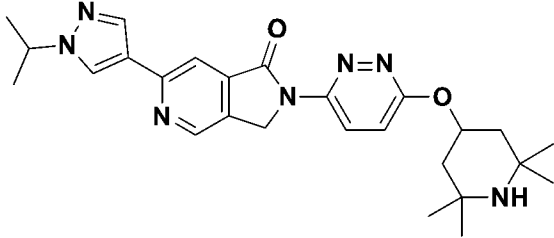
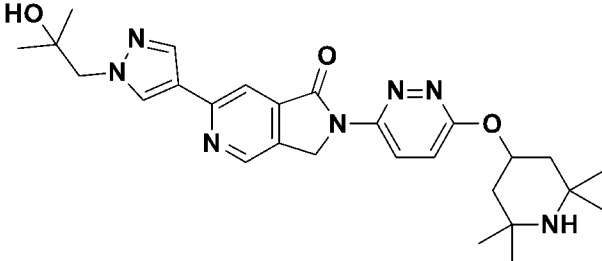
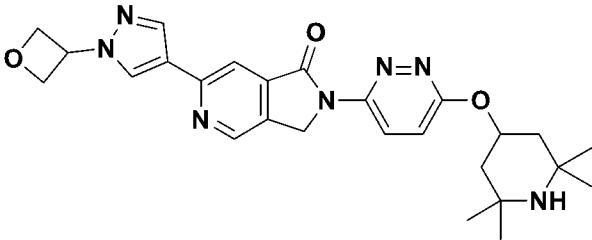
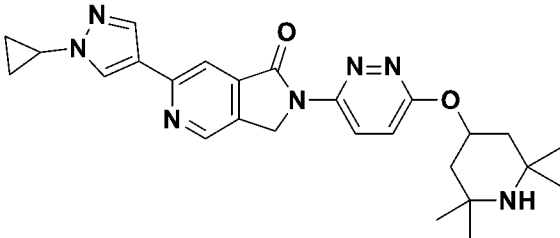
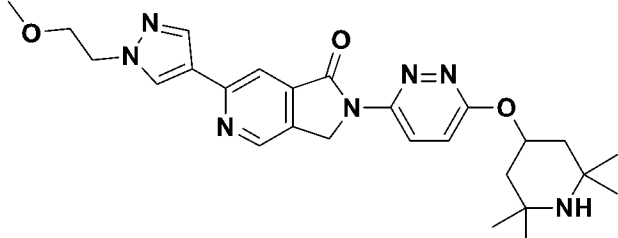
**[0128]** Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

**[0129]** In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, is one of the compounds in **Table 1A**, **Table 1B**, or **Table 1C**.

**TABLE 1A.**

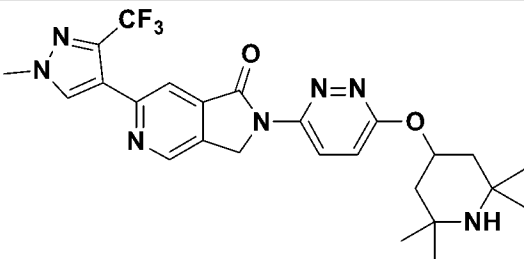
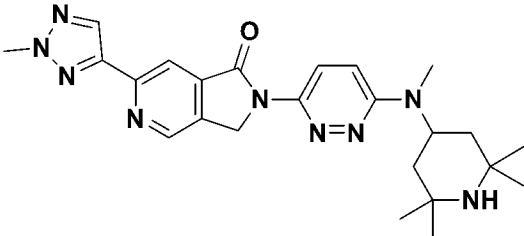
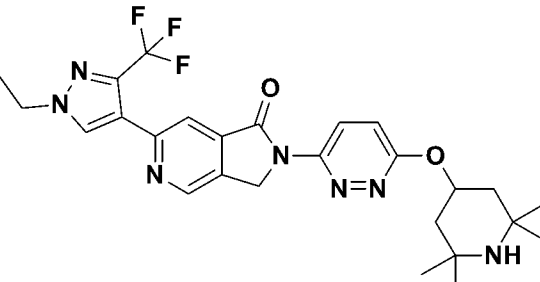
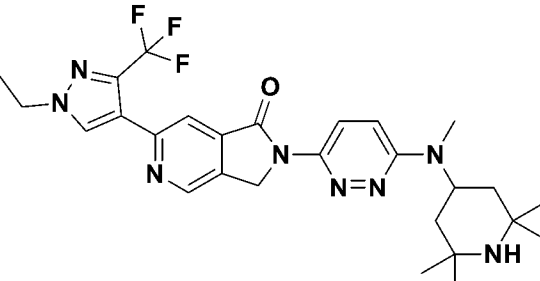
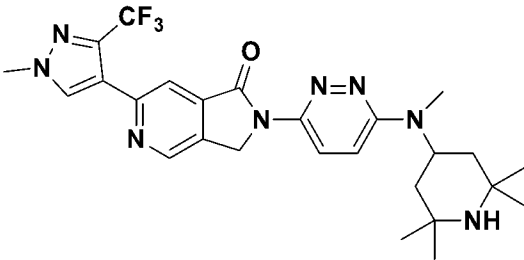
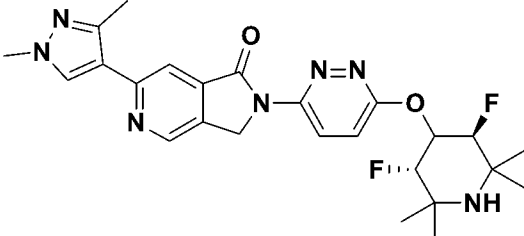
| No. | Chemical Structure                                                                  | Name                                                                                                                      |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| 1   |  | 2-(6-(methyl(piperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |

| No. | Chemical Structure | Name                                                                                                                                         |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 2   |                    | 6-(1-methyl-1H-pyrazol-4-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 3   |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 6   |                    | 6-(1-methyl-1H-pyrazol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 7   |                    | 6-(1,5-dimethyl-1H-pyrazol-4-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 8   |                    | 6-(2,4-dimethoxypyrimidin-5-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 9   |                    | 6-(2-methyl-2H-indazol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 10  |                    | 6-(6-(dimethylamino)pyridin-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                     |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15  |    | 6-(1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                              |
| 17  |    | 6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                  |
| 18  |   | 6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                  |
| 21  |  | 6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 23  |  | 6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one              |
| 24  |  | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                |
| 26  |  | 6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |

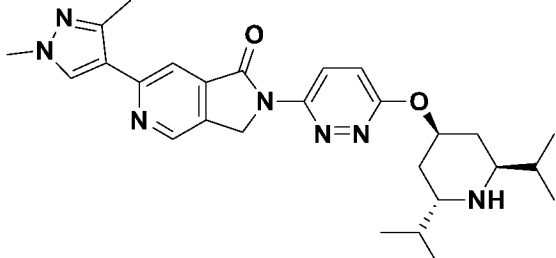
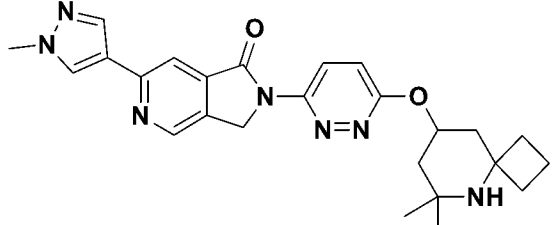
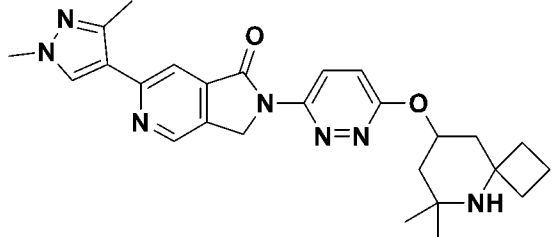
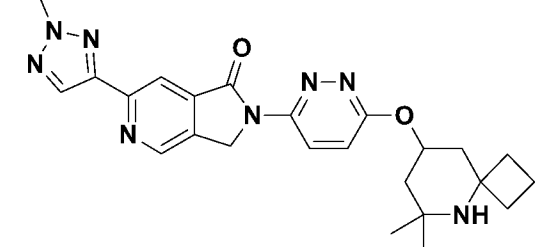
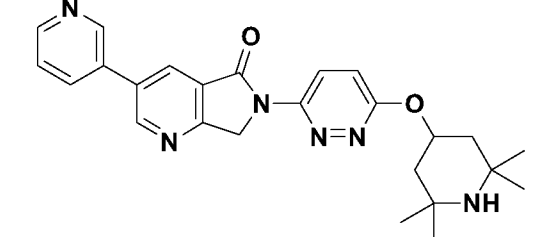
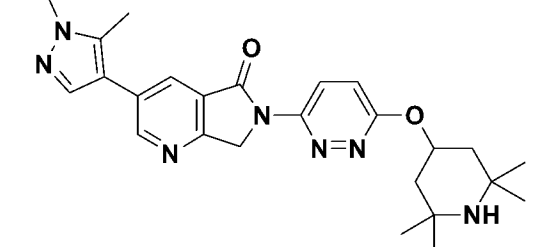
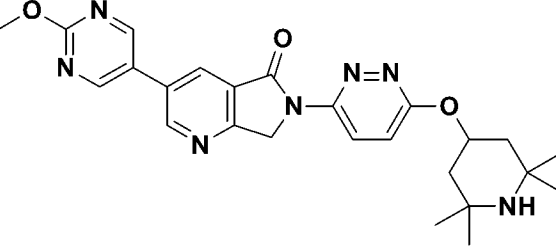
| No. | Chemical Structure | Name                                                                                                                                                   |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28  |                    | 6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 29  |                    | 6-(imidazo[1,5-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |
| 30  |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |
| 31  |                    | 6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one             |
| 35  |                    | 6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 43  |                    | 3-methyl-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one  |
| 47  |                    | 6-(1-ethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |

| No. | Chemical Structure | Name                                                                                                                                                    |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| 49  |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 51  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 54  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |
| 56  |                    | 2-(6-((4-azadispiro[2.1.2^5.3^3]decan-9-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one              |
| 57  |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 58  |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 59  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 63  |    | 6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 64  |    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one               |
| 65  |    | 6-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 66  |  | 6-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one  |
| 71  |  | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 75  |  | 2-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one    |

| No. | Chemical Structure | Name                                                                                                                                                    |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| 76  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                |
| 78  |                    | 6-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 80  |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 81  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 83  |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 84  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |
| 86  |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |

| No. | Chemical Structure | Name                                                                                                                                              |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 88  |                    | 2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 91  |                    | 6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 92  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((1,2,2,6,6-pentamethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 101 |                    | 2-(6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 103 |                    | 2-(6-(((7-azadispiro[5.1.5^8.3^6]hexadecan-15-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one  |
| 104 |                    | 2-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one    |

| No. | Chemical Structure                                                                  | Name                                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| 109 |    | 2-(6-(((2S,6S)-2,6-diisopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one    |
| 113 |    | 2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 115 |    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |
| 119 |   | 2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 134 |  | 3-(pyridin-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 135 |  | 3-(1,5-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 138 |  | 3-(2-methoxypyrimidin-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one             |

| No. | Chemical Structure | Name                                                                                                                                         |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 139 |                    | 3-(6-(dimethylamino)pyridin-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 140 |                    | 3-(imidazo[1,5-a]pyridin-6-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 141 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one     |
| 142 |                    | 3-(2-methyl-2H-indazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 143 |                    | 3-(1H-pyrazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |
| 144 |                    | 3-(1-methyl-1H-pyrazol-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 148 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                                                       |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 149 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 150 |                    | 3-(2,4-dimethylthiazol-5-yl)-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 156 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 160 |                    | 3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one     |
| 161 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-(methyl-d3)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 162 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 163 |                    | 3-(1-cyclopropyl-3-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                                                             |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 167 |                    | 3-(2,4-dimethylthiazol-5-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |
| 168 |                    | 3-(1-cyclopropyl-5-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 172 |                    | 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 173 |                    | 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 176 |                    | 3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 177 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 179 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |

| No. | Chemical Structure | Name                                                                                                                                                    |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| 180 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 182 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 184 |                    | 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 187 |                    | 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one   |
| 189 |                    | 6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 190 |                    | 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 191 |                    | 3-(2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one              |

| No. | Chemical Structure | Name                                                                                                                                                            |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 193 |                    | 3-(2,5-dimethylthiazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                    |
| 195 |                    | 3-(2,4-dimethylthiazol-5-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 198 |                    | 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 203 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(4-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one              |
| 205 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 207 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                      |
| 208 |                    | 2-chloro-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |

| No. | Chemical Structure | Name                                                                                                                                                                |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 210 |                    | 6-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 211 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((3S,4R)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 212 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((3R,4R)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 216 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(5-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |
| 218 |                    | 6-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 221 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                      |
| 222 |                    | 3-(1-methyl-1H-imidazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                               |

| No. | Chemical Structure | Name                                                                                                                                                       |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 223 |                    | 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 224 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one              |
| 225 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2-hydroxyethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 226 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 228 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 230 |                    | 3-(1,2-dimethyl-1H-imidazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |
| 231 |                    | 6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |

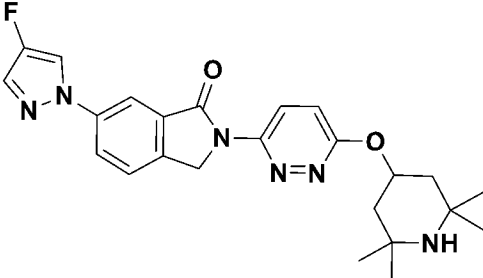
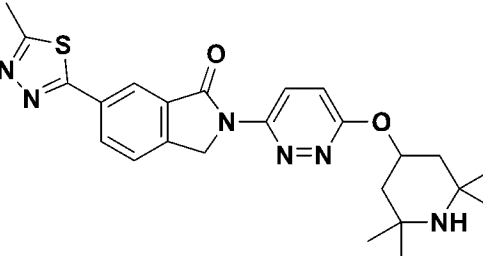
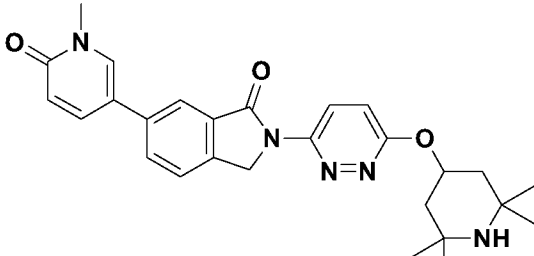
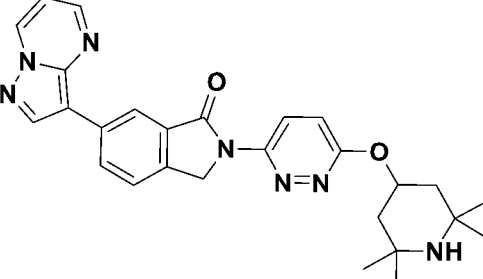
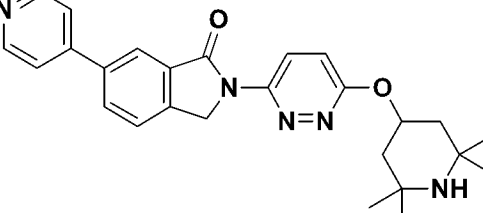
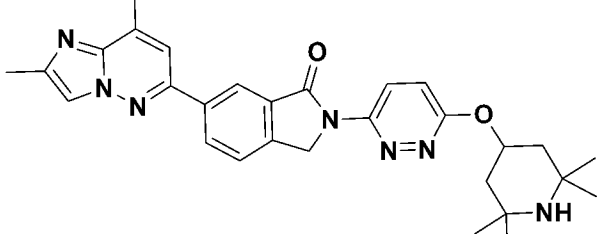
| No. | Chemical Structure | Name                                                                                                                                                                     |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 232 |                    | 6-(6-((4-azadispiro[2.1.2 <sup>5</sup> .3 <sup>3</sup> ]decan-9-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 234 |                    | 3-(2-methyl-1H-imidazol-1-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                    |
| 235 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((1,2,2,6,6-pentamethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                               |
| 237 |                    | 3-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 241 |                    | 6-(6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 243 |                    | 6-(6-(((7-azadispiro[5.1.5 <sup>8</sup> .3 <sup>6</sup> ]hexadecan-15-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 245 |                    | 6-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |

| No. | Chemical Structure | Name                                                                                                                                            |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| 247 |                    | 6-(6-(((2S,6S)-2,6-diisopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 249 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one   |
| 253 |                    | 6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 275 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one                  |
| 276 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                          |
| 277 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one             |
| 279 |                    | 4-fluoro-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one        |

| No. | Chemical Structure | Name                                                                                                                                        |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 280 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(((3R,4S)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one     |
| 282 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                |
| 284 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-4-fluoroisoindolin-1-one                 |
| 285 |                    | 2-(6-(((3R,5R)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one |
| 287 |                    | 6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                          |
| 288 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(((3S,4S)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one     |
| 290 |                    | 6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one                  |

| No. | Chemical Structure | Name                                                                                                                                 |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| 292 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)isoindolin-1-one          |
| 293 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one |
| 308 |                    | 6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                            |
| 309 |                    | 6-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                                     |
| 310 |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(2H-1,2,3-triazol-2-yl)isoindolin-1-one                               |
| 311 |                    | 6-(5-methoxypyrazin-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                               |
| 312 |                    | 6-(2-methoxypyrimidin-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                             |

| No. | Chemical Structure | Name                                                                                                                    |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------|
| 313 |                    | 6-(1-methyl-1H-pyrazol-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one               |
| 314 |                    | 6-(pyrazolo[1,5-a]pyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one            |
| 315 |                    | 6-(7-fluoro-2-methyl-2H-indazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one      |
| 316 |                    | 6-(pyridin-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                           |
| 317 |                    | 6-(pyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                           |
| 318 |                    | 6-(1-methyl-1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one               |
| 319 |                    | 6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one |

| No. | Chemical Structure                                                                  | Name                                                                                                                  |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| 320 |    | 6-(4-fluoro-1H-pyrazol-1-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one                 |
| 321 |    | 6-(5-methyl-1,3,4-thiadiazol-2-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one           |
| 322 |   | 6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one   |
| 323 |  | 6-(pyrazolo[1,5-a]pyrimidin-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one            |
| 324 |  | 6-(pyridin-4-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one                             |
| 325 |  | 6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                      |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------|
| 326 |                    | 6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one   |
| 327 |                    | 6-(pyrimidin-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                           |
| 328 |                    | 6-(2,7-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one |
| 329 |                    | 6-(2,4-dimethoxypyrimidin-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one              |
| 330 |                    | 6-(pyrimidin-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                           |
| 331 |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(thiazol-2-yl)isoindolin-1-one                             |
| 332 |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(thiazol-5-yl)isoindolin-1-one                             |

| No. | Chemical Structure | Name                                                                                                             |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------|
| 333 |                    | 6-(3,5-dimethylisoxazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one       |
| 334 |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)isoindolin-1-one |
| 335 |                    | 6-(2-methyl-2H-indazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one        |
| 336 |                    | 6-(imidazo[1,5-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one      |
| 337 |                    | 6-(1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                 |
| 338 |                    | 6-(1-methyl-1H-imidazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one       |
| 339 |                    | 6-(1,5-dimethyl-1H-pyrazol-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one    |

| No. | Chemical Structure | Name                                                                                                                    |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------|
| 340 |                    | 6-(6-(dimethylamino)pyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one          |
| 341 |                    | 6-(2-methylimidazo[1,2-a]pyrimidin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one   |
| 342 |                    | 6-(1,2-dimethyl-1H-imidazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one          |
| 343 |                    | 6-(2-methylimidazo[1,2-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one     |
| 346 |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one               |
| 347 |                    | 6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one         |
| 348 |                    | 6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                   |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------|
| 349 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one      |
| 350 |                    | 6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one    |
| 351 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one |
| 352 |                    | 6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)isoindolin-1-one           |
| 353 |                    | 6-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)isoindolin-1-one                    |
| 354 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)isoindolin-1-one               |
| 355 |                    | 6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one           |

| No. | Chemical Structure | Name                                                                                                                              |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 356 |                    | 6-(1-methyl-1H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                   |
| 357 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                    |
| 358 |                    | 6-(2-methyl-2H-tetrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                        |
| 359 |                    | 2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one         |
| 360 |                    | 6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                  |
| 362 |                    | 6-(2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                   |
| 363 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one |

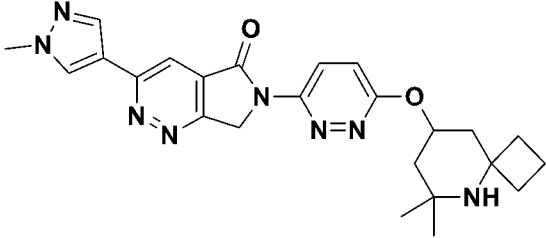
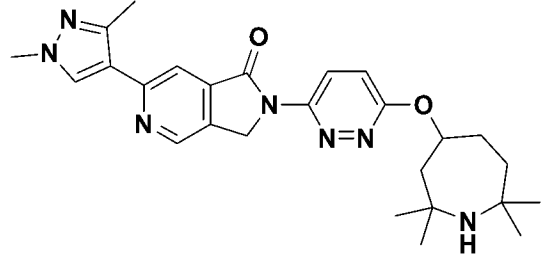
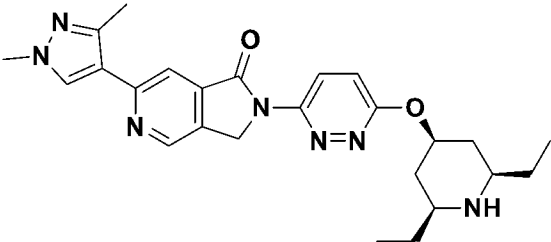
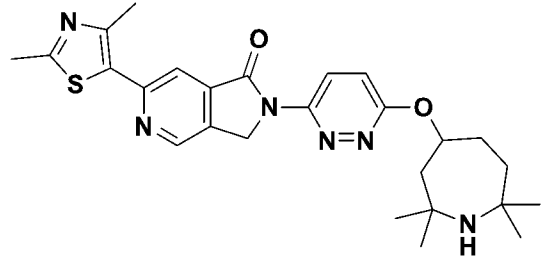
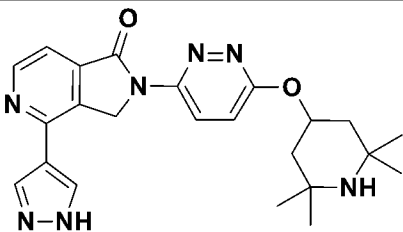
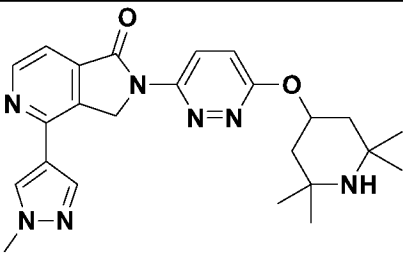
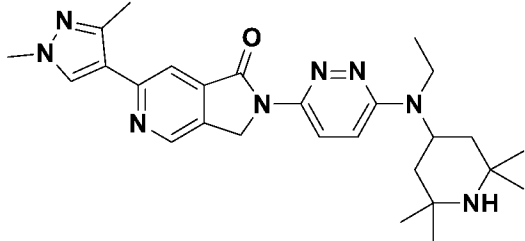
| No. | Chemical Structure | Name                                                                                                                          |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------|
| 364 |                    | 6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one   |
| 365 |                    | 6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one           |
| 368 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)isoindolin-1-one      |
| 369 |                    | 6-(1-methyl-1H-1,2,3-triazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one               |
| 370 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one       |
| 371 |                    | 6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one |
| 372 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-1,2,3-triazol-5-yl)isoindolin-1-one       |

| No. | Chemical Structure | Name                                                                                                                           |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------|
| 373 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-tetrazol-5-yl)isoindolin-1-one             |
| 375 |                    | 6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one           |
| 378 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4,5-tetrazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one      |
| 381 |                    | 5-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one     |
| 382 |                    | 5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one             |
| 383 |                    | 2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoindolin-1-one         |
| 385 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4,5-tetrazin-3-yl)isoindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                                  |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| 392 |                    | 6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one |
| 403 |                    | 5-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                   |
| 406 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one           |
| 410 |                    | 5-methoxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one           |
| 411 |                    | 5-hydroxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one           |
| 417 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one            |
| 420 |                    | 2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one          |

| No. | Chemical Structure | Name                                                                                                                   |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------|
| 421 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one          |
| 424 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one  |
| 430 |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one      |
| 431 |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one |
| 433 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one |
| 435 |                    | 6-(2,4-dimethylthiazol-5-yl)-2-(4-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one    |
| 438 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)isoindolin-1-one     |

| No. | Chemical Structure | Name                                                                                                                               |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------|
| 441 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(4-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one            |
| 442 |                    | 6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                 |
| 443 |                    | 2-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one |
| 444 |                    | 2-(6-(((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one                    |
| 448 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)isoindolin-1-one          |
| 449 |                    | 2-(6-(((4-azadispiro[2.1.2^5.3^3]decan-9-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one                   |
| 451 |                    | 5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                    |

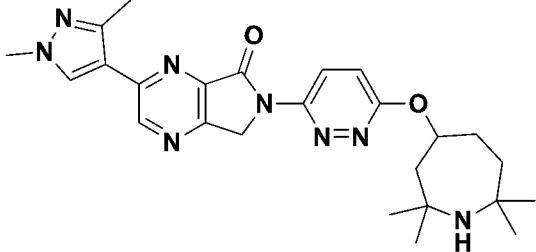
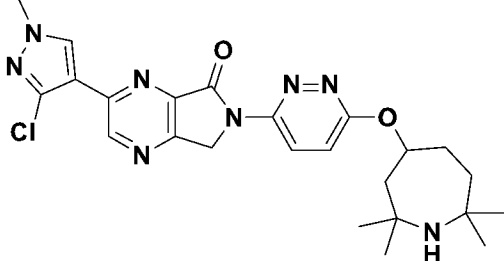
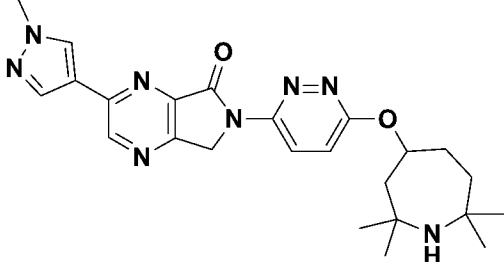
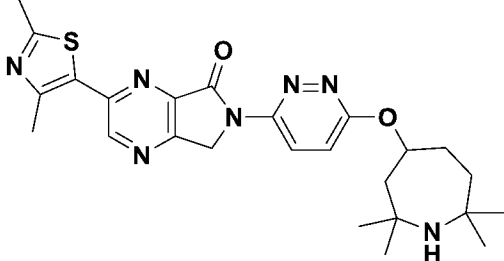
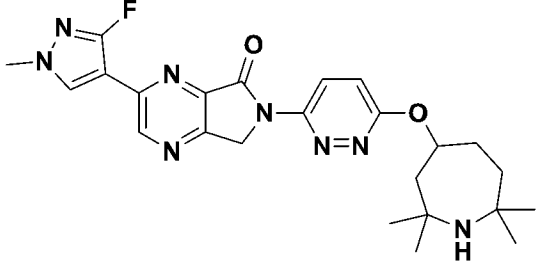
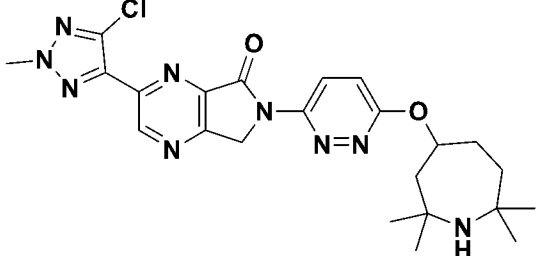
| No. | Chemical Structure                                                                  | Name                                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| 455 |    | 6-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one    |
| 457 |    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 459 |    | 2-(6-(((2S,4r,6R)-2,6-diethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 461 |   | 6-(2,4-dimethylthiazol-5-yl)-2-(6-(((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one              |
| 462 |  | 4-(1H-pyrazol-4-yl)-2-(6-(((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 463 |  | 4-(1-methyl-1H-pyrazol-4-yl)-2-(6-(((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |
| 464 |  | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(ethyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |

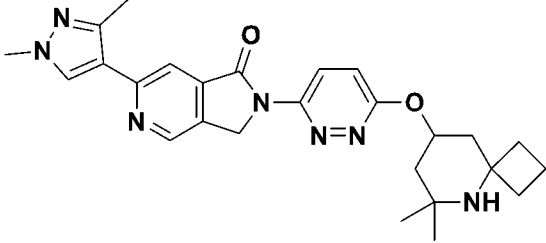
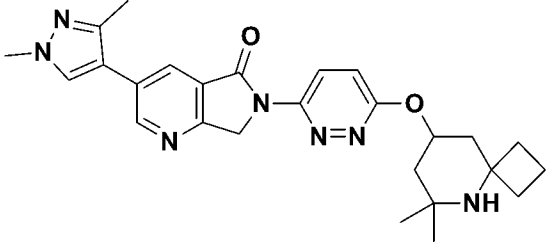
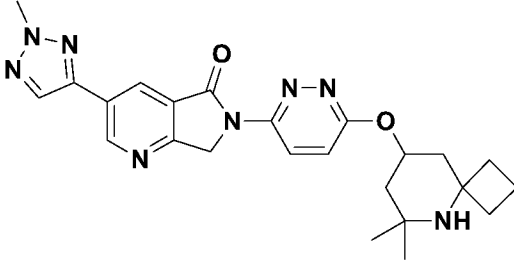
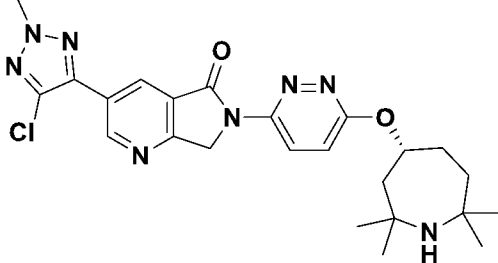
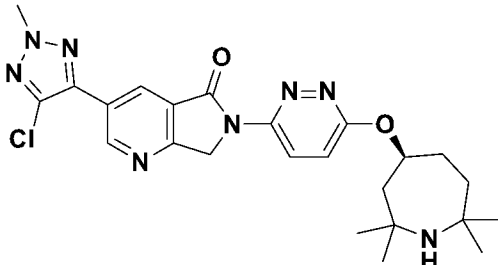
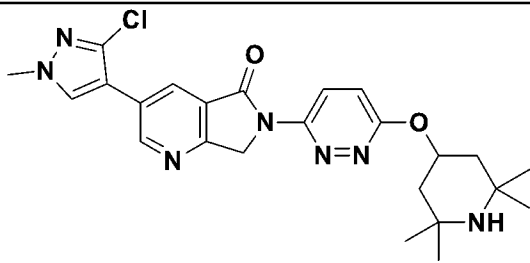
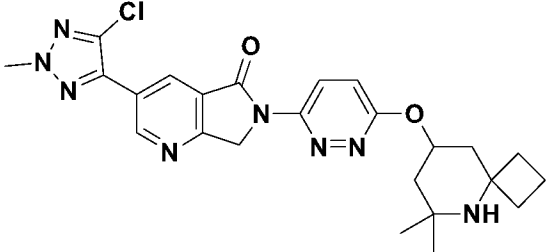
| No. | Chemical Structure | Name                                                                                                                                                                   |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 465 |                    | 6-(2-methyl-2H-1,2,3-triazol-4-yl)-2-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                   |
| 466 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one      |
| 468 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(8-(2,2,6,6-tetramethylpiperidin-4-yl)-7,8-dihydro-6H-pyridazino[4,3-b][1,4]oxazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 469 |                    | 6-(1-methyl-1H-pyrazol-4-yl)-2-(6-(2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                       |
| 471 |                    | 6-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(6-(2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                              |
| 472 |                    | 6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-(2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                              |

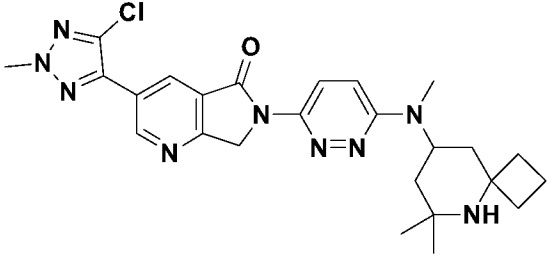
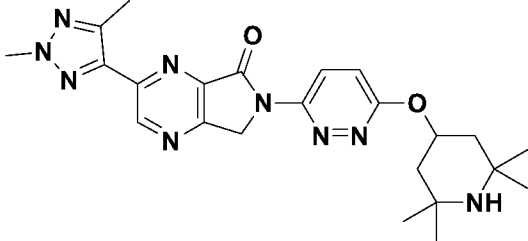
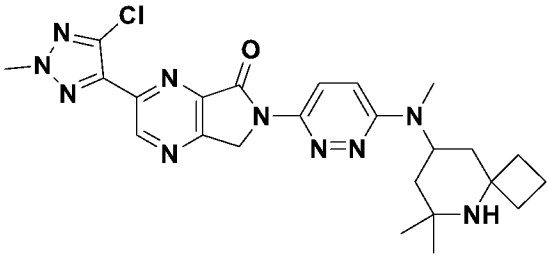
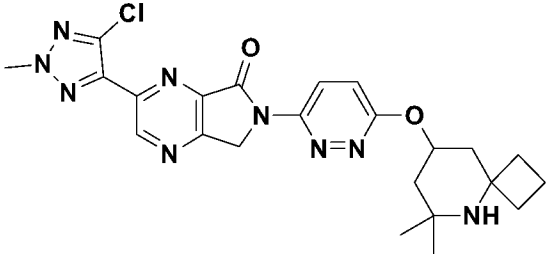
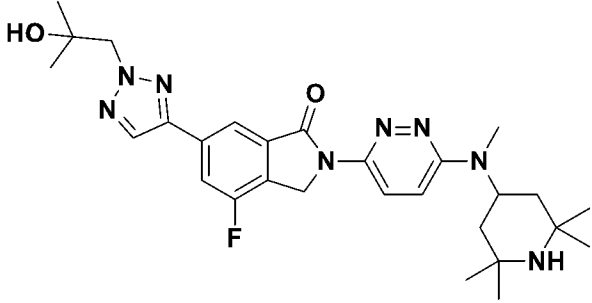
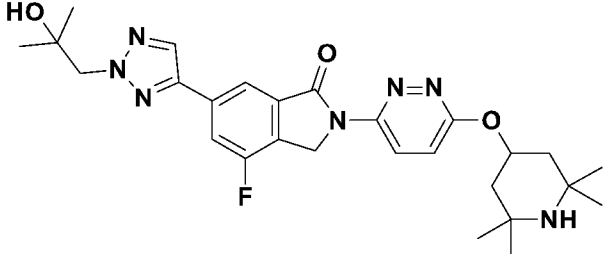
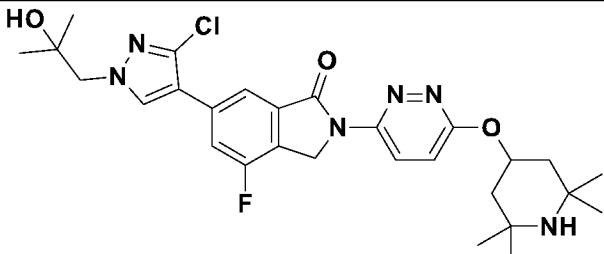
| No. | Chemical Structure | Name                                                                                                                                                         |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 473 |                    | (S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 474 |                    | (R)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 475 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(8-(2,2,6,6-tetramethylpiperidin-4-yl)-7,8-dihydropyrido[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 476 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 479 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 481 |                    | 6-(6-(((2S,4r,6R)-2,6-diethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |
| 482 |                    | 3-(2,4-dimethylthiazol-5-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                            |

| No. | Chemical Structure | Name                                                                                                                                                   |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 483 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(ethyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 484 |                    | 3-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 485 |                    | 3-(2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                |
| 486 |                    | 4-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 487 |                    | 6-(6-(cyclopropyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 488 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 489 |                    | 3-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                      |

| No. | Chemical Structure | Name                                                                                                                                                              |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 491 |                    | 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 492 |                    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 493 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 494 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 497 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 499 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                  |
| 500 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |

| No. | Chemical Structure                                                                  | Name                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 504 |    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one            |
| 505 |    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one       |
| 506 |   | 3-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                |
| 507 |  | 3-(2,4-dimethylthiazol-5-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                |
| 508 |  | 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one       |
| 509 |  | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                     |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 593 |    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 597 |    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 601 |    | 6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 605 |   | (R)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one     |
| 607 |  | (S)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one     |
| 608 |  | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 619 |  | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

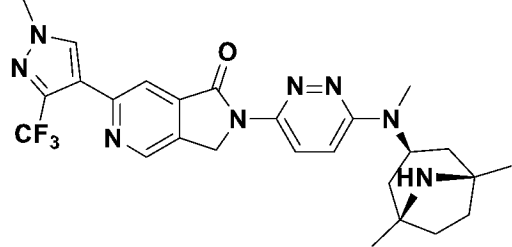
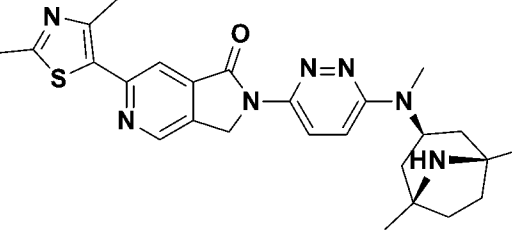
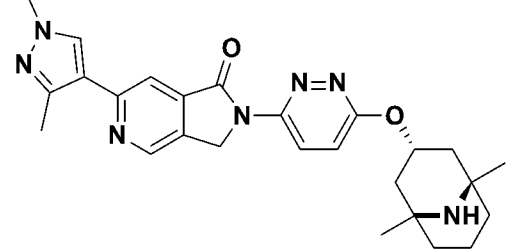
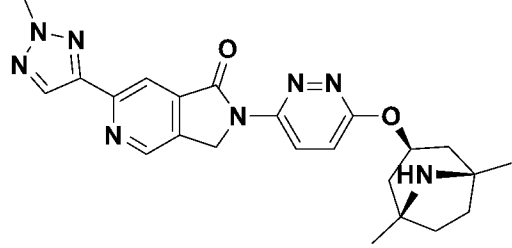
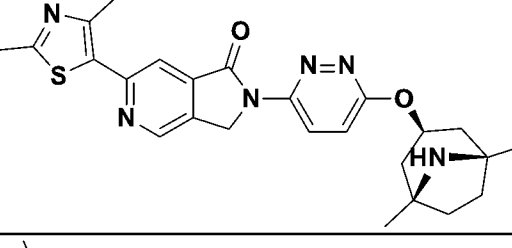
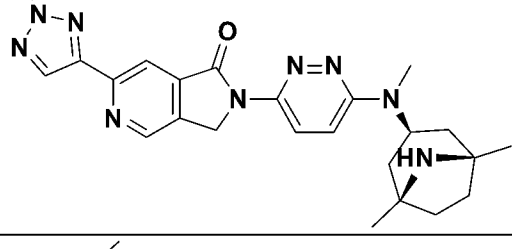
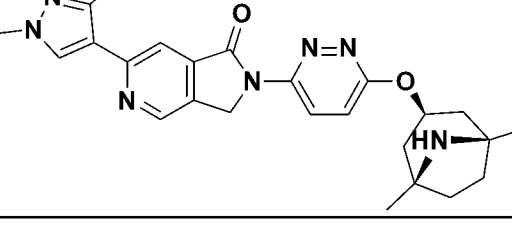
| No. | Chemical Structure                                                                  | Name                                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 621 |    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 624 |    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                     |
| 626 |    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one |
| 628 |   | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one           |
| 633 |  | 4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one               |
| 635 |  | 4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                       |
| 649 |  | 6-(3-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                    |

| No. | Chemical Structure | Name                                                                                                                                             |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 664 |                    | 4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                     |
| 677 |                    | 4-chloro-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                |
| 678 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile      |
| 680 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-1-oxo-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindoline-4-carbonitrile         |
| 682 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile |
| 683 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-methoxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one            |
| 688 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-methoxy-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one                    |

| No. | Chemical Structure | Name                                                                                                                    |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------|
| 696 |                    | 4-fluoro-5-((5-fluoropyridin-2-yl)methoxy)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one |

TABLE 1B.

| No. | Chemical Structure | Name                                                                                                                                                                        |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19  |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 20  |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 27  |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(pyrimidin-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                 |
| 42  |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                  |
| 55  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 60  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 61  |    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 62  |    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                     |
| 67  |    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                           |
| 68  |   | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                         |
| 69  |  | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                               |
| 70  |  | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one               |
| 72  |  | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                           |

| No. | Chemical Structure | Name                                                                                                                                                                            |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 73  |                    | 2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |
| 74  |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one    |
| 77  |                    | 6-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 79  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1S,2S,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 82  |                    | 2-(6-(((1R,2S,3R,4S,5S)-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 85  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 89  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(5-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyrazin-2-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |

| No. | Chemical Structure | Name                                                                                                                                                                            |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 90  |                    | 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 93  |                    | 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |
| 94  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5,8-trimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |
| 95  |                    | 2-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                           |
| 96  |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one              |
| 97  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one               |
| 98  |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1S,3R,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                |

| No. | Chemical Structure | Name                                                                                                                                                                    |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 99  |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                |
| 100 |                    | 2-(6-(((1R,3s,5S)-1,5-diethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one             |
| 102 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 105 |                    | 4-chloro-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 106 |                    | 4-chloro-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 107 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 108 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |

| No. | Chemical Structure | Name                                                                                                                                                                    |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 110 |                    | 4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 111 |                    | 6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2-(2,4-dimethylthiazol-5-yl)-5,6-dihydro-7H-pyrrolo[3,4-d]pyrimidin-7-one              |
| 112 |                    | 2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 114 |                    | 2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(4-methylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 116 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one   |
| 117 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one      |
| 118 |                    | 2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |

| No. | Chemical Structure | Name                                                                                                                                                                         |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 164 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 166 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 169 |                    | 3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 171 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                 |
| 174 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |
| 175 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 178 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                                                                                   |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 181 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3S,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 183 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 185 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3r,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 186 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 188 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 194 |                    | 6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                               |
| 196 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2,5-dimethylthiazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |

| No. | Chemical Structure | Name                                                                                                                                                                         |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 197 |                    | 6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,5-dimethylthiazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |
| 199 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 200 |                    | 6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 201 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 202 |                    | 6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 206 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 209 |                    | 2-chloro-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |

| No. | Chemical Structure | Name                                                                                                                                                                             |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 213 |                    | 3-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 214 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2S,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 215 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 217 |                    | 6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 219 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(3,5-dimethylisoxazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 220 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(pyridin-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                     |
| 227 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(3-methyl-1,2,4-thiadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |

| No. | Chemical Structure | Name                                                                                                                                                              |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 233 |                    | 6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 236 |                    | 6-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                             |
| 238 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3S,5S)-1,5,8-trimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one   |
| 239 |                    | 6-(6-(((1R,3S,5S)-1,5-diethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 240 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,3R,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 242 |                    | 6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one   |
| 244 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                                                                   |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 246 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 248 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 250 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 251 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 261 |                    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 274 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-(methylamino)pyridazin-3-yl)-4-fluoroisindolin-1-one |
| 278 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one                              |

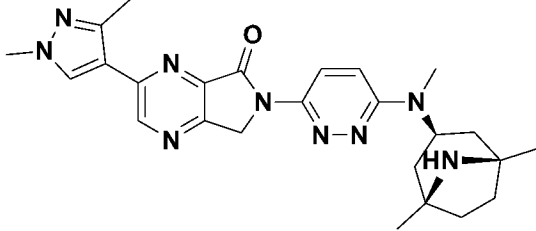
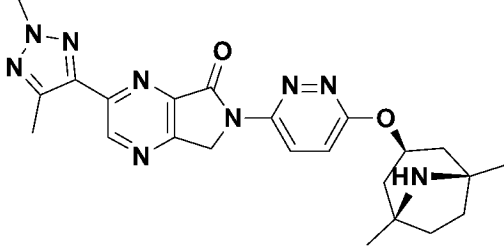
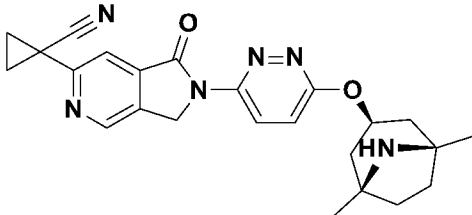
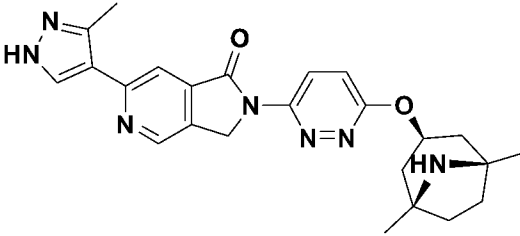
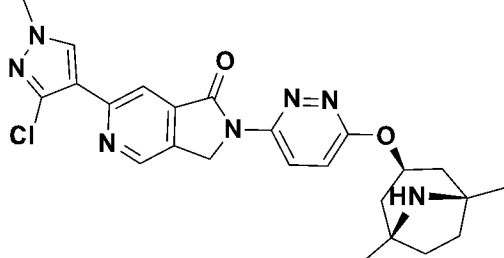
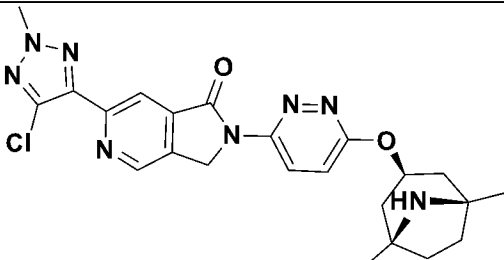
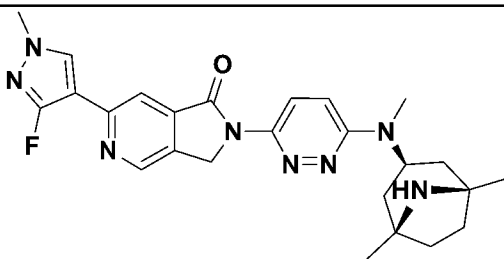
| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 281 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-((1R,2R,3S,5S)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one       |
| 283 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisoindolin-1-one             |
| 286 |                    | 2-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one                       |
| 289 |                    | 2-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one             |
| 291 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-4-fluoroisoindolin-1-one |
| 294 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoroisoindolin-1-one   |
| 303 |                    | 2-((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                 |

| No. | Chemical Structure | Name                                                                                                                                             |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 366 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                       |
| 367 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one          |
| 376 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one       |
| 377 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(pyrimidin-5-yl)isoindolin-1-one                                 |
| 386 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one |
| 387 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoindolin-1-one     |
| 396 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one              |
| 397 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one           |

| No. | Chemical Structure | Name                                                                                                                                      |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 398 |                    | 2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-5-fluoroisindolin-1-one   |
| 413 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-fluoroisindolin-1-one |
| 415 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isindolin-1-one              |
| 416 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isindolin-1-one          |
| 418 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isindolin-1-one              |
| 419 |                    | 2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isindolin-1-one              |
| 422 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-fluoroisindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                                               |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| 423 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one        |
| 425 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                |
| 426 |                    | 2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                |
| 427 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one   |
| 428 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one                  |
| 429 |                    | 2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one |
| 432 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one            |

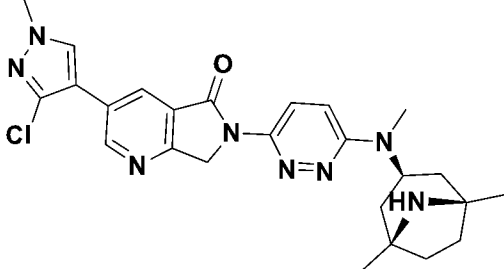
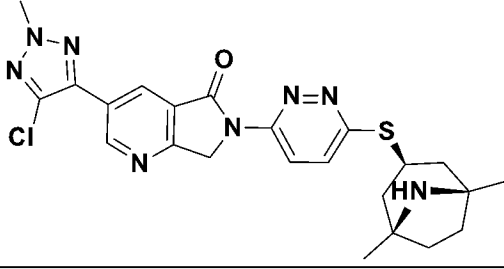
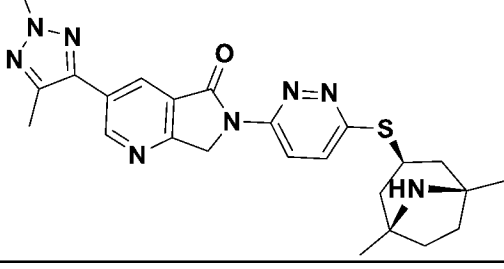
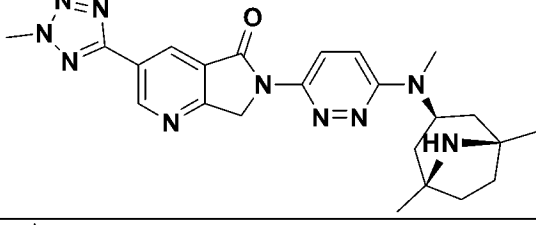
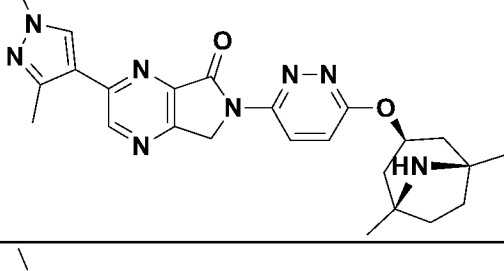
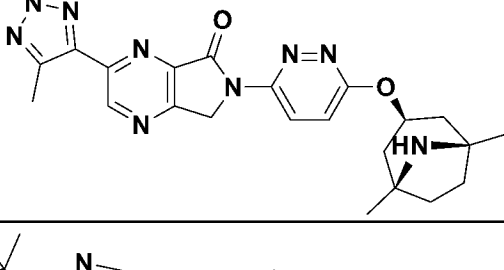
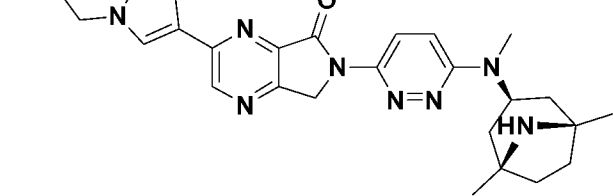
| No. | Chemical Structure | Name                                                                                                                                                 |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| 434 |                    | 2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one                        |
| 436 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-methoxyisoindolin-1-one          |
| 437 |                    | 2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one         |
| 439 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one              |
| 445 |                    | 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one |
| 446 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile    |
| 447 |                    | 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one           |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                                        |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 452 |    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one      |
| 453 |    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one          |
| 454 |    | 1-(2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)cyclopropane-1-carbonitrile             |
| 456 |   | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(3-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 458 |  | 6-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |
| 460 |  | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 467 |  | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |

| No. | Chemical Structure | Name                                                                                                                                                                   |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 470 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-ylthio)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 477 |                    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 478 |                    | 1-(6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-3-yl)cyclopropane-1-carbonitrile         |
| 480 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 490 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-ylthio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 495 |                    | (E)-3-(6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-3-yl)-N-methylacrylamide             |
| 496 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one   |

| No. | Chemical Structure | Name                                                                                                                                                                              |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 498 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                    |
| 502 |                    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                 |
| 503 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one           |
| 589 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 590 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one      |
| 591 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(4-methyl-1H-1,2,3-triazol-1-yl)-1-oxoisindoline-4-carbonitrile                                |
| 592 |                    | 2-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5,6-dihydro-7H-pyrrolo[3,4-d]pyrimidin-7-one              |

| No. | Chemical Structure | Name                                                                                                                                                                                   |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 594 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one           |
| 595 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one                         |
| 596 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one                   |
| 598 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                   |
| 599 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                         |
| 604 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 606 |                    | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                                                  |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 609 |    | 3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 610 |    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one              |
| 611 |   | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 612 |  | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-(2-methyl-2H-tetrazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                    |
| 622 |  | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                          |
| 623 |  | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                    |
| 625 |  | 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one |

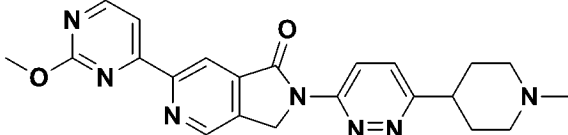
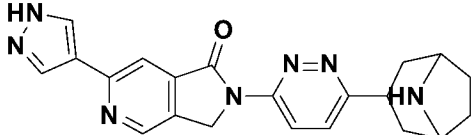
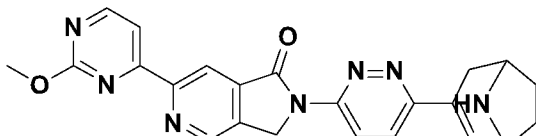
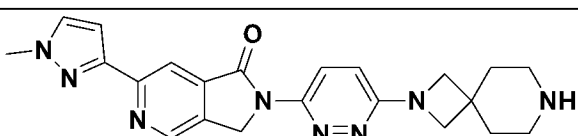
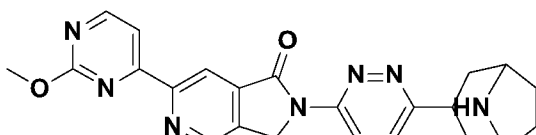
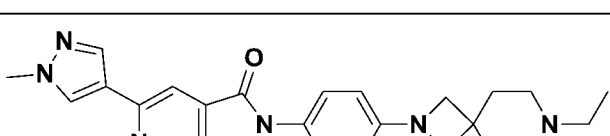
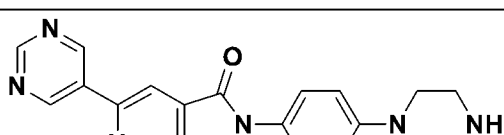
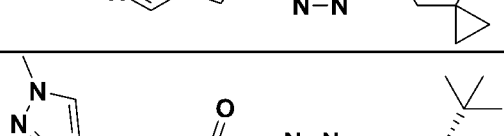
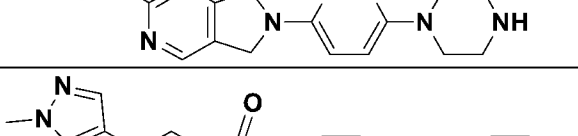
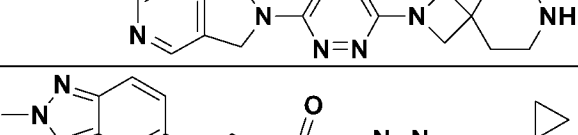
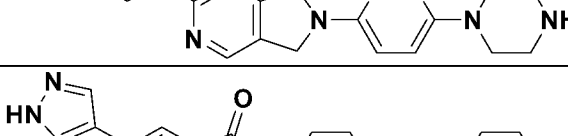
| No. | Chemical Structure | Name                                                                                                                                                                              |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 627 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one |
| 631 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                                      |
| 632 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)isoindolin-1-one              |
| 634 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)isoindolin-1-one        |
| 660 |                    | 4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one                        |
| 661 |                    | 4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one                                  |
| 673 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(2H-1,2,3-triazol-2-yl)isoindolin-1-one                                     |

| No. | Chemical Structure | Name                                                                                                                                                               |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 676 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-1-oxoisindoline-4-carbonitrile   |
| 679 |                    | 4-chloro-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isindolin-1-one     |
| 681 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxoisindoline-4-carbonitrile             |
| 684 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-methoxyisindolin-1-one              |
| 685 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-1-oxoisindoline-4-carbonitrile |
| 686 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-methoxyisindolin-1-one    |
| 687 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-methoxyisindolin-1-one         |

| No. | Chemical Structure | Name                                                                                                                                                             |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 689 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-hydroxyisoindolin-1-one |
| 693 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2-methyl-2H-tetrazol-5-yl)-1-oxoisindoline-4-carbonitrile          |
| 694 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 695 |                    | 2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(4-methyl-1H-1,2,3-triazol-1-yl)-1-oxoisindoline-4-carbonitrile     |

TABLE 1C.

| No. | Chemical Structure | Name                                                                                                                        |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------|
| 4   |                    | 2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 5   |                    | 6-(1-methyl-1H-pyrazol-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 11  |                    | 2-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 12  |                    | 2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |

| No. | Chemical Structure                                                                  | Name                                                                                                                                |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| 13  |    | 6-(2-methoxypyrimidin-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |
| 14  |    | 2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                  |
| 16  |    | 2-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one       |
| 22  |    | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 25  |    | 2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 32  |   | 2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 33  |  | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(pyrimidin-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                   |
| 34  |  | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one      |
| 36  |  | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 37  |  | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 38  |  | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                  |

| No. | Chemical Structure | Name                                                                                                                                                   |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 39  |                    | (S)-2-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                          |
| 40  |                    | 2-(6-((3aR,6aS)-5-ethylhexahydropyrrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 41  |                    | (S)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                            |
| 44  |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                            |
| 45  |                    | (S)-2-(6-(3-isopropylpiperidin-1-yl)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 46  |                    | 2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                        |
| 48  |                    | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                        |
| 50  |                    | 2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one               |
| 52  |                    | 2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                      |
| 53  |                    | 2-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                        |

| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 95  |                    | 2-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                    |
| 120 |                    | 2-(6-(1,4-diazepan-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                      |
| 121 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                             |
| 122 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((3R,5S)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                     |
| 123 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                          |
| 124 |                    | (S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                          |
| 125 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 126 |                    | 2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                          |
| 127 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |

| No. | Chemical Structure | Name                                                                                                                                        |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 128 |                    | 2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 129 |                    | 2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 130 |                    | 2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 131 |                    | 2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |
| 132 |                    | 2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one             |
| 133 |                    | 2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 136 |                    | 6-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                 |
| 137 |                    | 3-(1-methyl-1H-pyrazol-4-yl)-6-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 145 |                    | 6-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                 |
| 146 |                    | 6-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 147 |                    | 6-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                       |

| No. | Chemical Structure | Name                                                                                                                                                  |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 151 |                    | 6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 152 |                    | 6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 153 |                    | 6-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                   |
| 154 |                    | (S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                        |
| 155 |                    | (S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                         |
| 157 |                    | (S)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                           |
| 158 |                    | 6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                       |
| 159 |                    | 6-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 165 |                    | 6-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |
| 170 |                    | 6-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                       |

| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 252 |                    | (S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                 |
| 254 |                    | (S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 255 |                    | 3-(2,4-dimethylthiazol-5-yl)-6-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                        |
| 256 |                    | (S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                       |
| 257 |                    | 6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                         |
| 258 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 259 |                    | 6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                      |
| 260 |                    | 6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 263 |                    | 6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                              |
| 264 |                    | 6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |

| No. | Chemical Structure | Name                                                                                                                                        |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 265 |                    | 6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 266 |                    | 6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one             |
| 267 |                    | (R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 268 |                    | 6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 270 |                    | 6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 271 |                    | 6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 272 |                    | 2-(6-(2,6-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                                |
| 273 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one                        |
| 295 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                             |

| No. | Chemical Structure | Name                                                                                                                                   |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 296 |                    | (S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one                          |
| 297 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one                          |
| 298 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one                 |
| 299 |                    | (S)-6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one                              |
| 300 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one                              |
| 301 |                    | (S)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                        |
| 302 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one                     |
| 304 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one                                    |
| 305 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)isoindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                      |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------|
| 306 |                    | 2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one |
| 344 |                    | 6-(2-methoxypyrimidin-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)isoindolin-1-one                                  |
| 345 |                    | 2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)isoindolin-1-one                           |
| 361 |                    | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                          |
| 374 |                    | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-3-yl)isoindolin-1-one                          |
| 379 |                    | (S)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                          |
| 380 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                          |
| 384 |                    | 2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one                 |
| 388 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(pyrimidin-5-yl)isoindolin-1-one                                    |
| 389 |                    | 2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one               |
| 390 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)isoindolin-1-one             |

| No. | Chemical Structure | Name                                                                                                                            |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 391 |                    | 2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one      |
| 394 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                       |
| 395 |                    | 2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                            |
| 399 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                             |
| 400 |                    | 2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                        |
| 401 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one |
| 402 |                    | 2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one   |
| 404 |                    | 2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                           |
| 405 |                    | 6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)isoindolin-1-one                       |

| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 407 |                    | (S)-2-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                                                       |
| 408 |                    | 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisoindolin-1-one                                            |
| 409 |                    | 6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)isoindolin-1-one                                                  |
| 412 |                    | 2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one                                                   |
| 414 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisoindolin-1-one                                    |
| 501 |                    | 6-(6-(azetidin-3-ylmethoxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                                   |
| 510 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 511 |                    | 2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                          |
| 512 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 513 |                    | 2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                      |

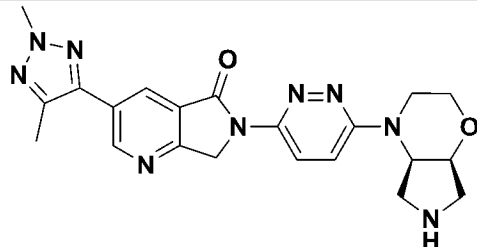
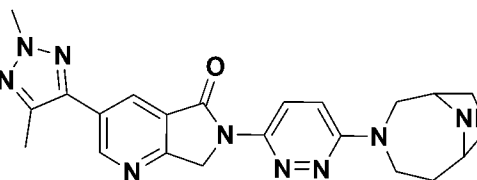
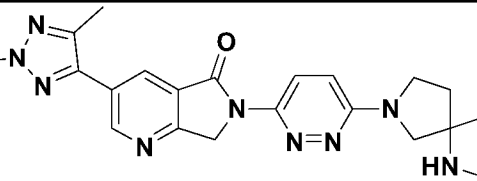
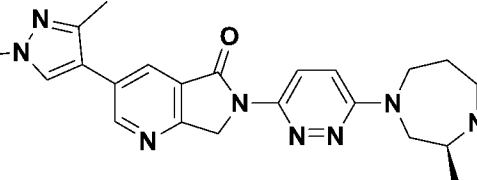
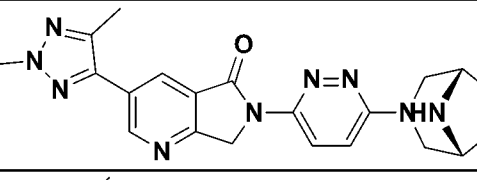
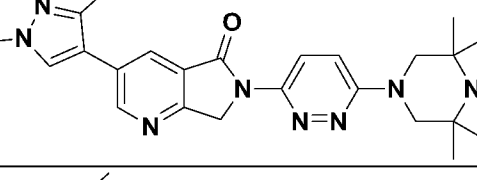
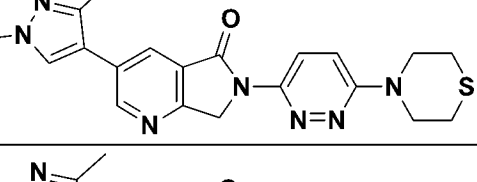
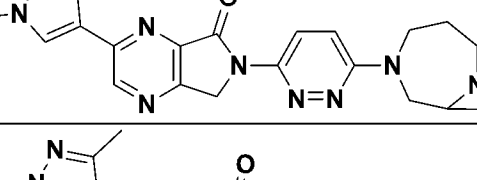
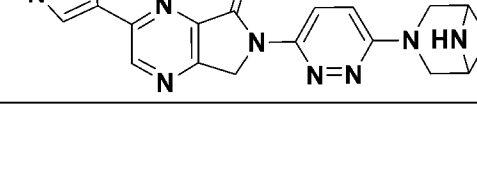
| No. | Chemical Structure | Name                                                                                                                                        |
|-----|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 514 |                    | 2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |
| 515 |                    | 2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one |
| 516 |                    | 2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                 |
| 517 |                    | 2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one             |
| 518 |                    | 2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridine-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 519 |                    | (R)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one          |
| 520 |                    | 2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one        |
| 521 |                    | 2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one     |
| 522 |                    | 2-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one         |
| 523 |                    | 2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one            |

| No. | Chemical Structure | Name                                                                                                                                                                                                                                    |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 524 |                    | 2-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                    |
| 525 |                    | 2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one<br>Chemical Formula: C <sub>23</sub> H <sub>26</sub> N <sub>8</sub> O<br>Molecular Weight: 430.5160 |
| 526 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                 |
| 527 |                    | 2-(6-(4-amino-4-methylpiperidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                        |
| 528 |                    | 2-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                 |
| 529 |                    | 2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                    |
| 530 |                    | 2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                             |
| 531 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                        |
| 532 |                    | 2-(6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                     |
| 533 |                    | (S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                                                                                                        |

| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 534 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                      |
| 535 |                    | 2-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one                       |
| 536 |                    | (S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                       |
| 537 |                    | 6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                         |
| 538 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 539 |                    | 6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                      |
| 540 |                    | 6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 541 |                    | 6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                              |
| 542 |                    | 6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                     |
| 543 |                    | 6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one              |

| No. | Chemical Structure | Name                                                                                                                                    |
|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 544 |                    | 6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one         |
| 545 |                    | (R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 546 |                    | 6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 547 |                    | 6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 548 |                    | 6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 549 |                    | (R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 550 |                    | 6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 551 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 552 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |
| 553 |                    | 6-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one     |

| No. | Chemical Structure | Name                                                                                                                                       |
|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 554 |                    | 6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 555 |                    | 6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 556 |                    | 6-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one    |
| 557 |                    | 6-(6-(4-amino-4-methylpiperidin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 558 |                    | 6-(6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one        |
| 559 |                    | 6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 560 |                    | 6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |
| 561 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one           |
| 562 |                    | 6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                |
| 563 |                    | 6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one  |

| No. | Chemical Structure                                                                  | Name                                                                                                                                                                                                                                          |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 564 |    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-((4aR,7aS)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                   |
| 565 |    | 6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one<br>Chemical Formula: C <sub>22</sub> H <sub>25</sub> N <sub>9</sub> O<br>Molecular Weight: 431.5040 |
| 566 |    | 6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                                         |
| 567 |   | (S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                                              |
| 568 |  | 6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                             |
| 569 |  | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                                           |
| 570 |  | 6-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                                                                                                            |
| 571 |  | 6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                                                                                                           |
| 572 |  | 6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one                                                                                                          |

| No. | Chemical Structure | Name                                                                                                                                   |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 573 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one       |
| 574 |                    | 6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one   |
| 575 |                    | 6-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one    |
| 576 |                    | 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one    |
| 577 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one                                    |
| 578 |                    | 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)isoindolin-1-one |
| 579 |                    | 2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one              |
| 580 |                    | 2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one                     |
| 581 |                    | 2-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one                  |

| No. | Chemical Structure | Name                                                                                                                                     |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 582 |                    | 2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                             |
| 583 |                    | 2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                        |
| 584 |                    | 2-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                        |
| 585 |                    | 2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                             |
| 586 |                    | 2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                         |
| 587 |                    | 2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one                         |
| 588 |                    | (S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isindolin-1-one                            |
| 600 |                    | (S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                                                     |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 602 |                    | (S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                          |
| 603 |                    | 6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one                    |
| 613 |                    | 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one               |
| 614 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one          |
| 615 |                    | (S)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one      |
| 616 |                    | (R)-6-(6-(3-(tert-butylamino)piperidin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one            |
| 617 |                    | (R)-6-(6-(3-(tert-butylamino)piperidin-1-yl)pyridazin-3-yl)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one       |
| 618 |                    | 3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one             |
| 620 |                    | (S)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one |

| No. | Chemical Structure | Name                                                                                                                          |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------|
| 629 |                    | (S)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one               |
| 630 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one            |
| 636 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one |
| 637 |                    | (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one   |
| 638 |                    | (R)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one      |
| 639 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(5-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one              |
| 640 |                    | (R)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one           |
| 641 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one      |
| 642 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one         |

| No. | Chemical Structure | Name                                                                                                                          |
|-----|--------------------|-------------------------------------------------------------------------------------------------------------------------------|
| 643 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one               |
| 644 |                    | 2-(6-(2,6-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one       |
| 645 |                    | 2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one   |
| 646 |                    | 2-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one            |
| 647 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one      |
| 648 |                    | (R)-2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one   |
| 650 |                    | 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one            |
| 651 |                    | 2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one        |
| 652 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one |

| No. | Chemical Structure | Name                                                                                                                                     |
|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 653 |                    | 2-(6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one             |
| 654 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one |
| 655 |                    | 2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one            |
| 656 |                    | (R)-2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one        |
| 657 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one              |
| 658 |                    | 2-(6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one                  |
| 659 |                    | 2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one             |
| 662 |                    | 2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one                 |
| 663 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one      |

| No. | Chemical Structure | Name                                                                                                                                   |
|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 665 |                    | (S)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one      |
| 666 |                    | 2-(6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one                   |
| 667 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one             |
| 668 |                    | 6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(5-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one                  |
| 669 |                    | 2-(6-(1,4-diazepan-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one                                |
| 670 |                    | 2-(6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one              |
| 671 |                    | (S)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one |
| 672 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one                  |
| 674 |                    | 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one               |

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

**[0130]** 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 (R ), 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.

*Labeled compounds*

**[0131]** In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as  $^2\text{H}$  (D),  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3\text{H}$  and carbon-14, i.e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability.

**[0132]** In some embodiments, the abundance of deuterium in each of the substituents disclosed herein 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. In some embodiments, one or more of the substituents disclosed herein comprise deuterium at a percentage higher than the natural abundance of deuterium. In some embodiments, one or more  $^1\text{H}$  are replaced with one or more deuteriums in one or more of the substituents disclosed herein.

**[0133]** In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

*Pharmaceutically acceptable salts*

**[0134]** In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

**[0135]** In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of 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 a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

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

**[0137]** Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic

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

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

**[0139]** Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

#### *Solvates*

**[0140]** In some embodiments, the compounds described herein exist as solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering the compounds in the form of such solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering a composition comprising the compounds in the form of such solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents.

#### *Tautomers*

**[0141]** 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

[0142] Disclosed herein is a method of treating a neurodegenerative disease or disorder in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt or stereoisomer thereof, disclosed herein.

[0143] In some embodiments, the neurodegenerative disease or disorder is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Prion disease, and spinocerebellar ataxias. In some embodiments, the neurodegenerative disease or disorder is Alzheimer's disease. In some embodiments, the neurodegenerative disease or disorder is amyotrophic lateral sclerosis. In some embodiments, the neurodegenerative disease or disorder is Huntington's disease. In some embodiments, the neurodegenerative disease or disorder is Parkinson's disease. In some embodiments, the neurodegenerative disease or disorder is Prion disease. In some embodiments, the neurodegenerative disease or disorder is a spinocerebellar ataxia.

## Dosing

[0144] 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.

[0145] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[0146] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage, or the frequency of administration, or both, is reduced, as a function of the symptoms.

[0147] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[0148] In some embodiments, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In some embodiments, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In various embodiments, the daily and unit dosages are altered depending on a number

of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

### **Routes of Administration**

**[0149]** 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.

**[0150]** 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**

**[0151]** The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

**[0152]** In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, (N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

**[0153]** In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents,

dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

### EXAMPLES

[0154] The following examples are offered to illustrate, but not to limit the claimed invention. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[0155] The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein.

[0156] The compounds and salts of Formulas (I), (II), (III), (IIIa), (IIIb), and (IV) can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted in the synthesis schemes below, the steps in some cases may be performed in a different order than the order shown below. Numberings or R groups in each scheme do not necessarily correspond to that of the claims or other schemes or tables herein.

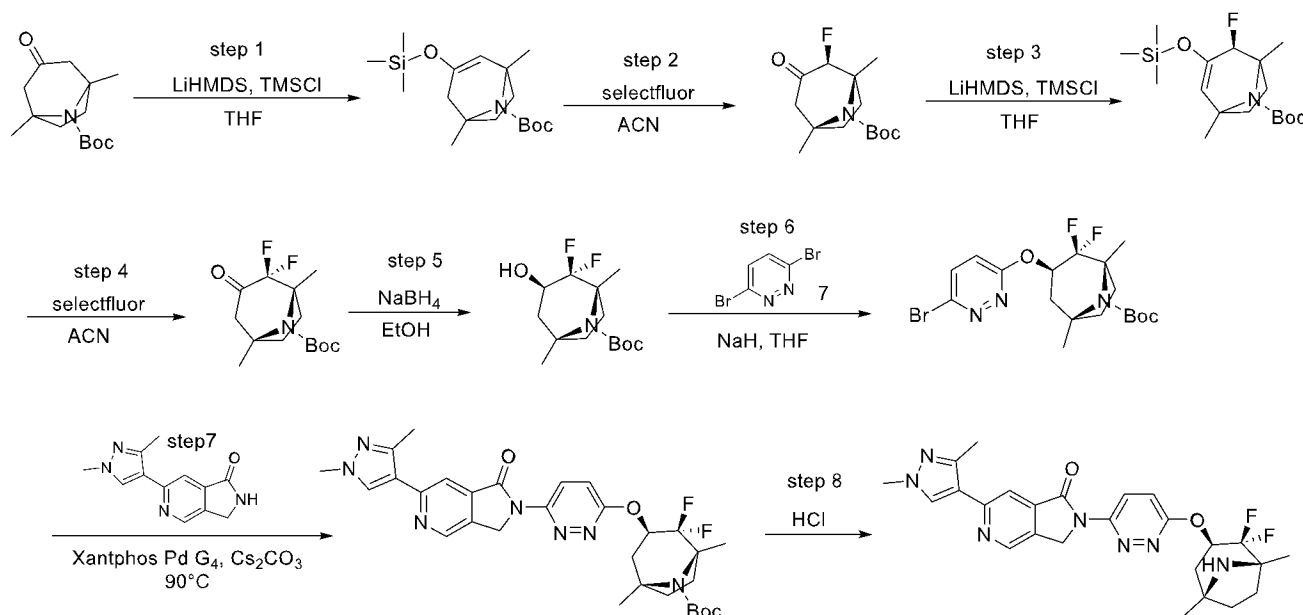
### Abbreviations

|                     |                                                              |
|---------------------|--------------------------------------------------------------|
| AcOH:               | Acetic acid                                                  |
| Boc <sub>2</sub> O: | Di-tert-butyl dicarbonate                                    |
| MeCN or ACN:        | Acetonitrile                                                 |
| DavePhos:           | 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl       |
| DCC:                | N,N'-Dicyclohexylcarbodiimide                                |
| DCM:                | Dichloromethane                                              |
| DDQ:                | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone                    |
| Dioxane:            | 1,4-Dioxane                                                  |
| DIPEA:              | N, N-Diisopropylethylamine                                   |
| DMF                 | Dimethylformamide                                            |
| DMSO                | Dimethyl sulfoxide                                           |
| EDCI:               | N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride |

|                                      |                                                                |
|--------------------------------------|----------------------------------------------------------------|
| eq                                   | Equivalents                                                    |
| EtOAc                                | Ethyl acetate                                                  |
| Et <sub>3</sub> N:                   | Triethylamine                                                  |
| g                                    | Grams                                                          |
| h                                    | Hour or hours                                                  |
| HATU:                                | Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium       |
| HOBT:                                | 1-Hydroxybenzotriazole                                         |
| HOSu:                                | N-hydroxysuccinimide                                           |
| LCMS:                                | Liquid chromatography–mass spectrometry                        |
| LAH:                                 | Lithium aluminum hydride                                       |
| MeOH:                                | Methanol                                                       |
| mg                                   | Milligrams                                                     |
| min                                  | Minute or minutes                                              |
| mL                                   | Milliliters                                                    |
| mmol                                 | Millimoles                                                     |
| MS                                   | Mass spectrometry                                              |
| MTBE:                                | Methyl tertiary-butyl ether                                    |
| NCS:                                 | N-Chlorosuccinimide                                            |
| NMR:                                 | Nuclear Magnetic Resonance                                     |
| PCC:                                 | Pyridinium chlorochromate                                      |
| Pd:                                  | Palladium                                                      |
| Pd <sub>2</sub> (dba) <sub>3</sub> : | Tris(dibenzylideneacetone)dipalladium                          |
| Pd(dppf)Cl <sub>2</sub> :            | [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride |
| RP-HPLC:                             | Reversed-Phase High-Performance Liquid Chromatography          |
| rt or RT:                            | Room temperature, ambient, about 25 °C                         |
| THF:                                 | Tetrahydrofuran                                                |
| TLC:                                 | Thin-layer chromatography                                      |

**[0157] Example 1. Synthesis of 2-(6-(((1S,3R,5R)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 82)**

**[0158] Scheme 1.**



**[0159] Step 1:** To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.50 g, 9.87 mmol) in THF (30 mL) was added LiHMDS (15.8 mL, 15.8 mmol) at -65 °C. The reaction was stirred for 1.5 h and then TMSCl (1.6 mL, 12.83 mmol) was added and the reaction mixture stirring at -78 °C for another 2 h. After the reactants were consumed, the reaction was diluted with EA and H<sub>2</sub>O. The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo to afford 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (3.0 g, 93.4%) as a colorless oil which was used directly in the next step without further purification. MS (ESI, pos. ion) *m/z* 326.5 [M+H]<sup>+</sup>.

**[0160] Step 2:** To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (3.0 g, 9.22 mmol) in acetonitrile (15 mL) was added Selectfluor (5.24 g, 14.8 mmol) and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the reaction was quenched with water and then diluted with EA (100 mL). The organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH=20/1, to provided 2-methylpropan-2-yl (1R,4S,5S)-4-fluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.8 g, 71.98%) as a white solid. MS (ESI, pos. ion) *m/z* 272.3 [M+H]<sup>+</sup>.

**[0161] Step 3:** 2-Methylpropan-2-yl (1R,4S,5S)-4-fluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 4.79 mmol) was dissolved in THF (30 mL) and LiHMDS (7.67 mL, 7.67 mmol) was added at 80 °C. The reaction was stirred at -65 °C for 1.5 h, and then TMSCl (0.79 mL, 6.23 mmol) was added. The reaction mixture was stirred for another 2 h at -78 °C. After the reactants were consumed, the reaction was diluted with EA and H<sub>2</sub>O. The organic layer was separated,

washed with further saturated NaCl solution, and concentrated in vacuo to afford 2-methylpropan-2-yl (1S,5R)-2-fluoro-1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (1.6 g, 97.22%) as a colorless oil which was directly used in the next step without further purification. MS (ESI, pos. ion)  $m/z$  343.5  $[M+H]^+$ .

**[0162] Step 4:** To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (1.6 g, 4.66 mmol) in acetonitrile (15 mL) was Selectfluor (1.65 g, 4.66 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the reaction was quenched with water, and diluted with EA (100 mL). The organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH=20/1, to provided tert-butyl (1S,5R)-2,2-difluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (837 mg, 3.04 mmol, 65.39%) as a white solid. MS (ESI, pos. ion)  $m/z$  276.3  $[M+H]^+$ .

**[0163] Step 5:** 2-Methylpropan-2-yl (1S,2S,4R,5R)-2,4-difluoro-5-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.69 mmol) was dissolved in EtOH (1-5 mL) and  $NaBH_4$  (32 mg, 0.83 mmol) was added at 80 °C. The reaction was refluxed for 3h. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford tert-butyl (1S,3R,5R)-2,2-difluoro-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.29 mmol, 39.71%) as a white solid. MS (ESI, pos. ion)  $m/z$  291.1  $[M+H]^+$ .

**[0164] Step 6:** To a solution of 2-methylpropan-2-yl (1S,2S,4R,5R)-2,4-difluoro-3-hydroxy-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.29 mmol) in THF (6 mL), NaH (16.5 mg, 0.41 mmol) was added and the reaction mixture was stirred for 20 min. Next 3,6-dibromo-1,2-diazine (85 mg, 0.35 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford tert-butyl (1S,3R,5R)-3-((6-bromopyridazin-3-yl)oxy)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (55 mg, 40.62%) as a white solid. MS (ESI, pos. ion)  $m/z$  449.3  $[M+H]^+$ .

**[0165] Step 7:** To a solution of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (28 mg, 0.12) in dioxane (6 mL) was added 2-methylpropan-2-yl (1R,2R,3s,4S,5S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (55 mg, 0.12 mmol), XantPhos Pd G4 (11.81 mg, 0.01 m-mol) and  $Cs_2CO_3$  (119.91 mg, 0.37 mmol) and the reaction mixture was stirred at 90 °C overnight. After the reactants were consumed, the reaction was diluted with EA and  $H_2O$ . The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo and then purified using silica gel column chromatography eluting with DCM/MeOH to afford tert-

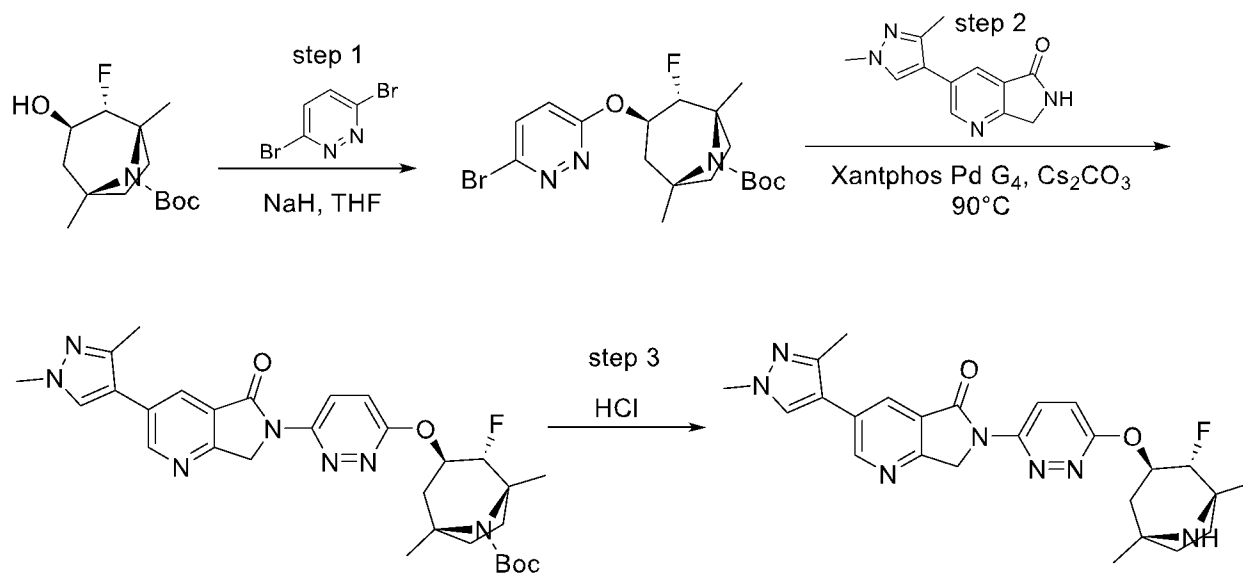
butyl (1S,3R,5R)-3-((6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)pyridazin-3-yl)oxy)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (15 mg, 0.03 mmol, 20.53%). MS (ESI, pos. ion)  $m/z$  596.6  $[M+H]^+$ .

**[0166] Step 8:** 2-Methylpropan-2-yl 3-((6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (15 mg, 20.53%) was dissolved in HCl (5 mL, in dioxane). The reaction mixture was stirred at room temperature for 3 h. After the reactants were consumed, the reaction was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford 2-(6-(((1S,3R,5R)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (8.9 mg, 71.2 %) as a white solid.

**[0167]**  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  = 8.99 (s, 1H), 8.76 (br d,  $J$  = 9.6 Hz, 1H), 8.39 (s, 1H), 7.90 (s, 1H), 7.49 (br d,  $J$  = 9.8 Hz, 1H), 5.72-5.84 (m, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.27-2.40 (m, 2H), 1.81-2.03 (m, 2H), 1.60-1.66 (m, 2H), 1.22 (s, 6H). LC/MS (ESI): 496.5  $[M+H]^+$ .

**[0168] Example 2. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 215)**

**[0169] Scheme 2.**



**[0170] Step 1:** To a solution of 2-methylpropan-2-yl (1S,3S,4S,5R)-4-fluoro-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.44 mmol) in THF (6 mL) was added NaH (15.80 mg, 0.66 mmol). The reaction mixture was stirred for 20 min and then 3,6-dibromo-1,2-diazine (156.64 mg, 0.66 mmol) was added. The reaction mixture was further stirred at room temperature overnight. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel

column chromatography with DCM/MeOH to afford 2-methylpropan-2-yl (1S,3S,4S,5R)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 26.47%) as a white solid.

**[0171]** MS (ESI, pos. ion)  $m/z$  431.3  $[M+H]^+$ .  $^1H$  NMR (CHLOROFORM- $d$ )  $\delta$  = 7.43 (d, 1H,  $J$  = 9.2 Hz), 6.81 (d, 1H,  $J$  = 9.2 Hz), 5.48-5.61 (m, 1H), 4.62 (dd, 1H,  $J$  = 51.0, 8.4 Hz), 2.37-2.44 (m, 1H), 1.97-2.09 (m, 1H), 1.67-1.89 (m, 3H), 1.54-1.59 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H).

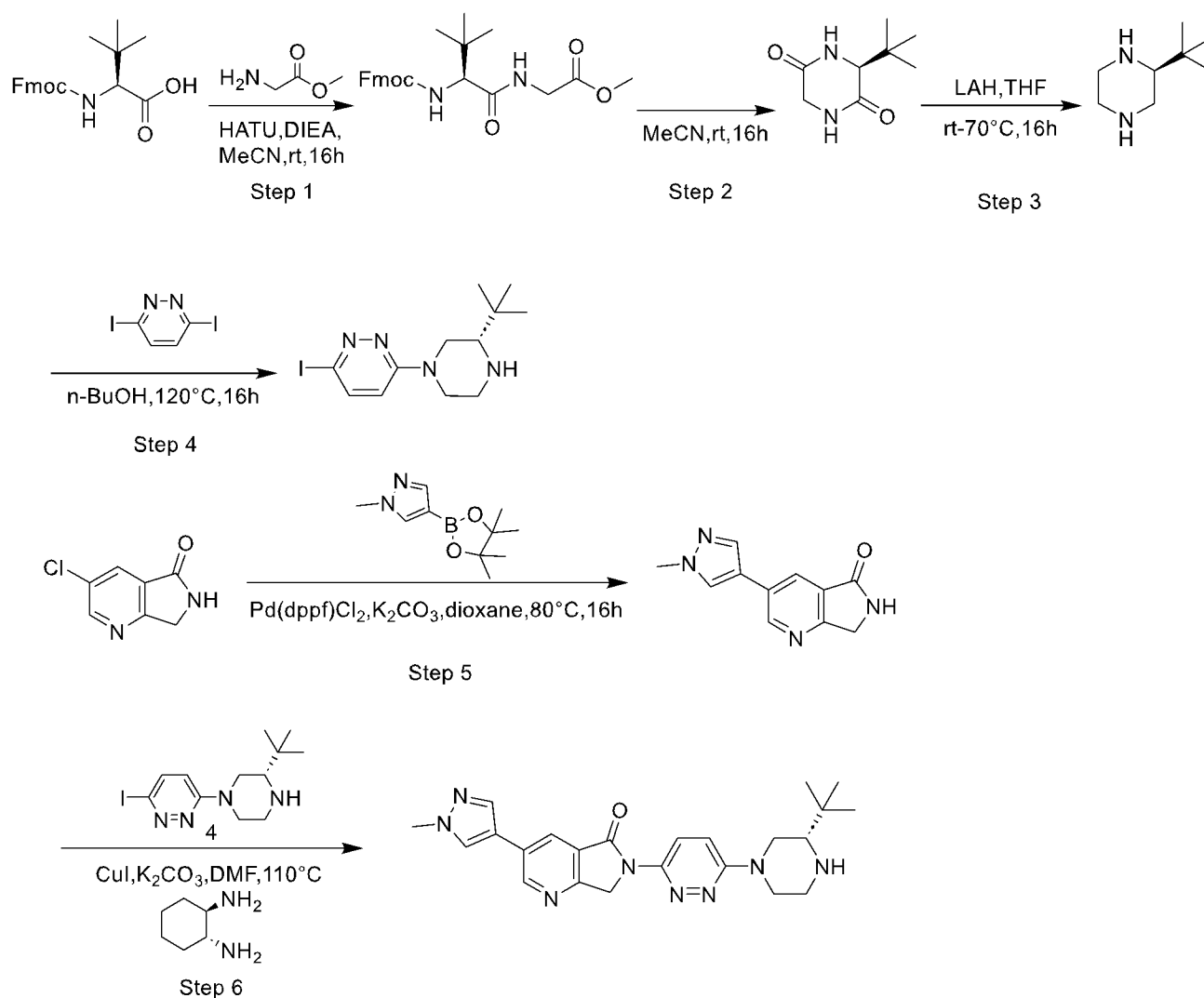
**[0172] Step 2:** To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-5-one (23 mg, 0.10 mmol) in dioxane (6 mL) were added 2-methylpropan-2-yl (1S,3S,4S,5R)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (43.36 mg, 0.10 mmol), XantPhos Pd G4 (9.70 mg, 0.01 mmol) and  $Cs_2CO_3$  (98.33 mg, 0.30 mmol). The reaction mixture was stirred at 90 °C overnight. After the reactants were consumed, the reaction was diluted with EA and  $H_2O$ . The organic layer was separated, washed with saturated NaCl solution, and concentrated in vacuo and then purified using silica gel column chromatography eluting with DCM/MeOH to afford 2-methylpropan-2-yl (1R,2S,5S)-3-({6-[3-(1,3-dimethylpyrazol-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-6-yl]-1,2-diazin-3-yl}oxy)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (13 mg, 22.33%). MS (ESI, pos. ion)  $m/z$  578.7  $[M+H]^+$ .

**[0173] Step 3:** 2-Methylpropan-2-yl (1R,2R,5S)-3-({6-[3-(1,3-dimethylpyrazol-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-6-yl]-1,2-diazin-3-yl}oxy)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (13 mg, 0.02 mmol) was dissolved in HCl (5 mL, in dioxane) and the reaction mixture was stirred at room temperature for 3 h. After the reactants were consumed, the mixture was concentrated in vacuo. The crude mixture was then purified by silica gel column chromatography with DCM/MeOH to afford 3-(1,3-dimethylpyrazol-4-yl)-6-(6-{[(1S,4S,5R)-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-5-one (8 mg, 0.02 mmol, 74.44%) as a white solid.

**[0174]**  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  = 8.95-9.02 (m, 1H), 8.75 (d,  $J$  = 9.6 Hz, 1H), 8.13-8.26 (m, 3H), 7.43 (d,  $J$  = 9.6 Hz, 1H), 5.43-5.57 (m, 1H), 5.19 (s, 2H), 4.34-4.77 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.95-2.23 (m, 2H), 1.67-1.95 (m, 2H), 1.50-1.64 (m, 2H), 1.22 (s, 6H). LC/MS (ESI): 478.2  $[M+H]^+$ .

**[0175] Example 3. Synthesis of 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisindolin-1-one (Compound No. 154)**

**[0176] Scheme 3.**



**[0177] Step 1:** To a solution of (2*S*)-2-((9H-fluoren-9-ylmethyl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and then the reaction mixture was stirred at room temperature for 16 h. After the reactants were consumed, the reaction mixture was filtered to afford 9H-fluoren-9-ylmethyl {[*(7S)*]-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (9.5 g, 22.38 mmol, 79.09%) as slightly a yellow solid. MS *m/z* 425.5 [M+H]<sup>+</sup>.

**[0178] Step 2:** A solution of 9H-fluoren-9-ylmethyl {[*(7S)*]-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred room temperature for 16 h. After the reactants were consumed, the solution was concentrated in vacuo to afford 9H-fluoren-9-ylmethyl {[*(7S)*]-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (4.85 g, 11.43 mmol, 97.00%) as a yellow solid. MS *m/z* 171.2 [M+H]<sup>+</sup>.

**[0179] Step 3:** LiAlH<sub>4</sub> (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (3*S*)-3-(2-methylprop-2-yl)piperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and the mixture was further stirred at 70 °C for 16 h. After the reactants were consumed, the mixture was poured into KOH (6N) in an ice bath. The resulting mixture was further stirred for 1 h, filtered, and the

filtrate was collected. The filtrate was extracted with EA, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided (2*S*)-2-(2-methylprop-2-yl)piperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. MS *m/z* 143.2 [M+H]<sup>+</sup>.

**[0180] Step 4:** DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2*S*)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51 mmol, 1.0 eq) in *n*-BuOH (7 mL) at room temperature, and the mixture was stirred at 120 °C for 16 h. After the reactants were consumed, the mixture was concentrated in vacuo to give a residue, which was diluted with EA, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. MS *m/z* 347.2 [M+H]<sup>+</sup>.

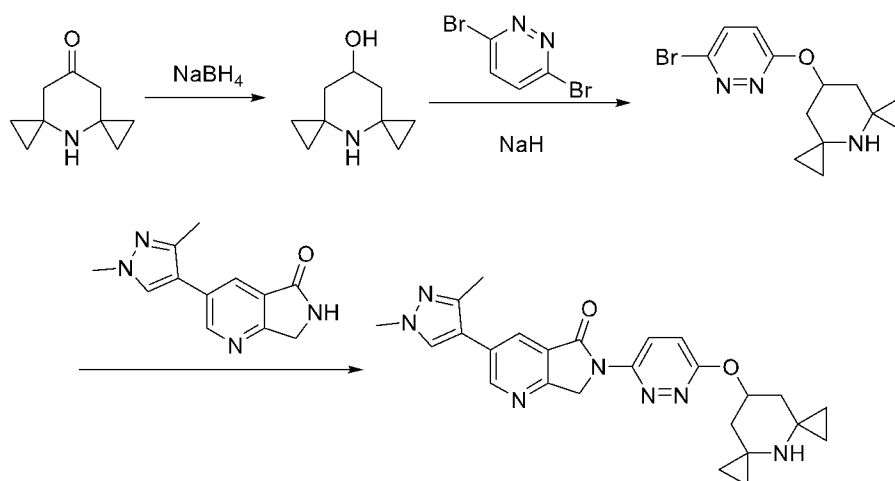
**[0181] Step 5:** Pd(dppf)Cl<sub>2</sub> (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K<sub>2</sub>CO<sub>3</sub> (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL). The mixture was stirred at 80 °C for 16 h. Then the reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 10/1, *v/v* to provide 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. MS *m/z* 215.2 [M+H]<sup>+</sup>.

**[0182] Step 6:** 6-(1-Methylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (50 mg, 0.23 mmol, 1.0 eq) and 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (80 mg, 0.23 mmol, 1.0 eq) was dissolved in DMF (2 mL) and CuI (4 mg, 0.02 mmol, 0.10 eq), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.70 mmol, 3.0 eq) and (1*R*,2*R*)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) was added and the reaction mixture was stirred at 100 °C for 16 h. After the reactants were consumed, the mixture was filtered and the filtrate was concentrated to give a crude product which was purified by pre-HPLC to provided 2-{6-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazin-3-yl}-6-(1-methylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (24.19 mg, 21.55%) as a white solid.

**[0183]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 9.12 (d, *J* = 2.0 Hz, 1H), 8.48 (d, *J* = 9.9 Hz, 1H), 8.44 (s, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 7.46 (d, *J* = 10.0 Hz, 1H), 5.13 (s, 2H), 4.39 - 4.31 (m, 1H), 4.10 (br d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.08 - 3.03 (m, 1H), 2.86 - 2.55 (m, 3H), 2.35 - 2.31 (m, 1H), 0.96 (s, 9H). LC/MS (ESI): 433.5 [M+H]<sup>+</sup>.

**[0184] Example 4. Synthesis of 6-(6-((4-azadispiro[2.1.25.33]decan-9-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (Compound No. 232)**

**[0185] Scheme 4.**



**[0186] Step 1:** To a 100 mL round-bottomed flask was added spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-one (500 mg, 3.31 mmol) in MeOH (5 mL). This was followed with the addition of NaBH<sub>4</sub> (0.18 mL, 4.96 mmol) at 0 °C over 5 min to give an off-white suspension. The resulting mixture was stirred for 1 h at room temperature. LCMS showed the desired MS (M+H: 154.1). The resulting mixture was cooled to 0 °C and quenched with HCl (2 M, 0.5 mL) and then concentrated in vacuo. The resulting mixture was added to a silica column and was eluted with DCM:MeOH (20:1) (0.1% TEA). Spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-ol (475 mg, 2.98 mmol, 90.00%) was obtained as a yellow solid. MS (ESI, pos. ion) m/z 154.1 [M+H]<sup>+</sup>.

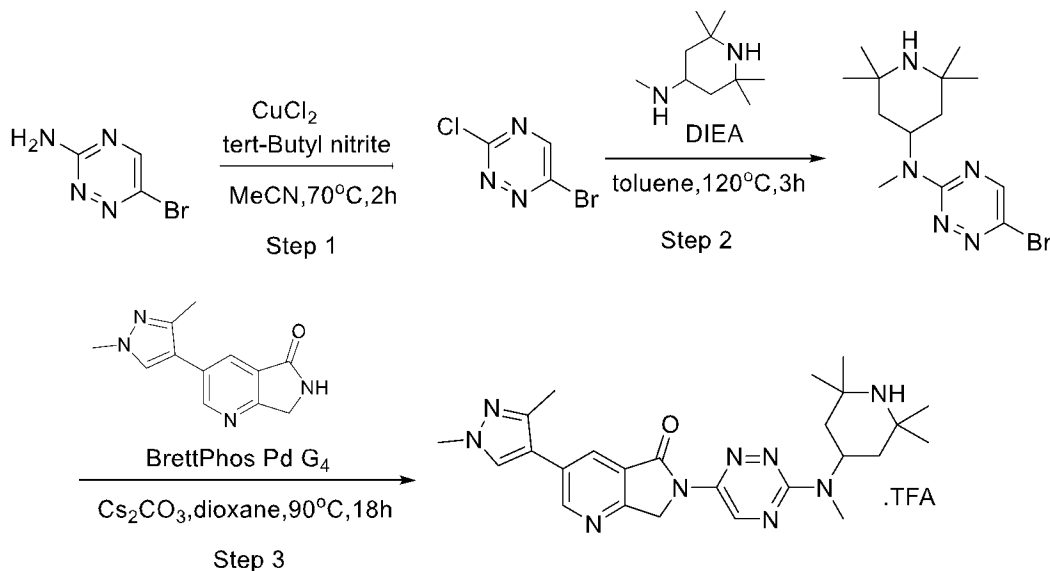
**[0187] Step 2:** To a solution of spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-ol (460 mg, 3.00 mmol) in THF (10 mL) was added NaH (270.20 mg, 4.50 mmol) at 0 °C and the resulting mixture was stirred for 30 min at room temperature. Next 3,6-dibromo-1,2-diazine (928.42 mg, 3.90 mmol) was added at 0 °C and the resulting mixture was stirred for 12 h at 60 °C. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (50 mL) and the aqueous layer was extracted with EA (50 mL\*3). The organic layer was concentrated under vacuum and residue was purified by column chromatography (SiO<sub>2</sub>, PE:EA=0~50%, 30 min) to afford 7-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane] (360 mg, 1.11 mmol, 37.11%). MS (ESI, pos. ion) m/z 310.05 [M+H]<sup>+</sup>.

**[0188] Step 3:** To a flask containing 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (40.47 mg, 0.18 mmol) in dioxane (2 mL) was added 7-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane] (50 mg, 0.16 mmol), Cs<sub>2</sub>CO<sub>3</sub> (157.56 mg, 0.48 mmol) and 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (26.11 mg, 0.02 mmol) under nitrogen. The mixture was stirred at 90 °C for 18 h. The reaction mixture was concentrated under vacuum. The residue was dissolved in DCM (3 mL) and ACN (2 mL) was added drop wise to get white slurry. The off-white solid was filtered to obtain 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (4 mg, 0.01 mmol, 5.05%) as an off-white solid.

**[0189]** MS (ESI, pos. ion) m/z 458.3 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.89 - 8.79 (m, 2H), 8.14 (d, *J* = 1.9 Hz, 1H), 7.56 (s, 1H), 7.05 (d, *J* = 9.6 Hz, 1H), 5.75 - 5.65 (m, 1H), 5.28 (s, 2H), 3.92 (s, 3H), 2.44 (s, 3H), 2.02 - 1.89 (m, 2H), 1.86 - 1.77 (m, 2H), 0.75 - 0.52 (m, 6H), 0.46 - 0.39 (m, 2H).

**[0190] Example 5. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 162)**

**[0191] Scheme 5.**



**[0192] Step 1:** To a solution of 6-bromo-1,2,4-triazin-3-amine (2.0 g, 11.43 mmol) and  $\text{CuCl}_2$  (1.47 g, 14.86 mmol) in MeCN (25 mL) was added isoamyl nitrite (2.18 mL, 18.29 mmol) and the reaction mixture was stirred at 70 °C for 2 h. Next the reaction mixture was concentrated and the residue was purified by column chromatography ( $\text{SiO}_2$ , PE:EA=10:1) to give 6-bromo-3-chloro-1,2,4-triazine (220 mg, 1.13 mmol, 9.90%) as a yellow solid.

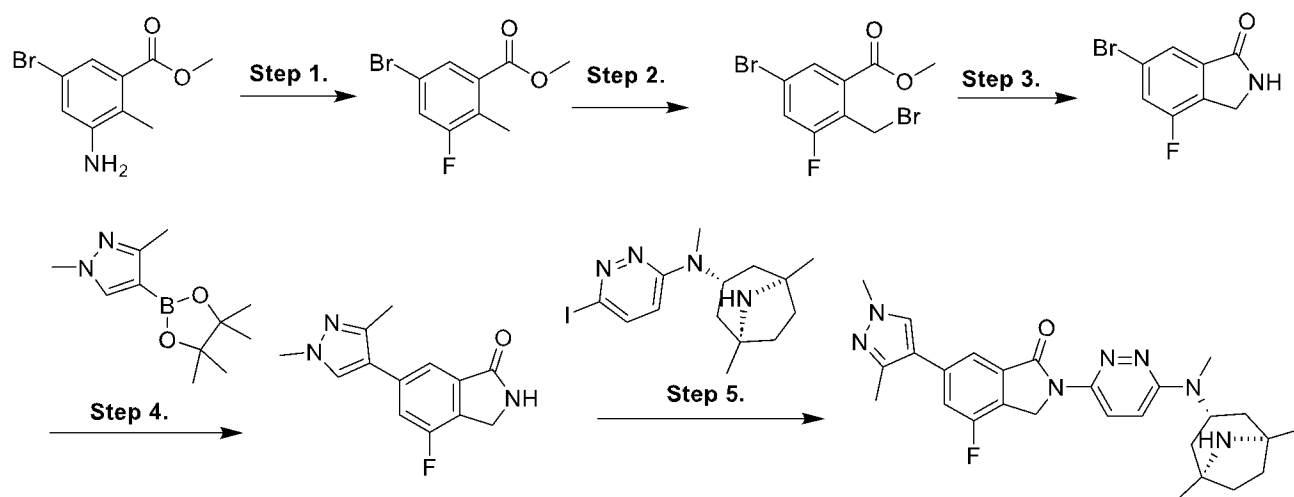
**[0193] Step 2:** To a solution of 6-bromo-3-chloro-1,2,4-triazine (200 mg, 1.03 mmol) and 2,2,6,6-tetramethyl-4-(methylamino)hexahydropyridine (192.71 mg, 1.13 mmol) in toluene (10 mL) was added DIEA (0.34 mL, 2.06 mmol) and the reaction mixture was stirred at 120 °C for 3 h. LCMS showed the reaction was completed. Next the reaction mixture was concentrated and the residue was purified by column chromatography ( $\text{SiO}_2$ , DCM : MeOH=10:1) to give 6-bromo-3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazine (0.23 g, 67.65%) as a yellow solid.

**[0194] Step 3:** To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (35 mg, 0.15 mmol) and 6-bromo-3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazine (52 mg, 0.16 mmol) in dioxane (10 mL) was added BrettPhos Pd G<sub>4</sub> (13.61 mg, 0.01 mmol) and  $\text{Cs}_2\text{CO}_3$  (146.62 mg, 0.45 mmol). The reaction mixture was stirred at 90 °C for 16 h under  $\text{N}_2$ . LCMS showed the reaction was completed. Next the reaction mixture was filtered and concentrated. The residue was purified by prep-HPLC (TFA) to give 3-(1,3-dimethylpyrazol-4-yl)-6-{3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazin-6-yl}-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (8 mg, 10.97%) as a yellow solid.

**[0195]** MS (ESI, pos. ion)  $m/z$ : 476.3[M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.41 (s, 1H), 8.95 (d,  $J$  = 2.0 Hz, 1H), 8.22 - 8.14 (m, 2H), 5.14 (m, 3H), 3.83 (s, 3H), 3.09 (s, 3H), 2.35 (s, 3H), 1.99 - 1.82 (m, 4H), 1.51 (s, 6H), 1.43 (s, 6H), 1H not observed (NH).

**[0196]** Example 6. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoroisindolin-1-one (Compound No. 274)

**[0197]** Scheme 6.



**[0198]** **Step 1:** To a solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL) was added nitrosonium tetrafluoroborate (480 mg, 4.10 mmol) portion wise at 0 °C under N<sub>2</sub> to obtain a yellow solution which was stirred at 0 °C for 1 h. Then oxylene (30 mL) was added the reaction mixture was refluxed at 130 °C for 3 h. Next the reaction mixture was cooled to room temperature and poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

**[0199]** **Step 2:** To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was added AIBN (57 mg, 0.35 mmol). The reaction mixture was stirred under N<sub>2</sub> at 100 °C for 16 h. Next, the reaction mixture was cooled to room temperature and poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

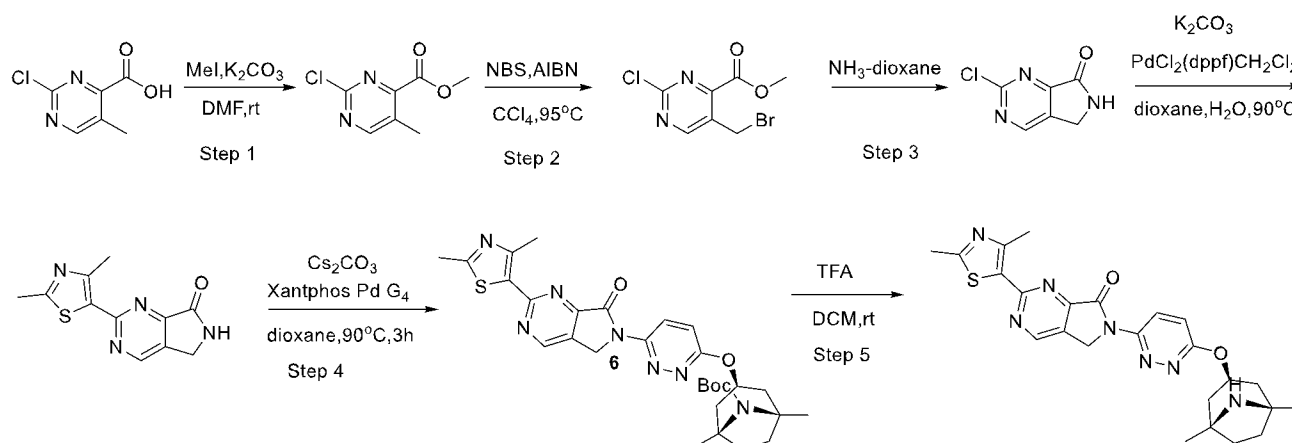
**[0200]** **Step 3:** Methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) was dissolved in THF (7 mL) and NH<sub>4</sub>OH (7 mL) was added. The reaction was stirred at room temperature for 4 h and was then filtered and concentrated under vacuum. The crude product was used directly in the next step without further purification.

**[0201] Step 4:** To the solution of 6-bromo-4-fluoroisoindolin-1-one (100 mg, 0.43 mmol) and 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (96 mg, 0.43 mmol) in dioxane:H<sub>2</sub>O (5:1) (2 mL : 0.4 mL), potassium carbonate (118 mg, 0.86 mmol) and PdCl<sub>2</sub>(dppf) (31 mg, 0.043 mmol) were added. The reaction mixture was stirred under N<sub>2</sub> at 100 °C for 16 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA. The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(1,3-dimethyl-1*H*-pyrazol-4-yl)-4-fluoroisoindolin-1-one (85 mg, 81%) as a yellow solid.

**[0202]** MS *m/z* 231.0 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 8.51 - 8.33 (m, 2H), 8.04 (s, 1H), 7.64 - 7.60 (m, 1H), 7.55 (d, *J* = 10.3 Hz, 1H), 7.31 (d, *J* = 10.0 Hz, 1H), 5.13 (s, 2H), 5.11 - 5.03 (m, 1H), 3.81 (s, 3H), 2.90 (s, 3H), 2.36 (s, 3H), 2.16 (br d, *J* = 8.1 Hz, 2H), 2.03 - 1.87 (m, 4H), 1.80 (br dd, *J* = 5.4, 13.6 Hz, 2H), 1.45 (s, 6H).

**[0203] Example 7. Synthesis of 6-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2-(2,4-dimethylthiazol-5-yl)-5,6-dihydro-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-one (Compound No. 111)**

**[0204] Scheme 7.**



**[0205] Step 1:** To a mixture of 2-chloro-5-methylpyrimidine-4-carboxylic acid (5.0 g, 28.97 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.01 g, 57.95 mmol) in DMF (10 mL) was added MeI (5.41 mL, 86.92 mmol) at room temperature, and the mixture was stirred for 16 h. After the reaction was completed, the mixture was filtrated, quenched with H<sub>2</sub>O, and extracted with EA. The combined organic layers were washed with aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The resulting residue was purified with chromatography on silica gel PE:EA=5:1 to give 2-chloro-5-methylpyrimidine-4-carboxylate (5.0 g, 92.49%) as a white solid.

**[0206] Step 2:** To a mixture of methyl 2-chloro-5-methylpyrimidine-4-carboxylate (5.0 g, 26.80 mmol) in CCl<sub>4</sub> (100 mL) was added NBS (6.20 g, 34.84 mmol) and AIBN (0.44 g, 2.68 mmol) at room temperature under N<sub>2</sub>, and the resulting mixture was stirred at 95 °C for 2 h. Next NBS (2.38 g, 13.40 mmol) was added and the mixture was stirred at 95 °C for 1 h. Then NBS (1.43 g, 8.04 mmol) was added and the mixture was stirred at 95 °C for 1 h. After the reaction was completed, the mixture was

cooled to room temperature and was quenched with H<sub>2</sub>O and extracted with DCM. The combined organic layers were washed with aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by chromatography on silica gel PE:EA=5:1 to give 5-(bromomethyl)-2-chloropyrimidine-4-carboxylate (4.0 g, 56.26%) as an oil.

**[0207] Step 3:** A mixture of methyl 5-(bromomethyl)-2-chloropyrimidine-4-carboxylate (4.0 g, 15.07 mmol) in NH<sub>3</sub>-dioxane (30 mL) was stirred at room temperature for 1 h. LCMS analysis showed the reaction was completed. The mixture was filtered and concentrated to afford 2-chloro-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (1.3 g, 50.98%) as a red solid.

**[0208] Step 4:** To a mixture of 2-chloro-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (110 mg, 0.65 mmol) and 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole (201.67 mg, 0.84 mmol) in dioxane: H<sub>2</sub>O=5:1 (6 mL) was added PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (52.98 mg, 0.06 mmol) and K<sub>2</sub>CO<sub>3</sub> (268.95 mg, 1.95 mmol) at room temperature under N<sub>2</sub>, and the mixture was stirred at 95 °C for 3 h. LCMS analysis showed the reaction was completed. Next the mixture was concentrated and the residue was purified by chromatography on silica gel DCM: MeOH=10:1 to give 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (0.1 g, 62.50%) as a yellow solid.

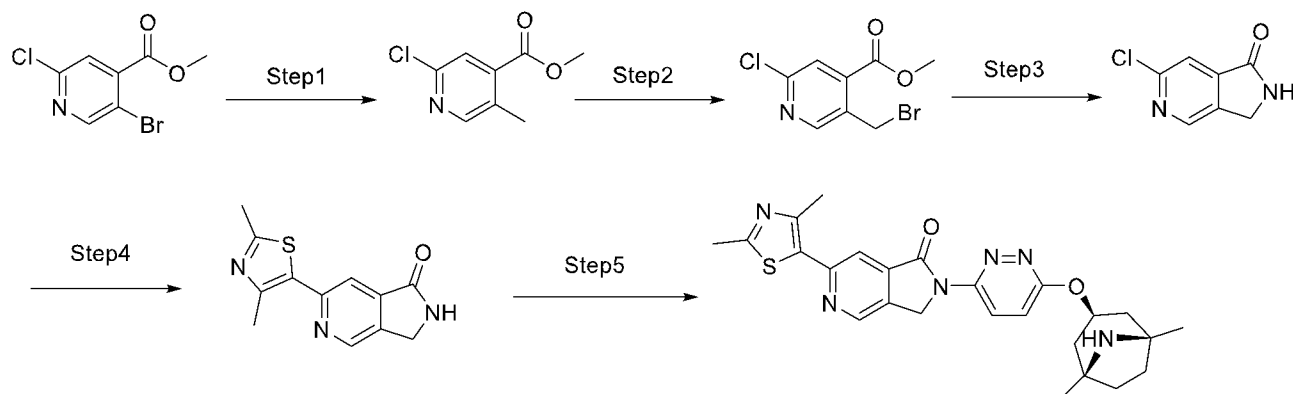
**[0209] Step 5:** To a mixture of 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (65 mg, 0.26 mmol), 2-methylpropan-2-yl (1R,3s,5S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (119.70 mg, 0.29 mmol) in dioxane (20 mL) was added XantPhos Pd G4 (42.76 mg, 0.03 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (257.97 mg, 0.79 mmol) at room temperature under N<sub>2</sub>, and the mixture was stirred at 95 °C for 16 h. LCMS analysis showed the reaction was completed. Next the mixture was filtered and concentrated to afford 2-methylpropan-2-yl (1S,3s,5R)-3-({6-[2-(2,4-dimethyl-1,3-thiazol-5-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 98.39%) as a yellow solid which was used in the next step without further purification.

**[0210] Step 6:** To a mixture of 2-methylpropan-2-yl (1S,3s,5R)-3-({6-[2-(2,4-dimethyl-1,3-thiazol-5-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.17 mmol) in DCM (10 mL) was added TFA (1 mL) at room temperature and the mixture was stirred at room temperature for 0.5 h. LCMS analysis showed the reaction was completed. Next the mixture was concentrated and the residue was purified with pre-HPLC(TFA) to give 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6-(6-[(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy)-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (72 mg, 87.09%) as a white solid.

**[0211]** MS (ESI, pos. ion) m/z: 478.3[M+H]<sup>+</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ = 9.32 (s, 1H), 8.94 (br s, 1H), 8.86 (br s, 1H), 8.74 (dd, *J* = 9.6, 0.9 Hz, 1H), 7.43 (d, *J* = 9.5 Hz, 1H), 5.49-5.60 (m, 1H), 5.21 (s, 2H), 2.84 (s, 3H), 2.67 (s, 3H), 2.42-2.48 (m, 2H), 2.17 (br d, *J* = 8.1 Hz, 2H), 1.89 (br d, *J* = 8.3 Hz, 2H), 1.76-1.85 (m, 2H), 1.46 (s, 6H).

**[0212] Example 8. Synthesis of (2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 69)**

**[0213] Scheme 8.**



**[0214] Step 1:** To a solution of methyl 5-bromo-2-chloroisonicotinate (5 g, 20 mmol, 1.0 eq), methylboronic acid (1.79 g, 29.8 mmol, 1.5 eq),  $K_3PO_4$  (14.8 g, 69.9 mmol, 3.5 eq),  $P(Cy)_3$  (1.11 g, 3.97 mmol, 0.2 eq) and  $Pd(OAc)_2$  (448 mg, 2.00 mmol, 0.1 eq) in toluene (95 mL) and  $H_2O$  (4.5 mL) was degassed and purged with  $N_2$  three times. Then the mixture was stirred at 100 °C for 2 hours under  $N_2$  atmosphere. When full conversion was achieved, the reaction mixture was quenched with water (40 mL) and extracted with ethyl acetate (3 x 20 mL). The extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to get the crude residue. The residue was purified by column chromatography ( $SiO_2$ , Petroleum ether/Ethyl acetate=20/1 to 15/1) to give methyl 2-chloro-5-methylisonicotinate (2 g, 54% yield) as a yellow solid.

**[0215] Step 2:** 2-Chloro-5-methylisonicotinate (15.0 g, 81.7 mmol, 1.0 eq), *N*-bromosuccinimide (20.3 g, 113.9 mmol, 1.4 eq) and benzoyl peroxide (448.0 mg, 1.85 mmol, 0.03 eq) were combined with carbon tetrachloride (250 mL). The reaction mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was cooled to rt and concentrated in vacuum. The obtained residue was purified by silica gel column chromatography with PE/EA to obtain methyl 5-(bromomethyl)-2-chloroisonicotinate (17.0 g, 79%) as a brown solid. LC/MS (ESI): 263.9, 265.9  $[M+H]^+$ .

**[0216] Step 3:** Methyl 5-(bromomethyl)-2-chloroisonicotinate (17.0 g, 64.6 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was kept stirring at rt for 8 hrs. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 169.0, 171.0  $[M+H]^+$ .

**[0217] Step 4:** 6-Chloro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (336.0 mg, 2.0 mmol, 1.0 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (526.1 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8.0 mL) and  $PdCl_2(dppf)$ .  $CH_2Cl_2$  adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask. The flask was evacuated and backfilled three times with nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, washing the filter cake with

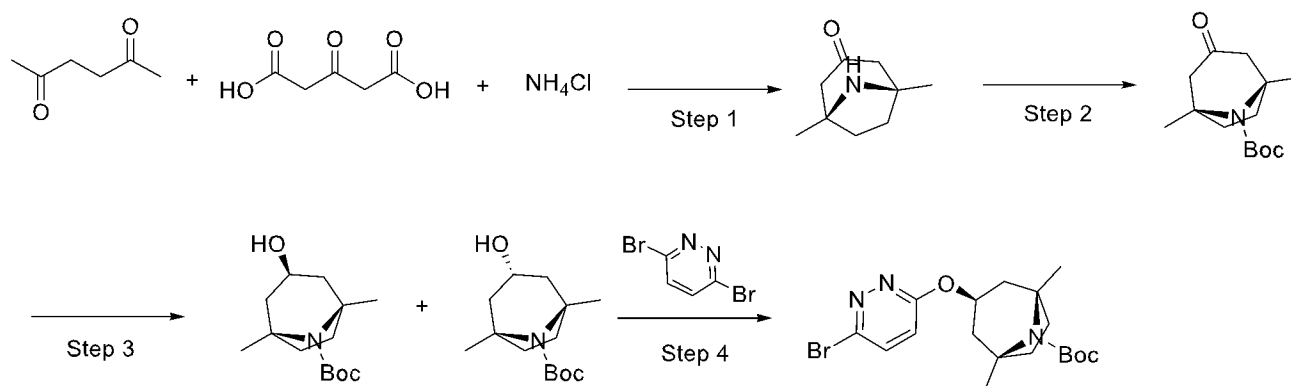
EtOAc (100 mL). The filtrate was washed with washed with brine, then the organic layer was collected and dried over sodium sulfate, then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (245 mg, 52%) as brown solid. LC/MS (ESI): 246.0 [M+H]<sup>+</sup>.

**[0218] Step 5:** To a round bottom flask charged with 6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (36.7 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(2,4-dimethylthiazol-5-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min then heated at 90 °C for 8 hrs. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(2,4-dimethylthiazol-5-yl)-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)pyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (42.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and then concentrated. The residue obtained was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 2-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (12.2 mg, 17.3 %) as a white solid.

**[0219]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ = 9.06 (s, 1H), 8.69 (d, *J* = 9.6 Hz, 1H), 8.24 (s, 1H), 7.92 (s, 1H), 7.35 (d, *J* = 9.6 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 2H), 2.65 (s, 6H), 2.22 (br dd, *J* = 5.9, 12.3 Hz, 2H), 1.88 (br d, *J* = 7.4 Hz, 2H), 1.60 (br d, *J* = 6.9 Hz, 2H), 1.49 (br t, *J* = 11.4 Hz, 2H), 1.25 (s, 6H); LC/MS (ESI): 477.2 [M+H]<sup>+</sup>.

**[0220] Example 9. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 72)**

**[0221] Scheme 9.**



**[0222] Step 1:** Potassium hydroxide (74.8 g, 1.33 mol, 4.5 eq) in water (60 mL) was added to a vigorous stirred solution of 3-oxopentanedioic acid (82.8 g, 0.566 mol, 4.5 eq) and hexane-2,5-dione (34.0 g, 0.298 mol, 1.0 eq) in water (120 mL) at 0 °C. After the addition, ammonium chloride (47.8 g, 0.896

mol, 3.0 eq) and sodium acetate (49.0 g, 0.596 mol, 2.0 eq) in water (200 mL) were added keeping the temperature at 5 °C. The pH value was adjusted to ~9 by using solid KOH. The mixture was stirred at room temperature for 4 days during which time the pH value was adjusted to ~9 by using additional solid KOH. The solution was diluted with 100 mL of water, cooled to 5 °C with vigorous stirring and acidified with pure sulfuric acid until pH = 2 (-60 mL). Gas evolution was observed during the acidification. Water layer was divided in two batches. Each batch was washed with EtOAc (2 x 100 mL) and basified with solid KOH with cooling until pH = 10. The water layer was extracted with 15% MeOH in DCM (4 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford 1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-one (17.3 g, 37.5 %) as a dark brown oil. LC/MS (ESI): 154.1 [M+H]<sup>+</sup>.

**[0223] Step 2:** To an ice-cold solution of 1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-one (3 g, 19.6 mmol, 1.0 eq) of DCM (60 mL) was added pyridine (4.0 mL, 49.0 mmol, 2.5 eq). Triphosgene (2.33g, 7.84 mmol, 0.4 eq) was dissolved in DCM (20mL) and added to the above solution dropwise. After 30 minutes, *t*-BuOH (3.78 mL, 39.2 mmol, 2.0 eq) was added and the mixture was gradually warmed to RT and stirred for 8 hrs. The reaction was quenched with water and diluted with DCM (300 mL). The mixture was washed with 1N HCl (1 x 50 mL), saturated sodium bicarbonate (1 x 50 mL), and brine (1 x 50 mL). The organic layer was collected and dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provide *tert*-butyl (1*R*,5*S*)-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.3 g, 9.1 mmol, 46.3%) as a slightly yellow oil. LC/MS (ESI): 254.2 [M+H]<sup>+</sup>.

**[0224] Step 3:** (1*R*,5*S*)-1,5-Dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.3 g, 9.1 mmol) was dissolved in EtOH (50 mL) and the solution was heated to reflux. Sodium borohydride (336 mg, 1.0 eq) and was added the mixture was stirred for 15 min. The mixture was cooled to RT and quenched with aqueous ammonium chloride. The organic solvent was removed under vacuum and the residue was redissolved in EtOAc (100 mL). The mixture was washed with brine, and the organic layer was collected and dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EtOAc to provided *tert*-butyl (1*R*,3*r*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.2g, 52%, PE/EtOAc 3/1, v/v) and *tert*-butyl (1*R*,3*s*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.1g, 48%, PE/EtOAc 2/1, v/v) as white solid. LC/MS (ESI): 256.2 [M+H]<sup>+</sup>.

**[0225] Step 4:** To a solution of (1*R*,3*s*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.10g g, 4.34 mmol, 1.0 eq) in anhydrous THF (20 mL) was added NaH (60 wt %, 208 mg, 5.21 mmol, 1.2 eq). The solution was stirred at room temperature for 30 min, then 3,6-dibromopyridazine (1.24 g, 5.21 mmol, 1.2 eq) was added and the mixture was stirred at RT for 8 hrs. The reaction mixture was quenched with saturated ammonium chloride and diluted with EtOAc (100 mL). The mixture was washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provide *tert*-

butyl (1*R*,3*s*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.28g, 72%) as white solid. LC/MS (ESI): 412.2, 414.2 [M+H]<sup>+</sup>.

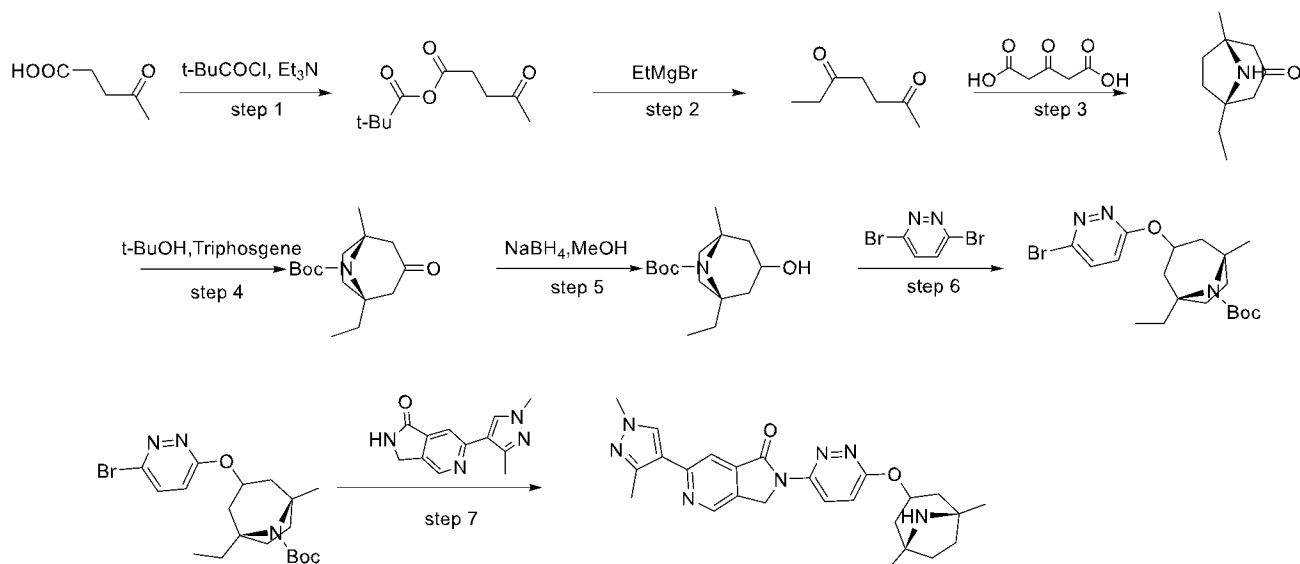
**[0226] Step 5:** A mixture of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (210 mg, 0.92 mmol), 2-methylpropan-2-yl (1*R*,3*s*,5*S*)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (379.36 mg, 0.92 mmol) in dioxane (30 mL) was added Xantphos Pd G4 (149.05 mg, 0.09 mmol), Cs<sub>2</sub>CO<sub>3</sub> (897.04 mg, 2.76 mmol) at RT under N<sub>2</sub> and the mixture was stirred at 95 °C for 16 h. The reaction mixture was concentrated and the residue was purification by chromatography on silica gel and eluted with DCM:MeOH=10:1 to give 2-methylpropan-2-yl (1*R*,3*s*,5*S*)-3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (400 mg, 77.68%) as a yellow solid.

**[0227] Step 6:** A mixture of 2-methylpropan-2-yl (1*R*,3*s*,5*S*)-3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (360 mg, 0.64 mmol) in DCM (10 mL) was added HCl-dioxane (20 mL) at RT and the mixture was stirred for 1 h. The reaction mixture was concentrated and the residue was purification by pre-HPLC(HCl) to give 6-(1,3-dimethylpyrazol-4-yl)-2-(6-[(1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy)-1,2-diazin-3-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (248 mg, 83.90%) as a yellow solid.

**[0228]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ = 8.98 (s, 1H), 8.71 (d, *J* = 9.6 Hz, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 5.51 (br t, *J* = 5.7 Hz, 1H), 5.23 (s, 2H), 3.81 (s, 3H), 2.47-2.48 (s, 3H), 2.36 (br dd, *J* = 13.0, 5.9 Hz, 2H), 2.06 (br d, *J* = 7.8 Hz, 2H), 1.79 (br d, *J* = 8.0 Hz, 2H), 1.69 (br t, *J* = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 460.2 [M+H]<sup>+</sup>.

**[0229] Example 10. Synthesis of 6-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-(6-(((1*S*,3*R*,5*R*)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (Compound No. 98)**

**[0230] Scheme 10.**



**[0231] Step 1:** A solution of pivaloyl chloride (41.96 mL, 341.03 mmol) in dry THF (50 mL) was added dropwise to a stirred and ice-cooled solution of 4-oxopentanoic acid (31.86 mL, 310.02 mmol) and triethylamine (128.92 mL, 930.07 mmol) in dry THF (300 mL) at 5 °C. The solution was stirred for 1.5 h at 5 °C, and the precipitated Et<sub>3</sub>N HCl was filtered off. The solid salt was washed with THF. The combined filtrate and washings were dried (MgSO<sub>4</sub>), and concentrated in vacuo to give 2,2-dimethylpropanoic 4-oxopentanoic anhydride (57 g, 284.67 mmol, 91.82%) as a colorless oil which was used immediately in the next step. LC/MS (ESI): 201.1 [M+H]<sup>+</sup>.

**[0232] Step 2:** A solution of EtMgBr in THF (1 M, 323.14 mL, 313.14 mmol) was added dropwise over 30 min to a stirred and cooled solution of 2,2-dimethylpropanoic 4-oxopentanoic anhydride (57 g, 284.67 mmol) in dry THF (300 mL) at -60 °C under N<sub>2</sub>. After the addition, the mixture was stirred for 30 min at -60 °C. Subsequently the cooling bath was removed and the mixture was stirred for an additional 1 h. The reaction was quenched with the addition of ice and NH<sub>4</sub>Cl solution, and was then extracted with EA. The EA solution was washed successively with water and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residues obtained from two runs were combined and distilled in vacuo to give heptane-2,5-dione (25 g, 195.05 mmol, 68.52%) as a colorless oil. LC/MS (ESI): 129.1 [M+H]<sup>+</sup>.

**[0233] Step 3:** KOH (49.25 g, 877.74 mmol) in water (50 mL) was added to a vigorous stirred solution of heptane-2,5-dione (25 g, 195.05 mmol) and 3-oxopentanedioic acid (42.30 mL, 370.60 mmol) in water (250 mL) at 0 °C. NH<sub>4</sub>Cl (20.59 mL, 585.16 mmol) and KOAc (38.29 g, 390.11 mmol) in water (200 mL) were added at 5 °C. The pH value was adjusted to ~9 by using solid KOH. The mixture was stirred at room temperature for 4 days during which time the pH value was adjusted to ~9 by using additional solid KOH. The solution was diluted with 300 mL of water and transferred to a 2 L beaker and cooled to 5 °C and acidified with pure sulfuric acid until pH = 2. Gas evolution was observed during the acidification. The aqueous layer divided in two batches. Each batch was washed with EA (2 x 1000 mL) and basified with solid KOH until pH = 10. The aqueous layer was extracted with 15% MeOH in DCM (4 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over sodium

sulfate, filtered, and concentrated in vacuo to afford (1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-one (9 g, 53.81 mmol, 27.59%) as a dark brown oil. LC/MS (ESI): 169.1 [M+H]<sup>+</sup>.

**[0234] Step 4:** To an ice-cold solution of (1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-one (9 g, 53.81 mmol) in DCM (80 mL) was added pyridine (10.86 mL, 134.53 mmol). Trichloromethyl [(trichloromethyl)oxy]methanoate (3.59 mL, 21.52 mmol) was dissolved in DCM (20 mL) and added dropwise to the reaction mixture. After 30 minutes, 2-methylpropan-2-ol (10.23 mL, 107.62 mmol) was added and the mixture was gradually warmed to RT and stirred for 8 h. The reaction was quenched with water and diluted with DCM (300 mL). The mixture was washed with 1N HCl (1 x 50 mL), saturated sodium bicarbonate (1 x 100 mL) and brine (1 x 100 mL). The organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provided 2-methylpropan-2-yl (1R)-5-ethyl-1-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (7.5 g, 28.05 mmol, 52.13%) as a slightly yellow oil. LC/MS (ESI): 268.2 [M+H]<sup>+</sup>.

**[0235] Step 5:** 2-Methylpropan-2-yl (1R)-5-ethyl-1-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (7.5 g, 28.05 mmol) was dissolved in EtOH (60 mL) and the solution was heated to reflux. NaBH<sub>4</sub> (0.31 mL, 8.42 mmol) was added and the mixture was stirred for 15 min. The mixture was cooled to RT and quenched with aqueous ammonium chloride. The organic solvent was removed under vacuum and the residue was redissolved in EA (200 mL). The mixture was washed with brine, then the organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The residue was purified by silica gel column chromatography with PE/EtOAc to provided 2-methylpropan-2-yl (1R)-5-ethyl-3-hydroxy-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 13.74 mmol, 48.97%). LC/MS (ESI): 270.2 [M+H]<sup>+</sup>.

**[0236] Step 6:** To a solution of 2-methylpropan-2-yl (1R)-5-ethyl-3-hydroxy-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 13.74 mmol) in anhydrous THF (35 mL) was added NaH (0.33 g, 13.74 mmol). The solution was stirred at room temperature for 30 min, then 3,6-dibromo-1,2-diazine (3.27 g, 13.74 mmol) was added and the mixture was stirred at RT for 8 h. The reaction mixture was quenched with saturated ammonium chloride and diluted with EA (200 mL). The mixture was washed with brine, the organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The crude was purified by silica gel column chromatography with PE/EA 20/1, v/v to provided 2-methylpropan-2-yl (1R)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-5-ethyl-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (2 g, 4.69 mmol, 34.15%) as a white solid. LC/MS (ESI): 426.1 [M+H]<sup>+</sup>.

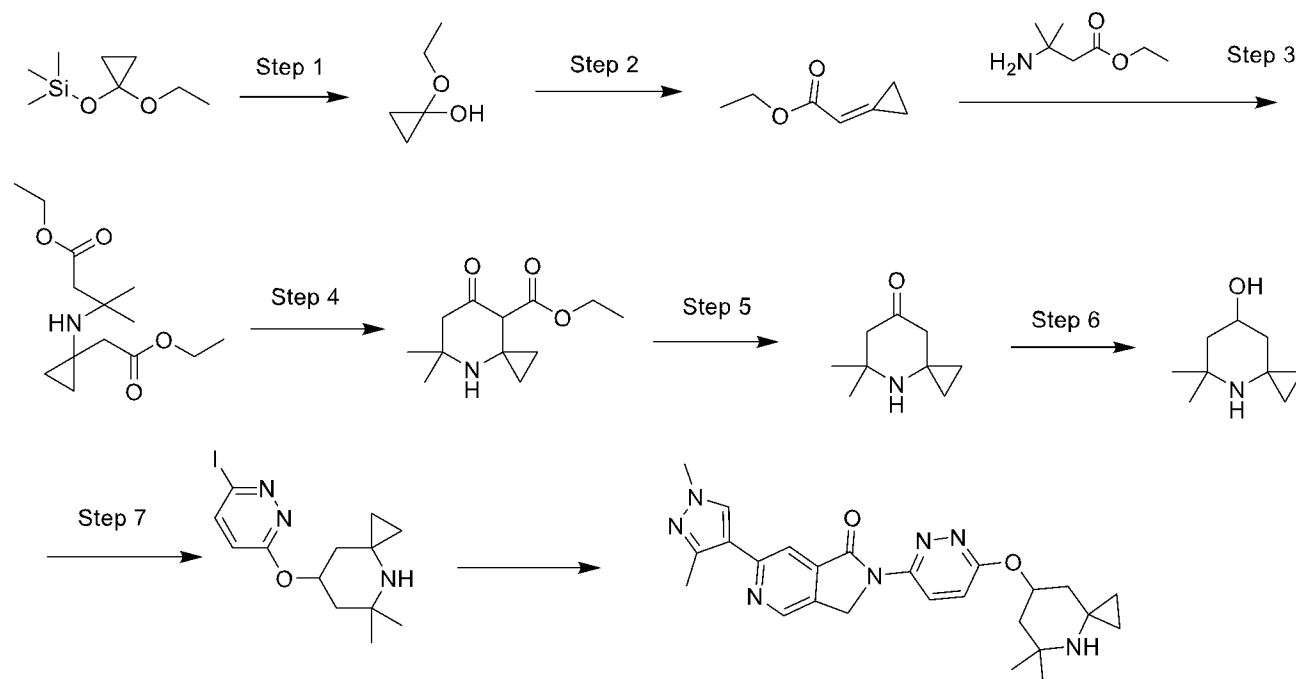
**[0237] Step 7:** To a round bottom flask charged with 2-methylpropan-2-yl (1S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.35 mmol), 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (88.33 mg, 0.39 mmol), Cs<sub>2</sub>CO<sub>3</sub> (102.23 mg, 0.31 mmol, and XantPhos Pd G4 (16.94 mg, 0.01 mmol) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude was purified by silica gel column

chromatography with DCM/MeOH 20/1, v/v to afford 2-methylpropan-2-yl ((1S,5R)-3-((6-((1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl)-1,2-diazin-3-yl)oxy)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and then concentrated. The residue was purified by RP HPLC using MeCN and H<sub>2</sub>O to provide 6-(1,3-dimethylpyrazol-4-yl)-2-(6-((1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (20 mg, 0.04 mmol, 12.00%) as a white solid.

**[0238]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  = 8.98 (s, 1H), 8.70 (d, *J* = 9.6 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.88 (s, 1H), 7.34 (d, *J* = 9.6 Hz, 1H), 5.51 (s, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.26 (br dd, *J* = 5.6, 12.4 Hz, 2H), 1.90 (br t, *J* = 7.1 Hz, 2H), 1.71 - 1.48 (m, 6H), 1.30 (s, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); LC/MS (ESI): 474.2 [M+H]<sup>+</sup>.

**[0239] Example 11. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 59)**

**[0240] Scheme 11.**



**[0241] Step 1:** A solution of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane (11.5 mL, 57.37 mmol, 1.0 eq) in MeOH (100 mL) was stirred at RT overnight. The reaction mixture was concentrated under vacuum and use directly in the next step without purification.

**[0242] Step 2:** A solution of 1-ethoxycyclopropan-1-ol (5.9 g, 57.38 mmol, 1.0 eq) and benzoic acid (1.4 g, 11.48 mmol, 0.2 eq) in toluene (6 mL) was stirred at 110 °C for 15 min. Then ethyl (triphenyl-λ<sup>5</sup>-phosphanylidene)acetate (20.0 g, 57.38 mmol, 1.0 eq) was added and the mixture was stirred at 110 °C for 48 hours. The reaction mixture was concentrated under vacuum. The crude product was purified by silica gel chromatography eluted with PE to give ethyl cyclopropylideneacetate (3.1 g, 42.4%).

**[0243] Step 3:** A solution of ethyl cyclopropylideneacetate (1.7 g, 13.47 mmol, 1.0 eq), ethyl 3-amino-3-methylbutanoate (2.3 g, 16.17 mmol, 1.2 eq) in DIEA (2.99 mL, 18.06 mmol, 1.34 eq) was stirred at 60 °C for 3 h. The reaction was monitored by TLC and LC/MS. The crude product was purified by silica gel chromatography eluted with PE:EA (5:1) to obtain ethyl 3-((1-(2-ethoxy-2-oxoethyl)cyclopropyl)amino)-3-methylbutanoate (1.2 g, 32.2%). LC/MS (ESI): 272.1 [M+H]<sup>+</sup>.

**[0244] Step 4:** To a solution of ethyl 3-((1-(2-ethoxy-2-oxoethyl)cyclopropyl)amino)-3-methylbutanoate (980 mg, 3.64 mmol, 1.0 eq) in THF (10 mL) was added t-BuOK (5.46 mL, 5.46 mmol) at 0 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at 0 °C for 1 h. LC/MS showed the desired mass. The reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (10 mL). The resulting mixture was extracted with EA (2 x 20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE/EA (3:1) to obtain ethyl 5,5-dimethyl-7-oxo-4-azaspiro[2.5]octane-8-carboxylate (618 mg, 76.1%). LC/MS (ESI): 226.1 [M+H]<sup>+</sup>.

**[0245] Step 5:** A solution of ethyl 7-oxospiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-8-carboxylate (618.0 mg, 2.77 mmol, 1.0 eq) in a mixture of H<sub>2</sub>O (5 mL) and H<sub>2</sub>SO<sub>4</sub> (5 mL) was stirred at 120 °C for 1 h. LC/MS showed desired mass. The reaction mixture was poured into ice water. The aqueous layer was adjusted to pH over 9 and extracted with EA (3 x 20 mL). The crude was concentrated under reduced pressure to yield 5,5-dimethyl-4-azaspiro[2.5]octan-7-one (326.0 mg, 77.9%). LC/MS (ESI): 154.1 [M+H]<sup>+</sup>.

**[0246] Step 6:** To a solution of spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-one (86.0 mg, 0.57 mmol, 1.0 eq) in MeOH (5 mL) was added NaBH<sub>4</sub> (64.5 mg, 1.71 mmol, 3.0 eq) at 0 °C. The mixture was stirred at RT for 1 h. LC/MS showed desired mass. The reaction mixture was diluted with H<sub>2</sub>O and the pH was adjusted to 7. The aqueous layer was extracted with EA (2 x 10 mL) and (DCM/propan-2-ol:IPA, 10:1). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was use directly in the next step without further purification. LC/MS (ESI): 156.1 [M+H]<sup>+</sup>.

**[0247] Step 7:** To a solution of 5,5-dimethyl-4-azaspiro[2.5]octan-7-ol (106.0 mg, 0.69 mmol, 1.0 eq) in THF (5 mL) was added NaH (39.0 mg, 0.98 mmol, 1.4 eq) at 0 °C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at 0 °C under N<sub>2</sub> atmosphere for 20 min. Then, 3,6-diiodo-1,2-diazine (252.5 mg, 0.76 mmol, 1.1 eq) was added the mixture was stirred at 60 °C overnight. The reaction was cooled to RT and diluted with DMF (5 mL) and then the reaction was stirred for another 3 h at 100 °C. LC/MS showed desired mass. The reaction was cooled to RT and then pouring into water. The aqueous layer was extracted with EA (3 x 10 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EA (1:1) to obtain 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (146.0 mg, 59.1%). LC/MS (ESI): 360.0 [M+H]<sup>+</sup>.

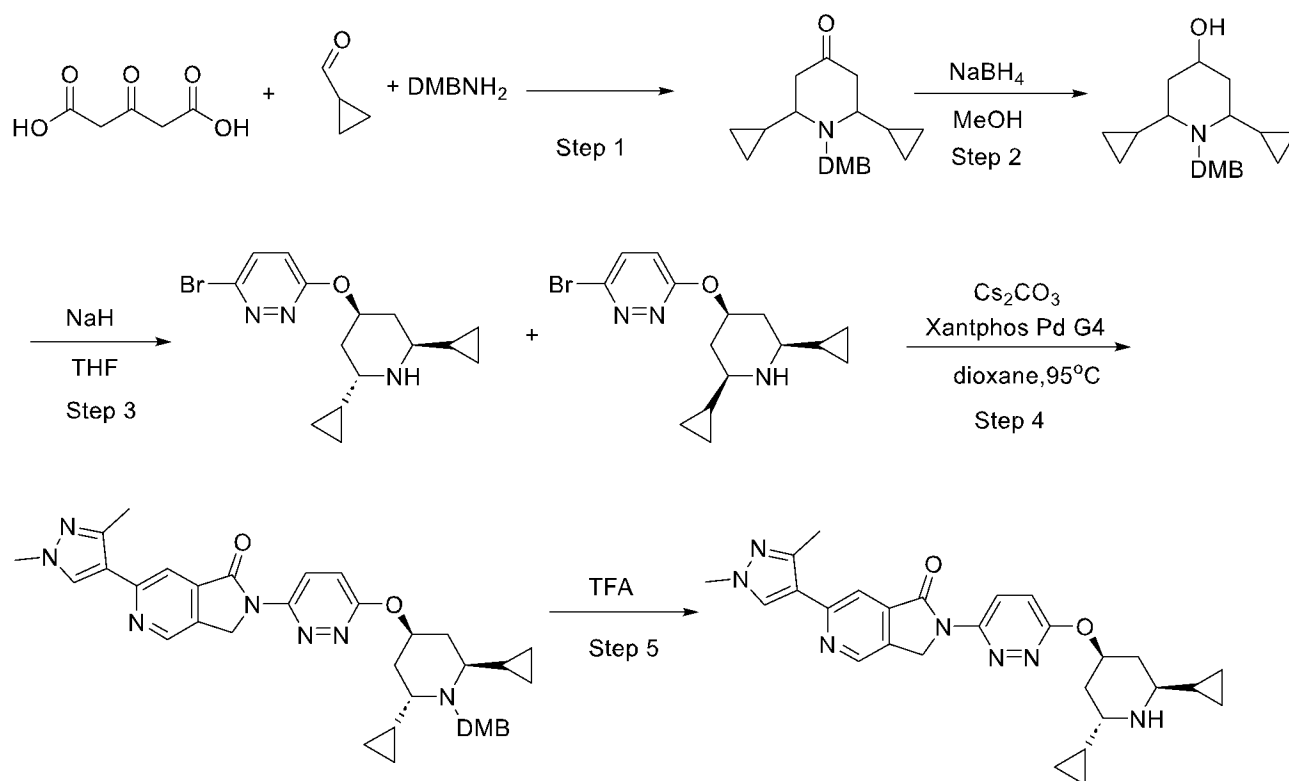
**[0248] Step 8:** A solution of 7-((6-iodopyridazin-3-yl)oxy)-5,5-dimethyl-4-azaspiro[2.5]octane (48.0 mg, 0.13 mmol, 1.0 eq), 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (32.2 mg, 0.14 mmol, 1.05 eq), (1*R*,2*R*)-cyclohexane-1,2-diamine (1.5 mg, 0.01 mmol, 0.1 eq), CuI (2.7 mg,

0.01 mmol, 0.1 eq),  $K_2CO_3$  (55.7 mg, 0.40 mmol, 3.0 eq) in DMF (3 mL) was stirred at 120 °C overnight under  $N_2$  atmosphere. LC/MS showed desired mass and reactant consumed. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel chromatography eluted with DCM/MeOH (10:1) then prep-HPLC(FA) to obtain 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (12.92 mg, 19.1%).

**[0249]**  $^1H$  NMR (DMSO- $d_6$ , 400MHz)  $\delta$  = 8.98 (s, 1H), 8.69 (d,  $J$  = 9.6 Hz, 1H), 8.37 (s, 1H), 8.19 (br s, 1H), 7.88 (s, 1H), 7.32 (d,  $J$  = 9.6 Hz, 1H), 5.63 - 5.53 (m, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.11 (br dd,  $J$  = 3.6, 12.3 Hz, 1H), 1.88 - 1.80 (m, 1H), 1.63 (br dd,  $J$  = 4.3, 11.8 Hz, 1H), 1.37 (t,  $J$  = 11.6 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.59 - 0.52 (m, 2H), 0.51 - 0.44 (m, 1H), 0.40 - 0.33 (m, 1H); LC/MS (ESI): 460.1  $[M+H]^+$ .

**[0250] Example 12. Synthesis of 2-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 104)**

**[0251] Scheme 13.**



**[0252] Step 1:** To a solution of acetone dicarboxylic acid (3.0g, 0.5mmol) in water (20mL) was added cyclopropanecarbaldehyde (2.876 g, 41 mmol) and then (2,4-dimethoxyphenyl)methanamine (2.8 g, 20.5 mmol) was added portionwise over 10 min. The resulting reaction was stirred at room temperature for 3 days. The reaction mixture was extracted with DCM (3 x 60 mL) and the combined extracts were washed with brine, dried over anhydrous  $Na_2SO_4$ , and dried under vacuum to give a brown residue. The isomeric

piperidones were separated by silica gel chromatography with hexane/ethyl acetate (7/1, v/v). The desired compound (3.4 g, 54 %) was obtained as a pale yellow oil.

**[0253] Step 2:** To a mixture of 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-one (5.0 g, 15.18 mmol) in MeOH (50 mL) was added NaBH<sub>4</sub> (0.57 g, 15.18 mmol) at RT under N<sub>2</sub> and the mixture was stirred at for 2 h. The mixture was concentrated and the residue was purification by chromatography on silica gel DCM : MeOH=10:1 to give 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-ol (2.0 g, 39.76%) as an oil.

**[0254] Step 3:** To a mixture of 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-ol (2.0 g, 6.03 mmol) in THF (30 mL) was added NaH (0.48 g, 12.07 mmol) at RT under N<sub>2</sub> and the mixture was stirred for 1 h. Then 3,6-dibromo-1,2-diazine (1.87 g, 7.84 mmol) was added and the mixture was stirred at 50 °C for 16 h. The mixture was quenched with MeOH and concentrated under vacuum. The resulting residue was purification by chromatography on silica gel PE:EA=10:1-5:1 to give 3-bromo-6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (440, 14.93%) and 3-bromo-6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (800 mg, 1.64 mmol, 27.16%) as a white solid.

**[0255] Step 4:** To a mixture of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-3-one (70 mg, 0.31 mmol) and 3-bromo-6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (149.79 mg, 0.31 mmol) in dioxane (10 mL) was added XantPhos Pd G4 (49.68 mg, 0.03 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (299.77 mg, 0.92 mmol) at RT under N<sub>2</sub> and the mixture was stirred at 95 °C for 3h. The mixture was concentrated under reduced pressure and the residue was purification by chromatography on silica gel DCM : MeOH=10 to give 2-(6-(((2S,6S)-2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (170 mg, 86.36%) as a yellow solid.

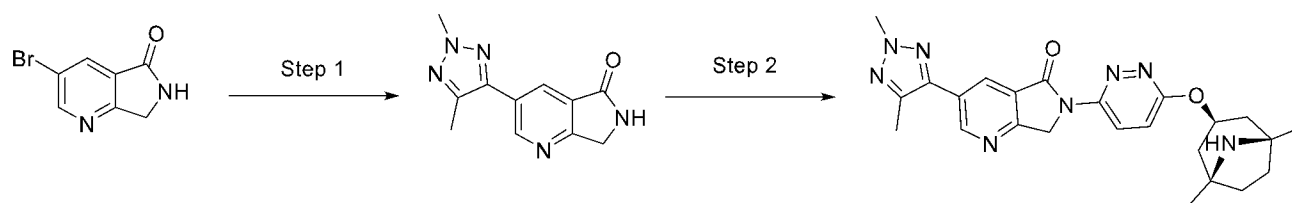
**[0256] Step 5:** A mixture of 2-(6-(((2S,6S)-2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo

**[0257]** [3,4-c]pyridin-1-one (170 mg, 0.27 mmol) in TFA (20 mL) was stirred at 110 °C for 48 h. After the reaction was completed, the mixture was concentrated under reduced pressure and the residue was purified by pre-HPLC(TFA) to give 6-(1,3-dimethylpyrazol-4-yl)-2-(6-(((2S,6S)-2,6-dicyclopropylhexahydropyridin-4-yl]oxy}-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (78.73 mg, 60.56%) as a yellow solid.

**[0258]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ = 8.98 (s, 1H), 8.73 (d, *J* = 9.6 Hz, 1H), 8.34 (s, 1H), 7.88 (s, 1H), 7.38 (d, *J* = 9.6 Hz, 1H), 5.64 (dt, *J* = 9.0, 4.7 Hz, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.90-3.00 (m, 2H), 2.46-2.49 (m, 3H), 2.40-2.46 (m, 1H), 2.29-2.38 (m, 1H), 1.85-2.06 (m, 2H), 1.24-1.34 (m, 1H), 1.18 (td, *J* = 8.5, 4.0 Hz, 1H), 0.53-0.70 (m, 5H), 0.35-0.51 (m, 3H), 1H not observed (NH); LC/MS (ESI): 486.2 [M+H]<sup>+</sup>.

**[0259] Example 13. Synthesis of 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 206)**

**[0260] Scheme 13.**



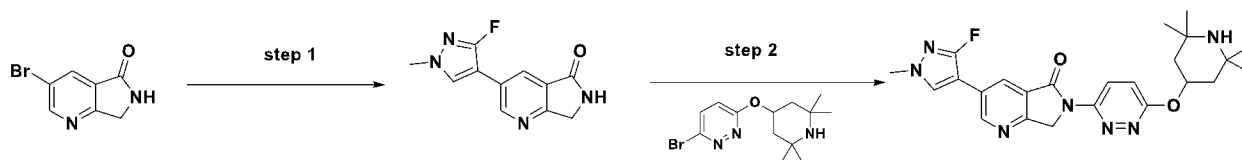
**[0261] Step 1:** 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq); 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf) were added to the CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) and the solids were degassed under N<sub>2</sub>. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. After the reaction was completed, the reaction mixture was cooled to room temperature. Next 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2mL) and PdCl<sub>2</sub>(dppf) were added and the mixture was heated to 90 °C. After the reaction was completed, the mixture was cooled, filtered through Celite, and washed with EA (100 mL). The filtrate was washed with brine and then the organic layer was collected, dried over sodium sulfate, and then concentrated under vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (116 mg, 51%) as a brown solid. LC/MS (ESI): 230.1 [M+H]<sup>+</sup>.

**[0262] Step 2:** To a round bottom flask charged with 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (37.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) 1,4-dioxane (4 mL) was added and the reaction mixture was degassed with argon for 5 min and then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v and was then dissolved in HCl in dioxane (2 mL, 4.0 mol/L) and stirred for 1 h at RT. The product was concentrated under reduced pressure and the resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (37.8 mg, 54.7 %) as a white solid.

**[0263]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ = 9.18 (d, J = 2.0 Hz, 1H), 8.87 (br d, J = 10.6 Hz, 1H), 8.79 (br s, 1H), 8.75 (d, J = 9.6 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 9.5 Hz, 1H), 5.55 (tt, J = 10.9, 5.6 Hz, 1H), 5.24 (s, 2H), 4.19 (s, 3H), 2.46 (br d, J = 6.1 Hz, 2H), 2.18 (br d, J = 8.0 Hz, 2H), 1.90 (br d, J = 8.3 Hz, 2H), 1.80 (br t, J = 12.1 Hz, 2H), 1.46 (s, 6H), 3H not observed (triazole methyl overlapped with DMSO-*d*<sub>6</sub> residue); LC/MS (ESI): 461.2 [M+H]<sup>+</sup>.

**[0264] Example 14. Synthesis of 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 190)**

**[0265] Scheme 14.**



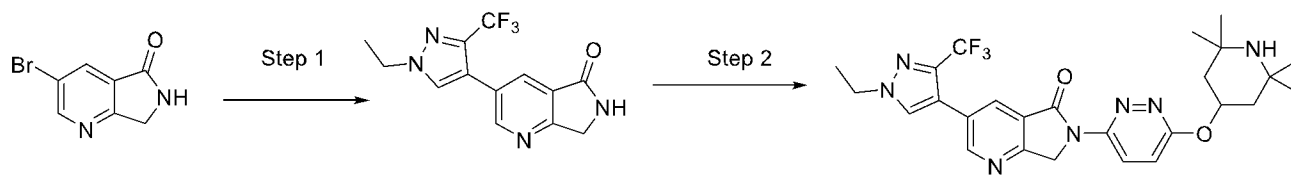
**[0266] Step 1:** 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. 4-Bromo-3-fluoro-1-methyl-1H-pyrazole (177.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (116mg, 51%) as a brown solid. LC/MS (ESI): 233.1  $[\text{M}+\text{H}]^+$ .

**[0267] Step 2:** 3-[1-(Trifluoromethyl)pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (106 mg, 0.46 mmol), 3-bromo-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazine (149.39 mg, 0.46 mmol), XantPhos Pd G4 (73.95 mg, 0.05 mmol) and  $\text{Cs}_2\text{CO}_3$  (446.18 mg, 1.37 mmol) was dissolved in dioxane (8 mL) and the reaction mixture was stirred at 90 °C overnight. After the reactants was consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (100 mL). The mixture was washed with brine, and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH to provided 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (24.1 mg, 0.05 mmol, 10.91%) as a white solid.

**[0268]**  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400MHz)  $\delta$  = 8.99-9.09 (m, 1H), 8.68 (d,  $J$  = 9.6 Hz, 1H), 8.37-8.47 (m, 1H), 8.22-8.31 (m, 1H), 7.24-7.36 (m, 1H), 5.57-5.68 (m, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 2.05-2.07 (m, 2H), 1.24-1.29 (m, 2H), 1.23 (s, 6H), 1.08-1.13 (m, 6H), 1H not observed (NH); LC/MS (ESI): 466.2  $[\text{M}+\text{H}]^+$ .

**[0269] Example 15. Synthesis of 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 172)**

**[0270] Scheme 15.**



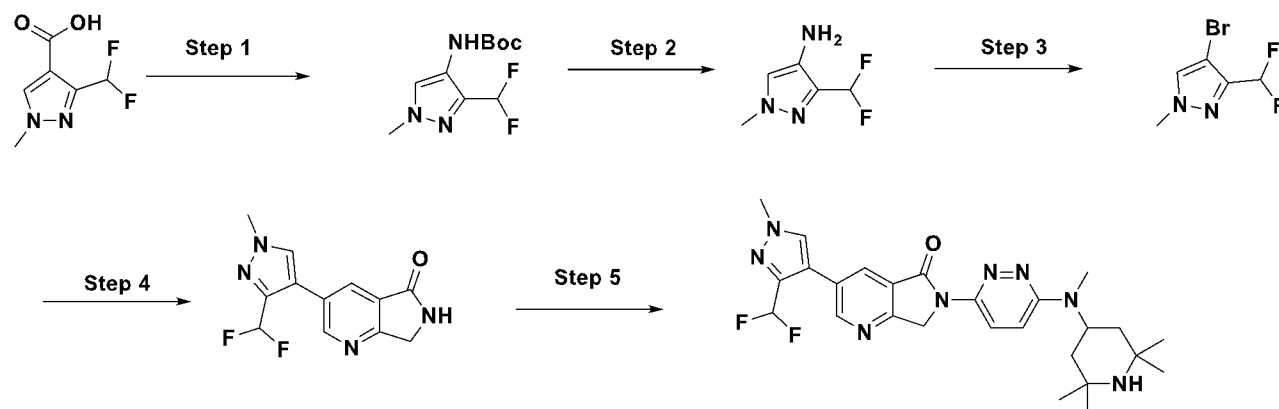
**[0271] Step 1:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), (1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)boronic acid (312. mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (183.2 mg, 62%) as a brown solid. LC/MS (ESI): 297.1 [M+H]<sup>+</sup>.

**[0272] Step 2:** To a round bottom flask charged with 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (44.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1R,3S,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v. The residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (42.35 mg, 53.3 %) as a white solid.

**[0273]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 8.92 (d, 1H, *J* = 2.0 Hz), 8.71 (d, 1H, *J* = 9.6 Hz), 8.50 (s, 1H), 8.32 (s, 1H), 8.19 (d, 1H, *J* = 2.0 Hz), 7.35 (d, 1H, *J* = 9.6 Hz), 5.64 (s, 1H), 5.24 (s, 2H), 4.30 (q, 2H, *J* = 7.3 Hz), 2.17 (dd, 2H, *J* = 3.9, 12.4 Hz), 1.5-1.5 (m, 3H), 1.4-1.5 (m, 2H), 1.34 (s, 6H), 1.24 (s, 6H); LC/MS (ESI): 530.2 [M+H]<sup>+</sup>.

**[0274] Example 16. Synthesis of 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 198)**

## [0275] Scheme 16.



**[0276] Step 1:** To a solution of 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (6.58 mL, 56.78 mmol) in 2-methylpropan-2-ol (200 mL) was added ethyl[di(prop-2-yl)]amine (18.82 mL, 113.56 mmol) and diphenyl azidophosphonate (15.99 mL, 73.81 mmol) and the reaction mixture was stirred at 90 °C for 4 h under N<sub>2</sub>. The mixture was diluted with EA (10 mL\*3) and H<sub>2</sub>O (30 mL) and the organic layer was washed with brine (5 mL\*3), dried over sodium sulfate, and then concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to provided tert-butyl (3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)carbamate (13.2 g, 53.39 mmol, 94.03%). LC/MS (ESI): 248.1 [M+H]<sup>+</sup>.

**[0277] Step 2:** To a solution of tert-butyl (3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)carbamate (13.2 g, 53.39 mmol) in MeOH (30 mL) was added 4M HCl-MeOH (60 mL) and the reaction mixture was stirred at 25 °C overnight. Then the reaction mixture was concentrated to obtain the cured product 3-(difluoromethyl)-1-methyl-1H-pyrazol-4-amine (10.2 g) which was used in the next step without further purification. LC/MS (ESI): 148.1[M+H]<sup>+</sup>.

**[0278] Step 3:** To a solution of 3-(difluoromethyl)-1-methyl-1H-pyrazol-4-amine (3 g, 20.39 mmol) in acetonitrile (30 mL) was added 2-methyl-2-(nitrosooxydanyl)propane (3.67 mL, 30.59 mmol) and copper bromide (I) (1.24 mL, 40.78 mmol) and the reaction mixture was stirred at 70 °C for 1 h. The mixture was diluted with EA (50 mL\*3) and H<sub>2</sub>O (50 mL) and then the organic layer was washed with brine (30 mL\*3), dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA (50/1-20/1-10/1, v/v) to provide 4-bromo-3-(difluoromethyl)-1-methyl-1H-pyrazole (2.3 g, 10.90 mmol, 53.46%). LC/MS (ESI): 210.9, 212.9 [M+H]<sup>+</sup>.

**[0279] Step 4:** 4-Bromo-3-(difluoromethyl)-1-methyl-1H-pyrazole (316.5 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Next 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture

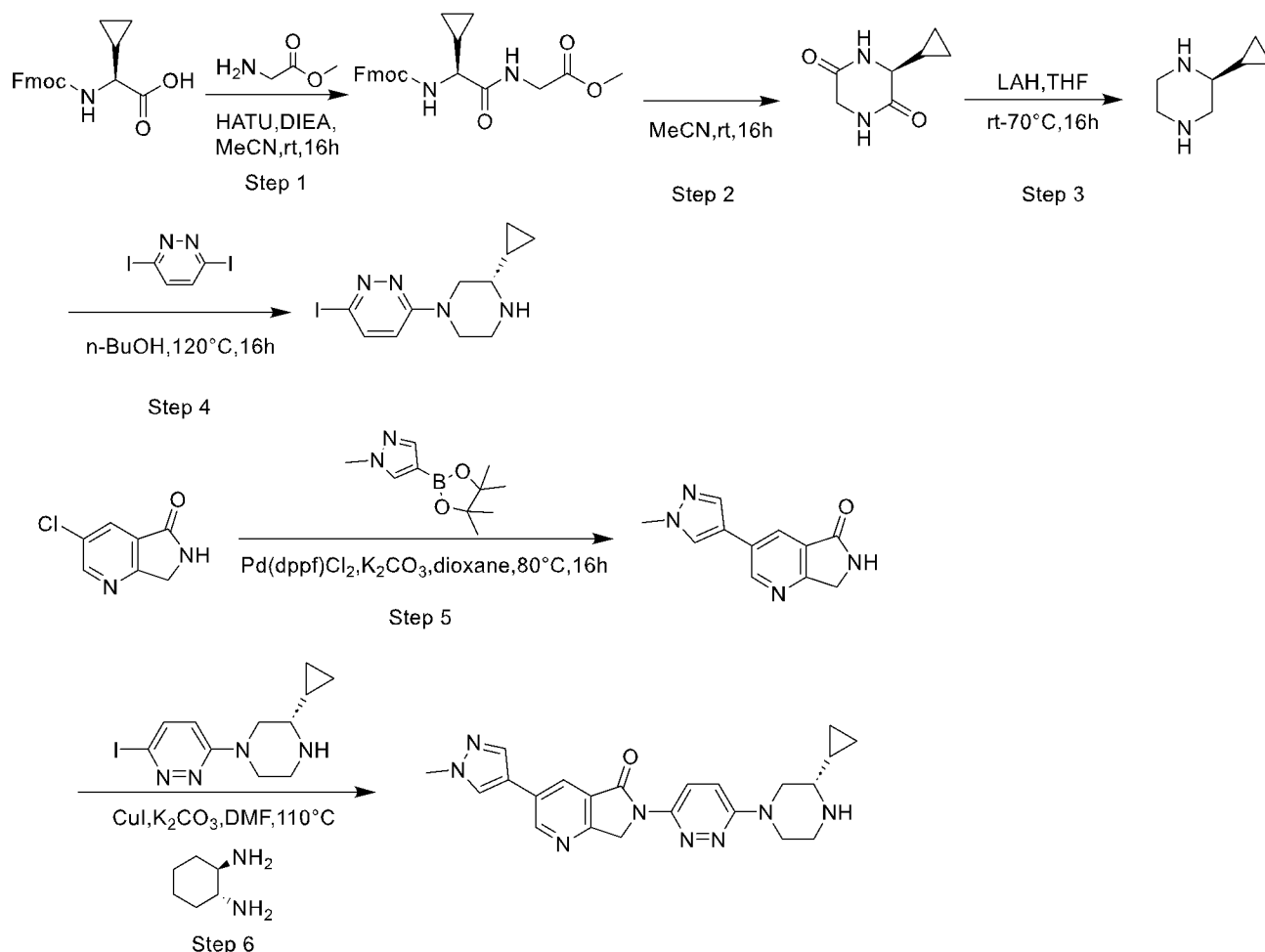
was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to obtain 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (164.7 mg, 62%) as a brown solid. LC/MS (ESI): 265.1 [M+H]<sup>+</sup>.

**[0280] Step 5:** To a round bottom flask charged with 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (39.4 mg, 0.15 mmol, 1.0 eq), 6-bromo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, and then the residue was further purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (3.83 mg, 5.0 %) as a white solid.

**[0281]** <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ : 8.97 (d, *J* = 2.0 Hz, 1H), 8.63 (d, *J* = 9.9 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 8.12 (s, 1H), 7.29 (d, *J* = 10.0 Hz, 1H), 7.03 - 6.74 (m, 1H), 5.22 (s, 2H), 4.00 (s, 3H), 2.99 (s, 3H), 1.83 - 1.69 (m, 4H), 1.50 (s, 6H), 1.35 (s, 6H); LC/MS (ESI): 511.2 [M+H]<sup>+</sup>.

**[0282] Example 17. Synthesis of (S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 155)**

## [0283] Scheme 17.



**[0284] Step 1:** To a solution of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and the reaction mixture was stirred at RT for 16 h. Next the reaction mixture was filtered to provided methyl (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetyl)glycinate (9.5 g, 22.38 mmol, 79.09%) as a slightly yellow solid. LC/MS (ESI): 409.2 [M+H]<sup>+</sup>.

**[0285] Step 2:** A solution of methyl (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetyl)glycinate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred RT for 16 h. After the reaction was completed, the solution was concentrated in vacuo to provided (S)-3-cyclopropylpiperazine-2,5-dione (4.85 g, 11.43 mmol, 97.00%) as a slightly yellow solid. LC/MS (ESI): 155.1 [M+H]<sup>+</sup>.

**[0286] Step 3:** LiAlH<sub>4</sub> (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (S)-3-cyclopropylpiperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and then the reaction mixture was stirred at 70 °C for 16 h. After the reaction was completed, the mixture was poured into KOH (6N) and stirred in an ice bath for 1 h. Next the mixture was filtered and the filtrate was extracted with EA, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided (S)-2-cyclopropylpiperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. LC/MS (ESI): 127.1 [M+H]<sup>+</sup>.

**[0287] Step 4:** DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2*S*)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51 mmol, 1.0 eq) in *n*-BuOH (7 mL), and the reaction mixture was stirred at 120 °C for 16 h. After the reaction was completed, the mixture was concentrated in vacuo and the residue was diluted with EA, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided (S)-3-(3-cyclopropylpiperazin-1-yl)-6-iodopyridazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. LC/MS (ESI): 331.1 [M+H]<sup>+</sup>.

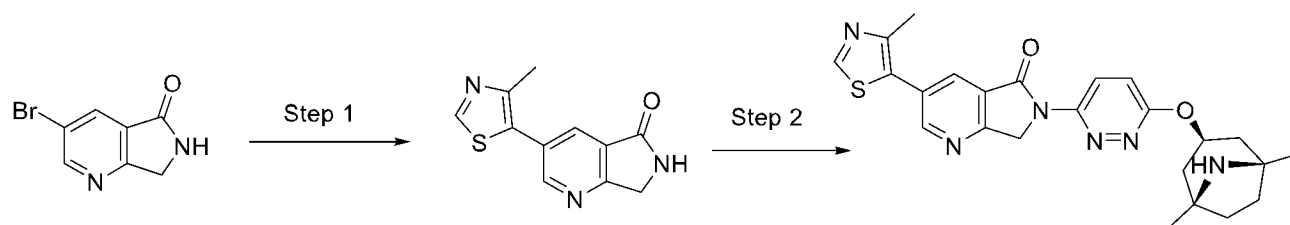
**[0288] Step 5:** Pd(dppf)Cl<sub>2</sub> (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K<sub>2</sub>CO<sub>3</sub> (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL). The reaction mixture was stirred at 80 °C for 16 h. Next the reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 10/1, *v/v* to give 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. LC/MS (ESI): 215.2 [M+H]<sup>+</sup>.

**[0289] Step 6:** 6-(1-Methylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (50 mg, 0.23 mmol, 1.0 eq) and (S)-3-(3-cyclopropylpiperazin-1-yl)-6-iodopyridazine (80 mg, 0.23 mmol, 1.0 eq) were dissolved in DMF (2 mL), and CuI (4 mg, 0.02 mmol, 0.10 eq), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.70 mmol, 3.0 eq) and (1*R*,2*R*)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) were added and the reaction mixture was stirred at 100 °C for 16 h. Next the reaction was filtered and the filtrate was concentrated. The crude product was purified by pre-HPLC to provide (S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (24.19 mg, 21.55%) as a white solid.

**[0290]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ = 9.12 (d, *J* = 1.6 Hz, 1H), 8.49 (d, *J* = 9.8 Hz, 1H), 8.44 (s, 1H), 8.36 (d, *J* = 1.8 Hz, 1H), 8.14 (s, 1H), 7.51 (d, *J* = 10.0 Hz, 1H), 5.13 (s, 2H), 4.27 (br d, *J* = 11.1 Hz, 1H), 4.15 (br d, *J* = 10.8 Hz, 1H), 3.89 (s, 3H), 3.14 - 3.03 (m, 2H), 2.95 (br t, *J* = 11.5 Hz, 1H), 2.84 - 2.74 (m, 2H), 0.84 (br d, *J* = 7.1 Hz, 1H), 0.48 (br s, 2H), 0.33 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 417.2 [M+H]<sup>+</sup>.

**[0291] Example 18. Synthesis of 6-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (Compound No. 248)**

**[0292] Scheme 18.**



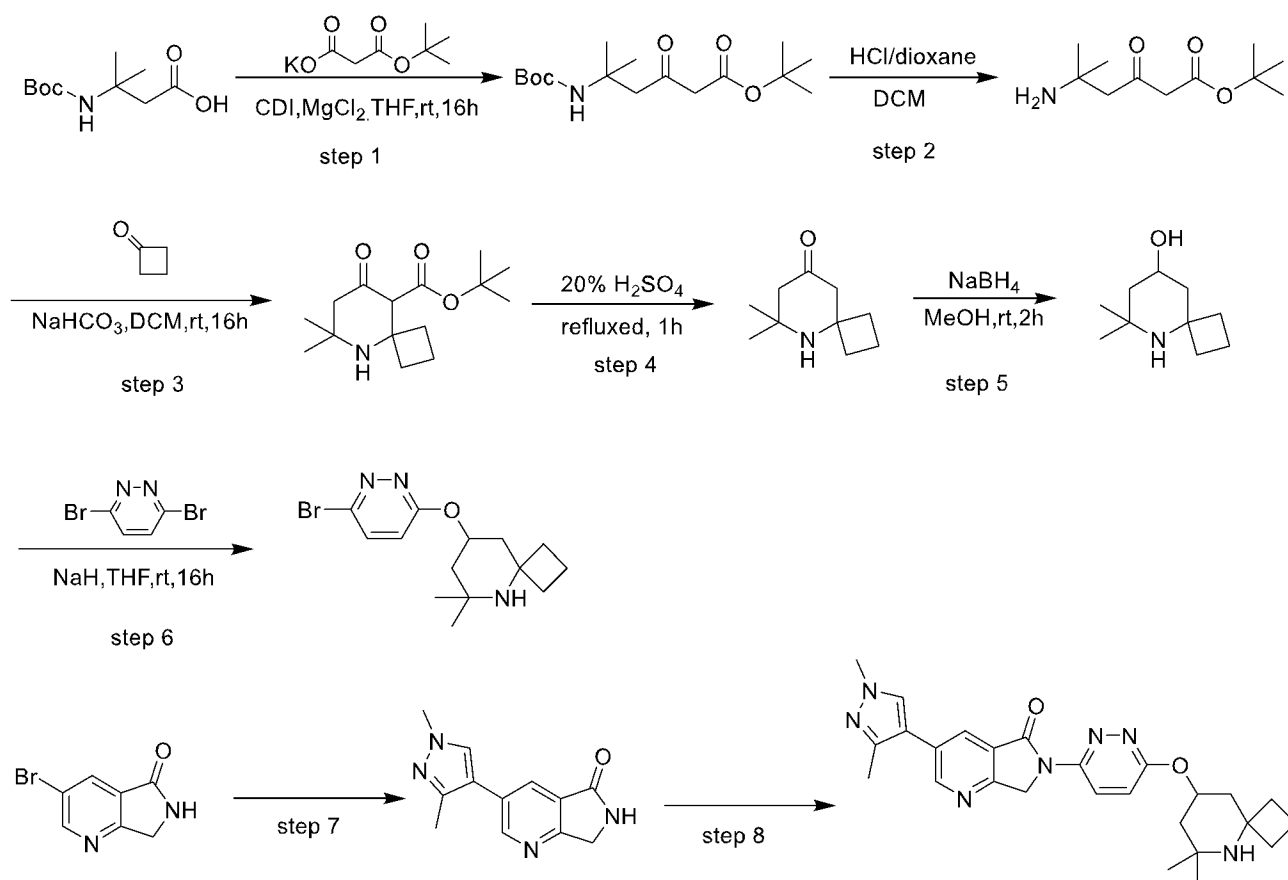
**[0293] Step 1:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (375 mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (143.2 mg, 62%) as brown solid. LC/MS (ESI): 232.1 [M+H]<sup>+</sup>.

**[0294] Step 2:** To a round bottom flask charged with 3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (44.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*s*,5*S*)-3-(((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction mixture was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 6-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (20.37 mg, 29.4 %) as a white solid.

**[0295]** <sup>1</sup>HNMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 9.15 (s, 1H), 9.00 (s, 1H), 8.72 (br d, J = 9.5 Hz, 1H), 8.29 (br d, J = 12.3 Hz, 3H), 7.38 (br d, J = 9.5 Hz, 1H), 5.56 - 5.48 (m, 1H), 5.24 (s, 2H), 2.53 - 2.51 (m, 3H), 2.35 (br dd, J = 5.3, 12.4 Hz, 2H), 2.06 (br d, J = 7.5 Hz, 2H), 1.88 - 1.73 (m, 4H), 1.41 (br s, 6H); LC/MS (ESI): 463.2 [M+H]<sup>+</sup>.

**[0296] Example 19. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 249)**

**[0297] Scheme 19.**



**[0298] Step 1:** To a solution of 3-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid (12.0 g, 55.23 mmol, 1.0 eq) in THF (100 mL) was added CDI (10.75 g, 66.28 mmol, 1.20 eq) and the reaction mixture was stirred at RT for 1 h. Then added  $MgCl_2$  (2.62 g, 43.08 mmol, 0.78 eq) and potassium 3-(*tert*-butoxy)-3-oxopropanoate (16.43 g, 82.85 mmol, 1.5 eq) were added and the reaction mixture was stirred at 50 °C overnight. Next the reaction mixture was concentrated and then diluted with  $H_2O$  (40 mL). The aqueous layer was extracted with EA (3 x 50 mL). The organic layer was dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EA (10:1) to give *tert*-butyl 5-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxohexanoate (10.5 g, 20.27%). LC/MS (ESI): 260.2  $[M+H]^+$ .

**[0299] Step 2:** To a solution of *tert*-butyl 5-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxohexanoate (5.0 g, 15.85 mmol, 1.0 eq) in DCM (10 mL) was added HCl/dioxane (5 mL) and the reaction mixture was stirred at RT for 1 h. After the reaction was completed, the reaction mixture was concentrated to give *tert*-butyl 5-amino-5-methyl-3-oxohexanoate (3.4 g, 99.9%). LC/MS (ESI): 216.2  $[M+H]^+$ .

**[0300] Step 3:** To a solution of *tert*-butyl 5-amino-5-methyl-3-oxohexanoate (3.1 g, 16.84 mmol, 1.0 eq) in DCM (18 mL) was added  $K_2CO_3$  (4.98 g, 36.0 mmol, 2.5 eq) and cyclobutanone (5.43 mL, 70.09 mmol, 5.0 eq) and the reaction mixture was stirred at RT for 72 h. LC/MS showed desired mass. The reaction mixture was filtered and the filtrate was washed with water and brine, dried over  $Na_2SO_4$  and concentrated. The crude product purified by silica gel chromatography eluted with PE: EA (3:1) to give *tert*-butyl 6,6-dimethyl-8-oxo-5-azaspiro[3.5]nonane-9-carboxylate (1.2 g, 31.1%). LC/MS (ESI): 268.2  $[M+H]^+$ .

**[0301] Step 4:** To a solution of tert-butyl 6,6-dimethyl-8-oxo-5-azaspiro[3.5]nonane-9-carboxylate (1200 mg, 4.49 mmol, 1.0 eq) in a mixture of H<sub>2</sub>O (18 mL) and H<sub>2</sub>SO<sub>4</sub> (2 mL) was added and the reaction mixture was stirred at 120 °C for 1 h. LC/MS showed desired mass. The reaction mixture was poured into ice water and the pH was adjusted to over 9. The aqueous layer was extracted with EA (3 x 20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1) to give 6,6-dimethyl-5-azaspiro[3.5]nonan-8-one (620 mg, 81.27%). LC/MS (ESI): 168.2 [M+H]<sup>+</sup>.

**[0302] Step 5:** To a solution of 6,6-dimethyl-5-azaspiro[3.5]nonan-8-one (620 mg, 3.71 mmol, 1.0 eq) in MeOH (10 mL) was added NaBH<sub>4</sub> (140 mg, 3.71 mmol, 1.0 eq) at 0 °C. The reaction mixture was stirred at RT for 1 h. LC/MS showed the desired mass. The reaction mixture was diluted with H<sub>2</sub>O and the pH was adjusted to around 7. The aqueous layer was extracted with EA (2 x 10 mL) and (DCM/propan-2-ol:IPA, 10:1). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1, 0.5% TEA) to give 6,6-dimethyl-5-azaspiro[3.5]nonan-8-ol (540 mg, 86.01%). LC/MS (ESI): 170.2 [M+H]<sup>+</sup>.

**[0303] Step 6:** To a solution of 6,6-dimethyl-5-azaspiro[3.5]nonan-8-ol (540.0 mg, 3.19 mmol, 1.0 eq) in THF (10 mL) was added NaH (153.13 mg, 3.83 mmol, 1.2 eq, 60%) at 0 °C under N<sub>2</sub> atmosphere and the reaction mixture was stirred for 20 min. Then, 3,6-dibromo-1,2-diazine (758.88 mg, 3.19 mmol, 1.0 eq) was added and the resulting mixture was stirred at 60 °C overnight. Next the reaction mixture was cooled to RT and the mixture was poured into water. The aqueous layer was extracted with EA (3 x 10 mL). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1, 0.5% TEA) to give 8-((6-bromopyridazin-3-yl)oxy)-6,6-dimethyl-5-azaspiro[3.5]nonane (860 mg, 82.60%). LC/MS (ESI): 326.2 [M+H]<sup>+</sup>.

**[0304] Step 7:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.0 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (244.1 mg, 1.10 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.3 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (150.1 mg, 68%) as a brown solid. LC/MS (ESI): 229.1 [M+H]<sup>+</sup>.

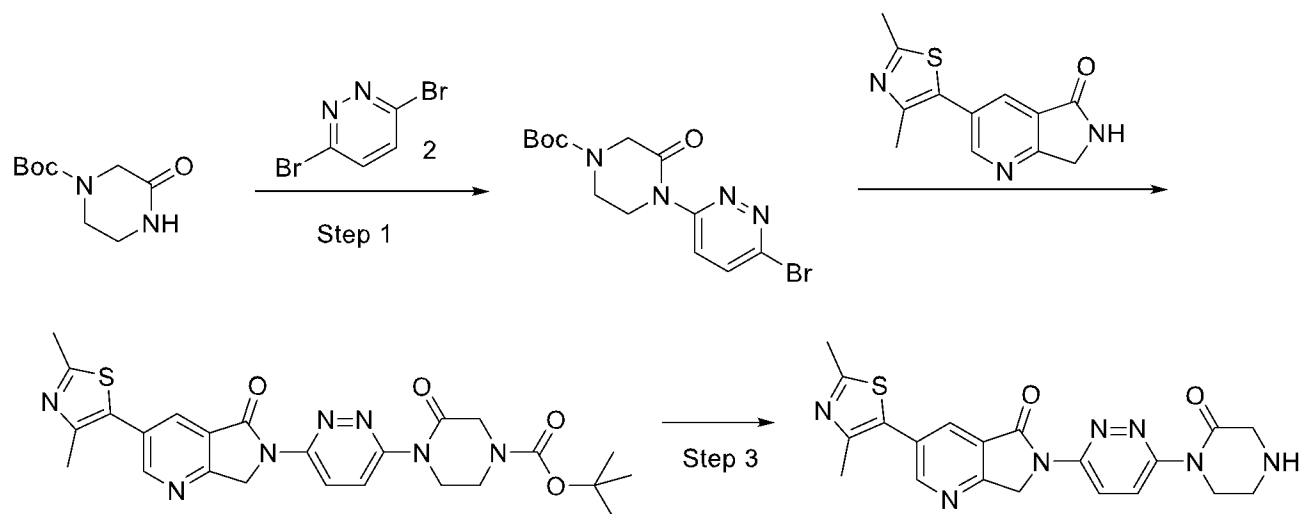
**[0305] Step 8:** To a round bottom flask charged with 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (34.2 mg, 0.15 mmol, 1.0 eq), 8-((6-bromopyridazin-3-yl)oxy)-6,6-dimethyl-5-azaspiro[3.5]nonane (48.9 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was

degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with A. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)isoindolin-1-one (42.2 mg), which was dissolved in HCl-dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (4.94 mg, 6.9 %) as a white solid.

**[0306]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ = 8.95 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 9.6 Hz, 1H), 8.22 (s, 1H), 8.19 - 8.15 (m, 2H), 7.35 (d, J = 9.6 Hz, 1H), 5.57 - 5.46 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.57 - 2.52 (m, 1H), 2.36 (s, 3H), 2.21 - 2.07 (m, 4H), 1.94 - 1.85 (m, 1H), 1.83 - 1.65 (m, 2H), 1.55 - 1.40 (m, 2H), 1.21 (s, 3H), 1.16 (s, 3H); LC/MS (ESI): 474.2 [M+H]<sup>+</sup>.

**[0307] Example 20. Synthesis of 3-(2,4-dimethylthiazol-5-yl)-6-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 255)**

**[0308] Scheme 20.**



**[0309] Step 1:** A solution of 2-methylpropan-2-yl 3-oxopiperazine-1-carboxylate (2.00 g, 9.99 mmol, 1.00 eq), 3,6-dibromo-1,2-diazine (11.89 g, 99.90 mmol, 5.00 eq), Cs<sub>2</sub>CO<sub>3</sub> (9.76 g, 29.97 mmol, 3.00 eq), Pd(dba)Cl<sub>2</sub> (1.00 g, 1.00 mmol, 0.10 eq) and Xantphos (1.00 g, 2.00 mmol, 0.20 eq) in 1,4-dioxane (150 mL) was stirred at 100 °C for 16 h. After completion, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with PE/EA 20/1~5/1, v/v to provided 2-methylpropan-2-yl 4-(6-bromo-1,2-diazin-3-yl)-3-oxopiperazine-1-carboxylate (655 mg, 1.83 mmol, 18.36%) as a yellow solid. LC/MS (ESI): 357.2 [M+H]<sup>+</sup>.

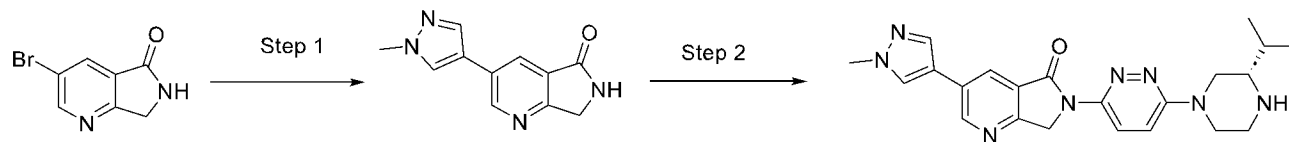
**[0310] Step 2:** A mixture of 3-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (100 mg, 0.41 mmol, 1.0 eq), 2-methylpropan-2-yl 4-(6-bromo-1,2-diazin-3-yl)-3-oxopiperazine-1-carboxylate (174.75 mg, 0.49 mmol, 1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (398.48 mg, 1.22 mmol, 3.0 eq) and XantPhos Pd G4 (66.04 mg, 0.04 mmol, 0.1 eq) in dioxane (1 mL) was stirred under N<sub>2</sub> at 100 °C for 3 h. The reaction

mixture was cooled to RT and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to provided 2-methylpropan-2-yl 4-{6-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-6-yl]-1,2-diazin-3-yl}-3-oxopiperazine-1-carboxylate (100 mg, 47.03%) as a brown solid. LC/MS (ESI): 522.18 [M+H]<sup>+</sup>.

**[0311] Step 3:** A solution of 2-methylpropan-2-yl 4-{6-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-6-yl]-1,2-diazin-3-yl}-3-oxopiperazine-1-carboxylate (100 mg, 0.19 mmol) in HCl (g) in 1,4-dioxane (4 M, 4 mL) was stirred at RT for 1 h. The reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography (SiO<sub>2</sub>, DCM:MeOH=50:1-25:1-10:1). The product was triturated with MeOH and filtered to provided 3-(2,4-dimethyl-1,3-thiazol-5-yl)-6-[6-(2-oxopiperazin-1-yl)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (20.28 mg, 25.09%) as a white solid. LC/MS (ESI): 422.1 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ= 9.77 (br s, 2H), 8.98 (d, *J* = 2.1 Hz, 1H), 8.84 (d, *J* = 9.6 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 9.8 Hz, 1H), 5.29 (s, 2H), 4.31 - 4.22 (m, 2H), 4.02 (s, 2H), 3.65 - 3.58 (m, 2H), 2.68 (s, 3H), 2.43 (s, 3H); LC/MS (ESI): 422.95 [M+H]<sup>+</sup>.

**[0312] Example 21. Synthesis of (S)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 157)**

**[0313] Scheme 21.**



**[0314] Step 1:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (312. mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake with rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (183.2 mg, 85.2%) as a brown solid. LC/MS (ESI): 215.1 [M+H]<sup>+</sup>.

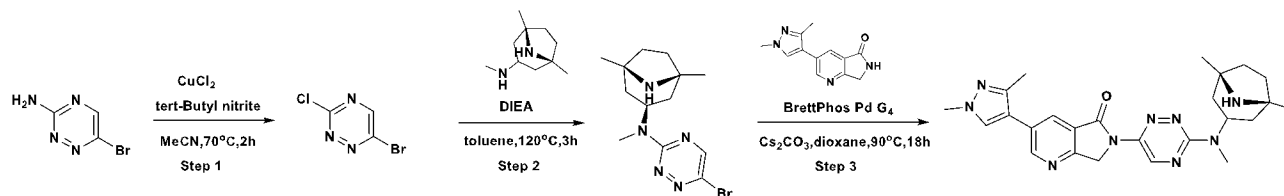
**[0315] Step 2:** To a round bottom flask charged with 3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (32.2 mg, 0.15 mmol, 1.0 eq), tert-butyl (S)-4-(6-bromopyridazin-3-yl)-2-isopropylpiperazine-1-carboxylate (57.6 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and was diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and was concentrated under vacuum. The crude product was purified by silica gel column chromatography

with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (9.51 mg, 15.2 %) as a white solid.

**[0316]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 9.12 (d, 1H, J = 2.0 Hz), 8.48 (d, 1H, J = 10.0 Hz), 8.44 (s, 1H), 8.37 (d, 1H, J = 2.1 Hz), 8.18 (s, 1H), 8.14 (s, 1H), 7.48 (d, 1H, J = 9.9 Hz), 5.14 (s, 2H), 4.27-4.34 (m, 1H), 4.11-4.19 (m, 1H), 3.90 (s, 3H), 3.02-3.15 (m, 1H), 2.82-2.92 (m, 1H), 2.79-2.86 (m, 1H), 2.62-2.72 (m, 2H), 1.66-1.72 (m, 1H), 0.97 (d, 6H, J = 6.8 Hz); LC/MS (ESI): 419.2 [M+H]<sup>+</sup>.

**[0317] Example 22. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 175)**

**[0318] Scheme 22.**



**[0319] Step 1:** To a solution of 6-bromo-1,2,4-triazin-3-amine (2.0 g, 11.43 mmol) and CuCl<sub>2</sub> (1.47 g, 14.86 mmol) in MeCN (25 mL) was added isoamyl nitrite (2.18 mL, 18.29 mmol) and the reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was then concentrated and the resulting residue was purified by column chromatography (SiO<sub>2</sub>, PE:EA=10:1) to give 6-bromo-3-chloro-1,2,4-triazine (220 mg, 1.13 mmol, 9.90%) as a yellow solid.

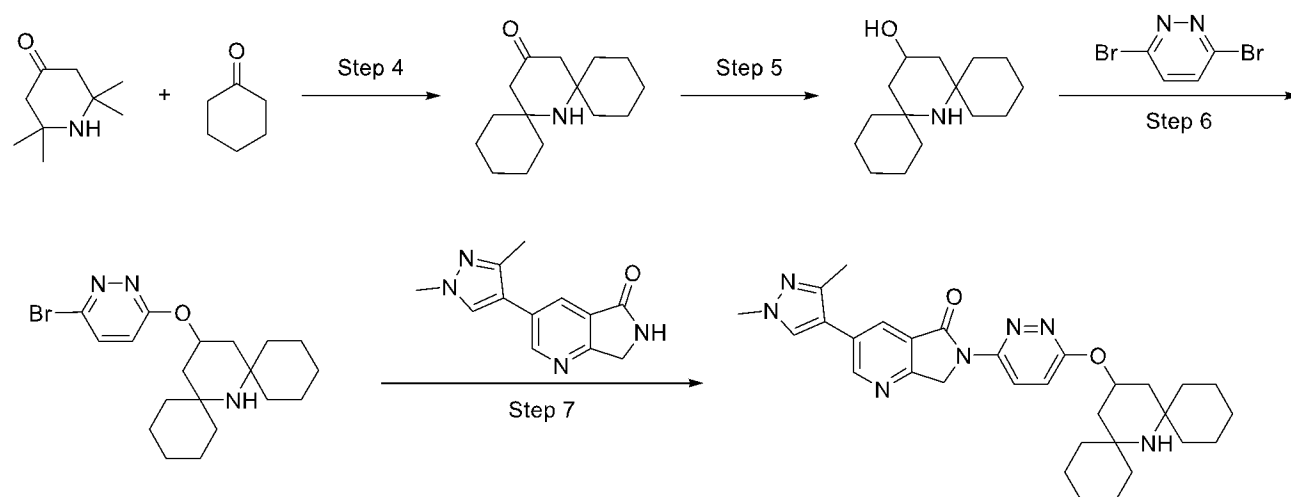
**[0320] Step 2:** To a solution of 6-bromo-3-chloro-1,2,4-triazine (200 mg, 1.03 mmol) and (1R,5S)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (192.71 mg, 1.13 mmol) in toluene (10 mL) was added DIEA (0.34 mL, 2.06 mmol) and the reaction mixture was stirred at 120 °C for 3 h. LC/MS showed the reaction was completed. The reaction mixture was concentrated and the resulting residue was purified by column chromatography (SiO<sub>2</sub>, DCM : MeOH=10:1) to give (1R,3S,5S)-N-(6-bromo-1,2,4-triazin-3-yl)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (0.23 g, 67.65%) as a yellow solid.

**[0321] Step 3:** To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (35 mg, 0.15 mmol) and (1R,3S,5S)-N-(6-bromo-1,2,4-triazin-3-yl)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (52 mg, 0.16 mmol) in dioxane (10 mL) was added BrettPhos Pd G4 (13.61 mg, 0.01 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (146.62 mg, 0.45 mmol); and the reaction mixture was stirred at 90 °C for 16 h under N<sub>2</sub>. LC/MS showed the reaction was completed. The reaction mixture was filtered and concentrated. The resulting residue was purified by pre-HPLC (TFA) to give 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (30.25 mg, 39.86%) as a yellow solid.

[0322]  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400MHz)  $\delta$  = 9.34 (s, 1H), 8.94 (d,  $J$  = 1.6 Hz, 1H), 8.18 (s, 2H), 5.13 (s, 2H), 5.01-5.10 (m, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.36 (s, 3H), 1.78 (br d,  $J$  = 7.4 Hz, 2H), 1.51-1.65 (m, 6H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3  $[\text{M}+\text{H}]^+$ .

[0323] Example 23. Synthesis of 6-(6-((7-azadispiro[5.1.58.36]hexadecan-15-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 243)

[0324] Scheme 23.



[0325] **Step 1:** A solution of ethyl 5-bromo-2-methylnicotinate (3.00 g, 12.35 mmol, 1.00 eq), benzoyl peroxide (5.98 g, 24.70 mmol, 2.00 eq) and N-bromosuccinimide (4.37 g, 24.70 mmol, 2.00 eq) in carbon tetrachloride (30 mL) was stirred at 80 °C for 16 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with PE/EA 20/1~5/1,  $v/v$  to provided ethyl 5-bromo-2-(bromomethyl)nicotinate (2.37 g, 7.41 mmol, 61.03%) as a white solid. LC/MS (ESI): 324.0  $[\text{M}+\text{H}]^+$ .

[0326] **Step 2:** A solution of ethyl 5-bromo-2-(bromomethyl)nicotinate (2.00 g, 6.23 mmol, 1.00 eq) and ammonia (1.06, 62.30 mmol, 10.0 eq) in isopropanol (10 mL) was stirred at 25 °C for 6 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~10/1,  $v/v$  to provided 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (1.06 g, 5.04 mmol, 81.32%) as a white solid. LC/MS (ESI): 214.0  $[\text{M}+\text{H}]^+$ .

[0327] **Step 3:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (1.00 g, 5.0 mmol, 1.00 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (1.31 g, 5.50 mmol, 1.10 eq), aqueous potassium carbonate (2 M, 8 mL) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (365.7 mg, 0.50 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1,  $v/v$  to obtain 3-(2,4-

dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (335 mg, 68%) as a brown solid. LC/MS (ESI): 246.0 [M+H]<sup>+</sup>.

**[0328] Step 4:** A solution of 2,2,6,6-tetramethylhexahydropyridin-4-one (10.0 g, 64.42 mmol, 1.00 eq), cyclohexanone (18.97 g, 193.25 mmol, 3.00 eq) and NH<sub>4</sub>Cl (20.67 g, 386.50 mmol, 6.00 eq) in DMSO (30 mL) was stirred at 80 °C for 48 h. After consumption of the starting material, the mixture was cooled to room temperature and diluted with 100 mL of water. The aqueous layer was extracted with EA (3 x 100 mL). The organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 20/1~1/1, v/v to provided spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-one (15 g, 57.99 mmol, 90.03%) as a white solid. LC/MS (ESI): 237.2 [M+H]<sup>+</sup>.

**[0329] Step 5:** To a solution of spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-one (6.40 g, 27.19 mmol, 1.00 eq) in MeOH (65 mL), NaBH<sub>4</sub> (0.51 g, 13.60 mmol, 0.50 eq) was added at 0 °C; and the reaction mixture was stirred at room temperature for 3 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~20/1, v/v to provided spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-ol (3.40 g, 14.32 mmol, 52.67%) as a yellow oil. LC/MS (ESI): 239.2 [M+H]<sup>+</sup>.

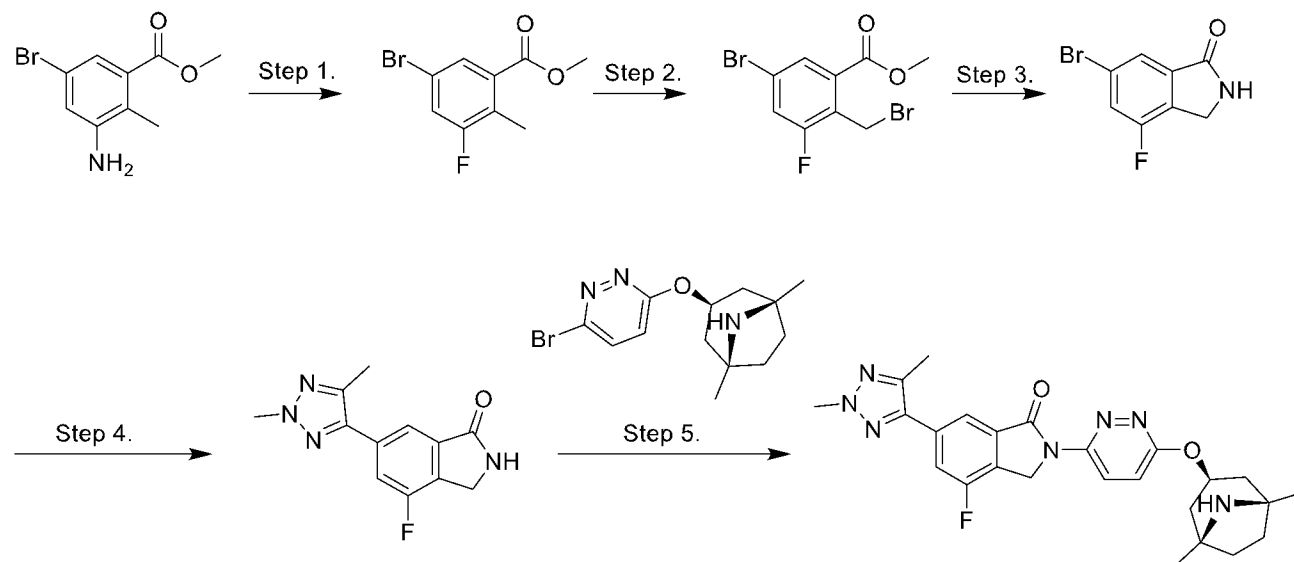
**[0330] Step 6:** To a solution of spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-ol (3.00 g, 12.64 mmol, 1.00 eq) in THF (30 mL), NaH (0.76 g, 31.59 mmol, 2.50 eq) was added dropwise over 30 min at 0 °C. Next the resulting mixture was stirred under N<sub>2</sub> at 25 °C for 0.5 h. Then 3,6-dibromo-1,2-diazine (3.61 g, 15.16 mmol, 1.20 eq) was added and the reaction mixture was stirred under N<sub>2</sub> at 25 °C for 24 h. After consumption of the starting material, the reaction mixture was quenched with saturated ammonium chloride and the reaction was concentrated under vacuum. The residue was extracted with EA (3 x 30 mL) and the organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EtOAc 20/1~1/1 to provided 4-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane] (1.80 g, 4.43 mmol, 35.03%) as a yellow solid. LC/MS (ESI): 395.3 [M+H]<sup>+</sup>.

**[0331] Step 7:** To a solution of 4-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane] (0.9 g, 2.28 mmol, 1.00 eq), 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (0.63 g, 2.74 mmol, 1.20 eq) and Cs<sub>2</sub>CO<sub>3</sub> (2.23 g, 6.85 mmol, 3.00 eq) in 1,4-dioxane (15 mL) was added XPhos Pd G4 (0.20 g, 0.23 mmol, 0.10 eq) at 25 °C; and the reaction mixture was stirred under N<sub>2</sub> at 90 °C for 4 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~10/1, v/v to provided 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (0.43 g, 0.79 mmol, 34.82%) as a white solid.

**[0332]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 8.95 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 9.6 Hz, 1H), 8.21 - 8.16 (m, 3H), 7.32 (d, J = 9.6 Hz, 1H), 5.61 - 5.51 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 1.79 - 1.49 (m, 10H), 1.49 - 1.30 (m, 14H); LC/MS (ESI): 542.4 [M+H]<sup>+</sup>.

**[0333] Example 24. Synthesis of 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisoindolin-1-one (Compound No. 283)**

**[0334] Scheme 24.**



**[0335] Step 1:** To the solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL), nitrosonium tetrafluoroborate, (480 mg, 4.10 mmol) was added portionwise at 0 ℃ under N<sub>2</sub>; and the reaction mixture was stirred at 0 ℃ for 1 h. Then oxylene (30 mL) was added and the reaction mixture was refluxed at 130 ℃ for 3 h. The reaction mixture was cooled to room temperature and poured into H<sub>2</sub>O and the aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to afford methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

**[0336] Step 2:** To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was added AIBN (57 mg, 0.35 mmol); and the reaction mixture was stirred under N<sub>2</sub> at 100 ℃ for 16 h. Then the reaction mixture was cooled to room temperature and was poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to afford methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

**[0337] Step 3:** To a solution of methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) in THF (7 mL), NH<sub>4</sub>OH (7 mL) was added and the reaction mixture was stirred at RT for 4 h. The reaction mixture was filtered and concentrated under vacuum. The crude product was used for directly in the next step.

**[0338] Step 4:** 6-Bromo-4-fluoroisoindolin-1-one (343.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0

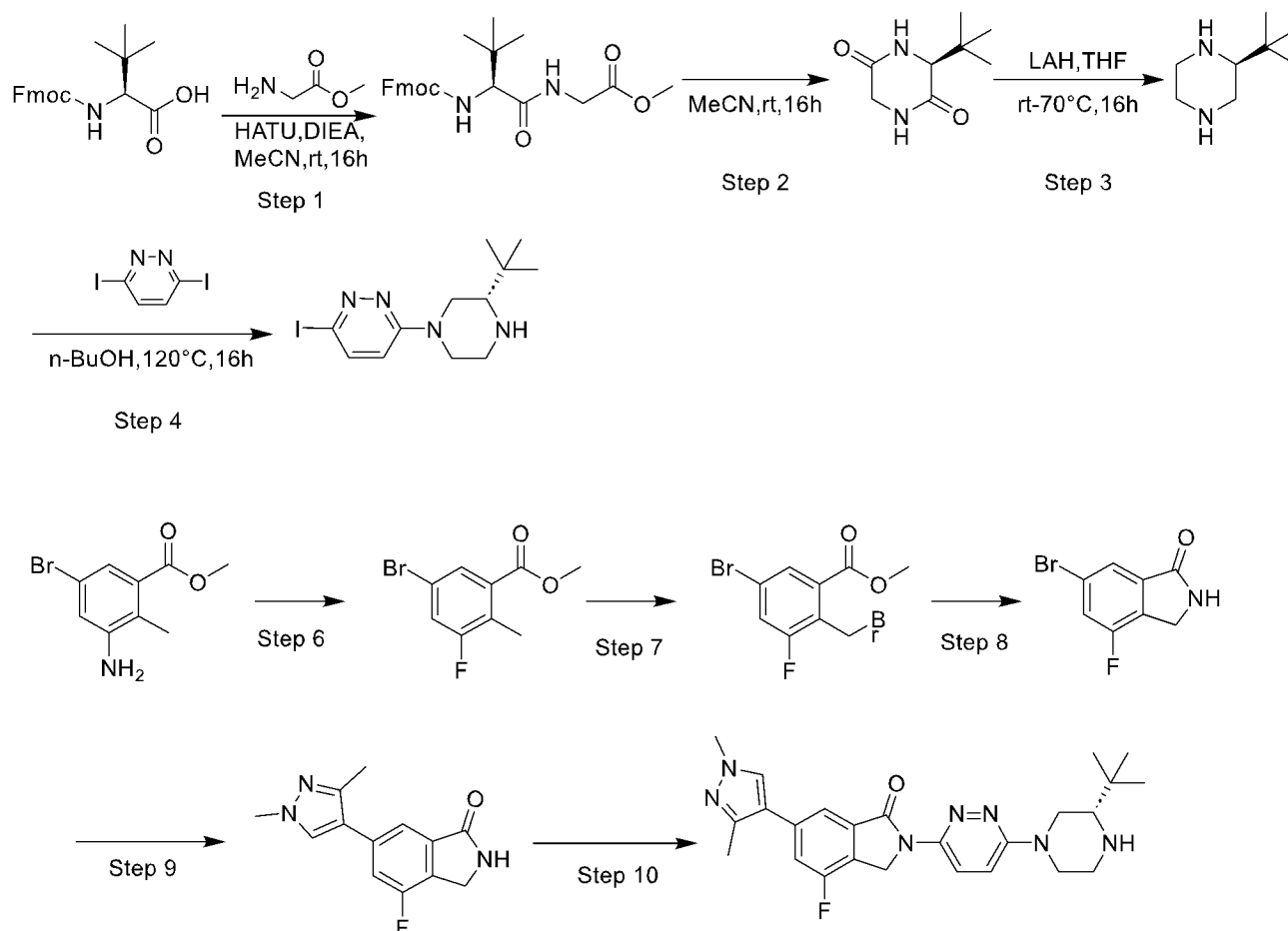
mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Then 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one (81.5 mg, 33%) as a brown solid. LC/MS (ESI): 247.1 [M+H]<sup>+</sup>.

**[0339] Step 5:** To a round bottom flask charged with 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one (36.9 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and was then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1*R*,3*S*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one (28.8 mg, 40.3 %) as a white solid.

**[0340]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ : 9.42 (br d, J = 7.4 Hz, 1H), 9.31 - 9.17 (m, 1H), 8.72 (d, J = 9.6 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, J = 0.8, 9.9 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H), 5.52 (td, J = 5.3, 10.8 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 3H), 2.48 (s, 3H), 2.41 (br dd, J = 5.8, 13.3 Hz, 2H), 2.13 (br d, J = 8.0 Hz, 2H), 1.95 - 1.81 (m, 4H), 1.48 (s, 6H); LC/MS (ESI): 478.2 [M+H]<sup>+</sup>.

**[0341] Example 25. Synthesis of (S)-2-(6-(3-(*tert*-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (Compound No. 295)**

**[0342] Scheme 25.**



**[0343] Step 1:** To a solution of (2*S*)-2-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-3,3-dimethylbutanoic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and the reaction mixture was stirred at RT for 16 h. Next the reaction mixture was filtered to provided 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (9.5 g, 22.38 mmol, 79.09%) as a slightly yellow solid. LC/MS (ESI): 425.5 [M+H]<sup>+</sup>.

**[0344] Step 2:** A solution of 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred RT for 16 h. After the reaction was completed, the reaction mixture was concentrated in vacuo to provided 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (4.85 g, 11.43 mmol, 97.00%) as a slightly yellow solid. LC/MS (ESI): 171.2 [M+H]<sup>+</sup>.

**[0345] Step 3:** LiAlH<sub>4</sub> (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (3*S*)-3-(2-methylprop-2-yl)piperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and the resulting reaction mixture was stirred at 70 °C for 16 h. Next the mixture was poured into KOH (6*N*), and the mixture was stirred in an ice bath for 1 h and was then filtered. The filtrate was extracted with EA, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided (2*S*)-2-(2-methylprop-2-yl)piperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. LC/MS (ESI): 143.2 [M+H]<sup>+</sup>.

**[0346] Step 4:** DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2*S*)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51

mmol, 1.0 eq) in *n*-BuOH (7 mL) at RT, and the reaction mixture was stirred at 120 °C for 16 h. Next the mixture was concentrated in vacuo and the resulting residue was diluted with EA, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to provided 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. LC/MS (ESI): 347.2 [M+H]<sup>+</sup>.

**[0347] Step 5:** Pd(dppf)Cl<sub>2</sub> (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K<sub>2</sub>CO<sub>3</sub> (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL) and the resulting reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 10/1, *v/v* to afford 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. LC/MS (ESI): 215.2 [M+H]<sup>+</sup>.

**[0348] Step 6:** To the solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL), was nitrosonium tetrafluoroborate, (480 mg, 4.10 mmol) was added portionwise at 0 °C under N<sub>2</sub> and the resulting reaction mixture was stirred at 0 °C for 1 h. Then oxylene (30 mL) was added and the reaction mixture was refluxed at 130 °C for 3 h. The reaction mixture was cooled to room temperature and poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, *v/v* to obtain methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

**[0349] Step 7:** To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was AIBN (57 mg, 0.35 mmol) was added; and the reaction mixture was stirred under N<sub>2</sub> at 100 °C for 16 h. The reaction mixture was then cooled to room temperature and poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, *v/v* to obtain methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

**[0350] Step 8:** To a solution of methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) dissolved in THF (7 mL), NH<sub>4</sub>OH (7 mL) was added and the reaction was stirred at RT for 4 . The reaction mixture was filtered and concentrated under vacuum. The crude product was used directly in the next step.

**[0351] Step 9:** 6-Bromo-4-fluoroisindolin-1-one (228 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (244.1 mg, 1.10 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.3 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the

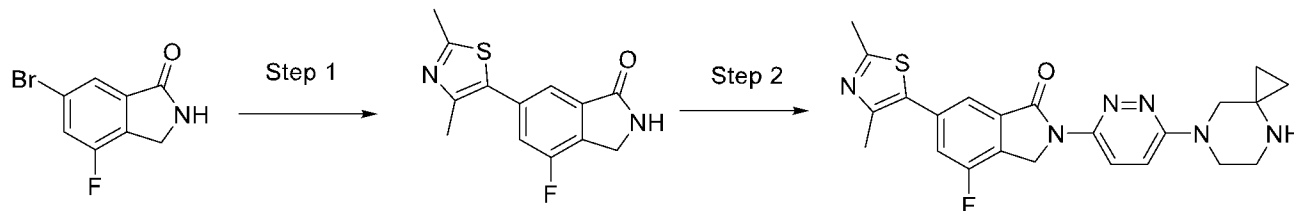
organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to obtain 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (134.7 mg, 55%) as a brown solid. LC/MS (ESI): 246.1 [M+H]<sup>+</sup>.

**[0352] Step 10:** 6-(1,3-Dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (50 mg, 0.23 mmol, 1.0 eq) and 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (80 mg, 0.23 mmol, 1.0 eq) were dissolved in DMF (2 mL), and CuI (4 mg, 0.02 mmol, 0.10 eq), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.70 mmol, 3.0 eq) and (1*R*,2*R*)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) were added and the resulting reaction mixture was stirred at 100 °C for 16 h. Next the reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by pre-HPLC to provided (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (24.19 mg, 21.55%) as a white solid.

**[0353]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400MHz) δ = 8.46 (d, *J* = 9.9 Hz, 1H), 8.13 (s, 1H), 7.64 (s, 1H), 7.61 - 7.56 (m, 1H), 7.47 (d, *J* = 10.0 Hz, 1H), 5.18 (s, 2H), 4.36 (br d, *J* = 12.1 Hz, 1H), 4.12 (br d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H), 3.08 (br d, *J* = 11.4 Hz, 1H), 2.89 - 2.71 (m, 2H), 2.65 - 2.57 (m, 1H), 2.39 (dd, *J* = 2.4, 10.8 Hz, 1H), 2.35 (s, 3H), 0.96 (s, 9H), 1H not observed (NH); LC/MS (ESI): 464.2 [M+H]<sup>+</sup>.

**[0354] Example 26. Synthesis of 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (Compound No. 300)**

**[0355] Scheme 26.**



**[0356] Step 1:** 6-Bromo-4-fluoroisindolin-1-one (457.9 mg, 2.0 mmol, 1.0 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (526.1 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to afford 6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (273.6 mg, 57%) as a brown solid. LC/MS (ESI): 263.1 [M+H]<sup>+</sup>.

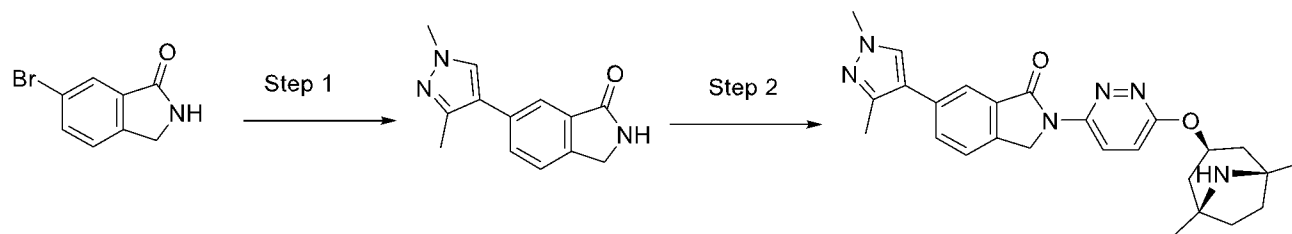
**[0357] Step 2:** To a round bottom flask charged with 6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (37.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl 7-(6-bromopyridazin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (55.2 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with

argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and was then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)isoindolin-1-one (42.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one (13.59 mg, 20.1 %) as a white solid.

**[0358]** <sup>1</sup>HNMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 8.44 (d, J = 9.9 Hz, 1H), 8.15 (d, J = 1.0 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.63 (s, 1H), 7.44 (d, J = 10.0 Hz, 1H), 5.24 (s, 2H), 3.58 - 3.53 (m, 2H), 3.44 (s, 2H), 2.89 (br d, J = 4.5 Hz, 2H), 2.66 (s, 3H), 2.43 (s, 3H), 0.51 (br d, J = 9.8 Hz, 4H); LC/MS (ESI): 451.1 [M+H]<sup>+</sup>.

**[0359]** Example 27. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one (Compound No. 416)

**[0360]** Scheme 27.



**[0361]** Step 1: 6-Bromoisoindolin-1-one (426.0 mg, 2.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (488 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one (335 mg, 68%) as a brown solid. LC/MS (ESI): 228.1 [M+H]<sup>+</sup>.

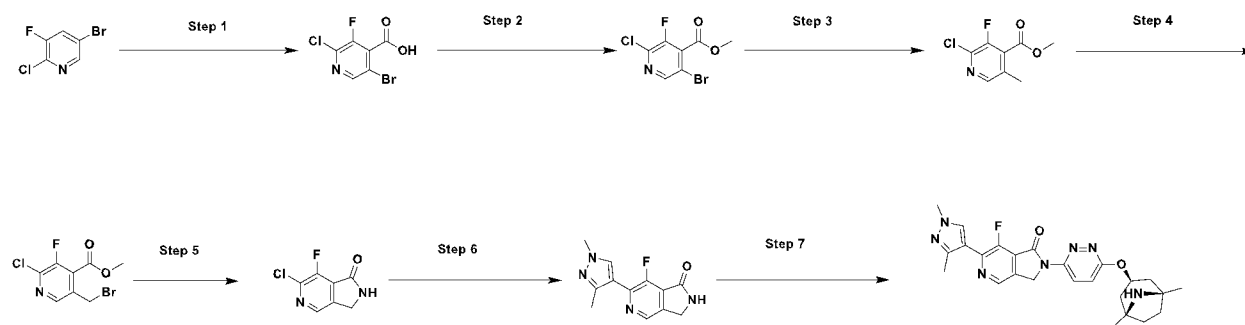
**[0362]** Step 2: To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one (34.2 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1R,3s,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled down to RT and was then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was

purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one (16.84 mg, 23.4%) as a white solid.

**[0363]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  = 8.73 (d, *J* = 9.6 Hz, 1H), 8.20 (br d, *J* = 4.5 Hz, 1H), 8.06 (s, 1H), 7.81 - 7.77 (m, 2H), 7.76 - 7.73 (m, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 5.49 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 2.33 - 2.29 (m, 2H), 2.03 - 1.93 (m, 2H), 1.72 (br d, *J* = 2.5 Hz, 2H), 1.66 - 1.56 (m, 2H), 1.34 (br s, 6H); LC/MS (ESI): 459.3 [M+H]<sup>+</sup>.

**[0364] Example 28. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridin-1-one (Compound No. 116)**

**[0365] Scheme 28.**



**[0366] Step 1:** LDA (48 mL, 2.0 mol in THF) was added dropwise into a solution of 5-bromo-2-chloro-3-fluoropyridine (10 g, 47.52 mmol) in THF (200 mL) at -78 °C under N<sub>2</sub> and the reaction mixture was stirred at -78 °C for 2 h. The mixture was poured into the CO<sub>2</sub> (solid) in THF. The reaction mixture was then concentrated under vacuum. The pH value of the residue was adjusted to 3 with 2 M HCl. The resulting mixture was extracted with EA, washed with brine, dried over MgSO<sub>4</sub>, and concentrated under vacuum to afford the desired product (12 g, crude) as a white solid.

**[0367] Step 2:** To a solution of 5-bromo-2-chloro-3-fluoroisonicotinic acid (12 g, 51.2 mmol) and K<sub>2</sub>CO<sub>3</sub> (5.7 g, 41.7 mmol) in DMF (80 mL), MeI (3.4 mL, 54.7 mmol) was added portionwise; and the reaction mixture was stirred at RT for 16 h. The reaction mixture was poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, *v/v* to obtain methyl 5-bromo-2-chloro-3-fluoroisonicotinate (10 g, 79%).

**[0368] Step 3:** To the solution of 5-bromo-2-chloro-3-fluoroisonicotinate (2500 mg, 9.4 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in dioxane (25 mL), was added potassium carbonate (2600 mg, 18.8 mmol) and PdCl<sub>2</sub>(dppf) (500 mg, 0.94 mmol); and the reaction mixture was stirred under N<sub>2</sub> at 110 °C for 1 h. Then the mixture was cooled, filtered through a pad of Celite and the filter cake was washed with EA. The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column

chromatography with PE/EA 10/1, v/v to afford methyl 2-chloro-3-fluoro-5-methylisonicotinate (673 mg, 35.3%).

**[0369] Step 4:** To a solution of methyl 2-chloro-3-fluoro-5-methylisonicotinate (320 mg, 1.6 mmol) and NBS (285 mg, 1.6 mmol) in CCl<sub>4</sub> (10 mL), was added BPO (40 mg, 0.16 mmol); and the reaction mixture was stirred under N<sub>2</sub> at 80 °C for 16 h. The mixture was cooled to room temperature and was then poured into H<sub>2</sub>O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 5-(bromomethyl)-2-chloro-3-fluoroisonicotinate (356 mg, 80%).

**[0370] Step 5:** Methyl 5-(bromomethyl)-2-chloro-3-fluoroisonicotinate (356 mg, 1.26 mmol) was dissolved in THF (5 mL) and NH<sub>4</sub>OH (5 mL) was added; and the reaction was stirred at RT for 3 h. The reaction mixture was filtered and concentrated under vacuum. The crude product was used directly in the next step.

**[0371] Step 6:** 6-Chloro-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (186.0 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (312 mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and then anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. The mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (100.8 mg, 41.2%) as a brown solid. LC/MS (ESI): 247.1 [M+H]<sup>+</sup>.

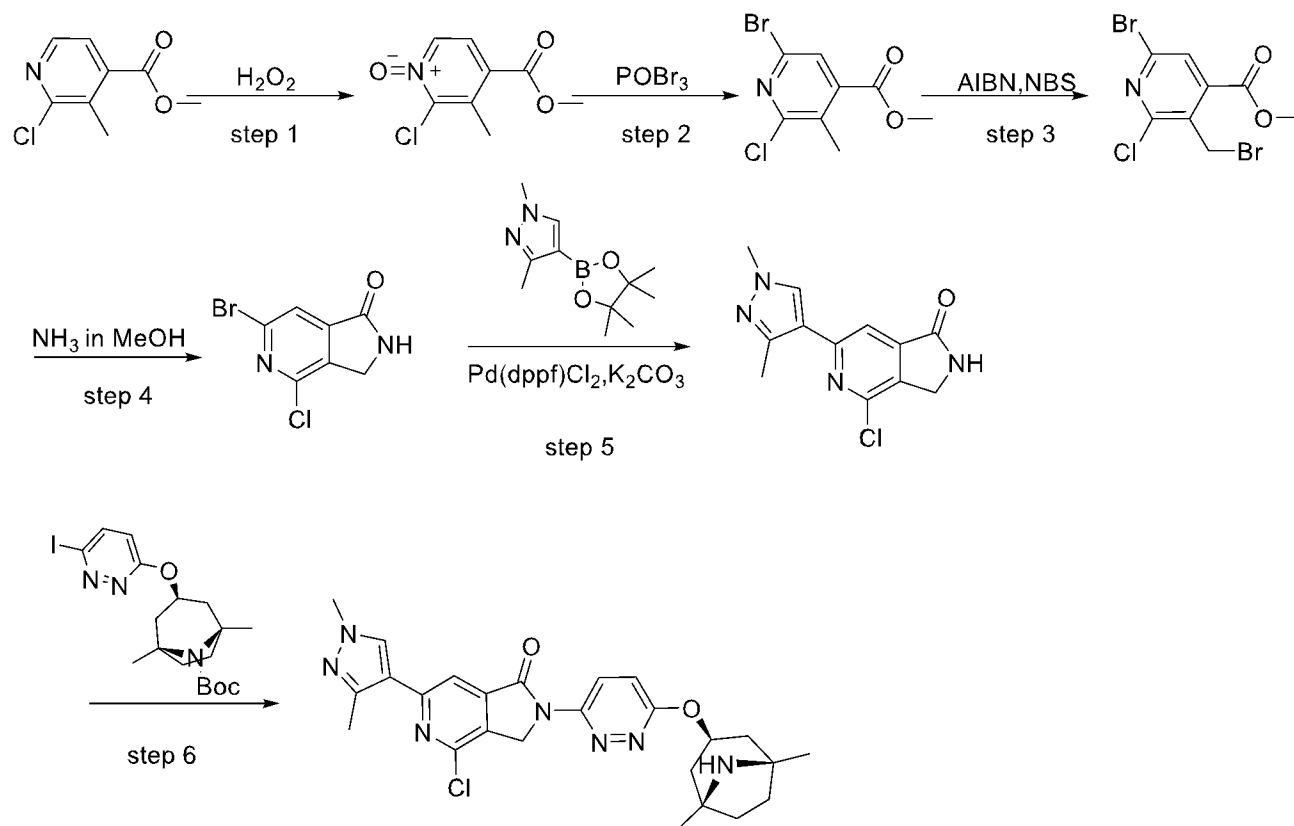
**[0372] Step 7:** To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (36.9 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (S)-4-(6-bromopyridazin-3-yl)-2-isopropylpiperazine-1-carboxylate (57.6 mg, 0.15 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and was diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (3.93 mg, 5.6 %) as a white solid.

**[0373]** <sup>1</sup>HNMR (400 MHz, METHANOL-*d*<sub>4</sub>) δ = 8.72 - 8.67 (m, 2H), 8.44 (s, 1H), 8.00 (d, *J* = 3.3 Hz, 1H), 7.15 (d, *J* = 9.6 Hz, 1H), 5.58 - 5.44 (m, 1H), 5.18 (s, 2H), 3.81 (s, 3H), 2.45 - 2.38 (m, 5H), 2.16 (br

d,  $J = 8.3$  Hz, 2H), 1.90 - 1.82 (m, 2H), 1.68 (br t,  $J = 12.0$  Hz, 2H), 1.40 (s, 6H); LC/MS (ESI): 478.2  $[M+H]^+$ .

**[0374] Example 29. Synthesis of 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 93)**

**[0375] Scheme 29.**



**[0376] Step 1:** To methyl 2-chloro-3-methylisonicotinate (5000 mg, 27.03 mmol) in TFA (50 mL),  $H_2O_2$  (42.16 mL, 351.35 mmol) was added and the mixture was stirred for 4 h. The mixture was cooled to RT and quenched with aqueous  $Na_2SO_3$ . The mixture was concentrated under vacuum and the residue was redissolved in EA (300 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EtOAc to provided 2-chloro-4-(methoxycarbonyl)-3-methylpyridine 1-oxide (3000 mg, 14.85 mmol, 54.95%). LC/MS (ESI): 202.0  $[M+H]^+$ .

**[0377] Step 2:**  $POBr_3$  (6398.79 mg, 22.32 mmol) was added to the solution of 2-chloro-4-(methoxycarbonyl)-3-methylpyridine 1-oxide (3000 mg, 14.88 mmol) in toluene (30 mL) at RT and the reaction mixture was stirred at 80  $^{\circ}C$  for 4 h. The reaction mixture was cooled to RT and was quenched with aqueous  $Na_2CO_3$ . This mixture was extracted with EA (3 x 100 mL) and the combined extracts were dried over  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EtOAc=2:1, to give methyl methyl 6-bromo-2-chloro-3-methylisonicotinate (1500 mg, 5.67 mmol, 38.11%) as a white solid. LC/MS (ESI): 263.9  $[M+H]^+$ .

**[0378] Step 3:** Methyl 6-bromo-2-chloro-3-methylpyridine-4-carboxylate (1500 mg, 5.67 mmol), NBS (1513.80 mg, 8.50 mmol) and AIBN (0.17 mL, 1.13 mmol) were combined with carbon tetrachloride (40 mL); and the reaction mixture was heated to 80 °C for 3 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford ethyl methyl 6-bromo-3-(bromomethyl)-2-chloropyridine-4-carboxylate (1150 mg, 3.35 mmol, 59.05%) as a brown solid. LC/MS (ESI): 341.8 [M+H]<sup>+</sup>.

**[0379] Step 4:** Methyl 6-bromo-3-(bromomethyl)-2-chloropyridine-4-carboxylate (1150 mg, 3.35 mmol) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 246.9 [M+H]<sup>+</sup>.

**[0380] Step 5:** 6-Bromo-4-chloro-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (550 mg, 2.22 mmol), 2,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3-triazole (545.35 mg, 2.44 mmol), K<sub>2</sub>CO<sub>3</sub> (921.41 mg, 6.67 mmol) and Pd(dppf)Cl<sub>2</sub> (162.62 mg, 0.22 mmol) were charged into a 100 mL round bottom flask. The flask was placed under nitrogen and anhydrous dioxane (9 mL) and water (1 mL) were added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and washed with EA (50 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated under vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 4-chloro-6-(2,5-dimethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (400 mg, 1.52 mmol, 68.26%) as a brown solid. LC/MS (ESI): 263.1 [M+H]<sup>+</sup>.

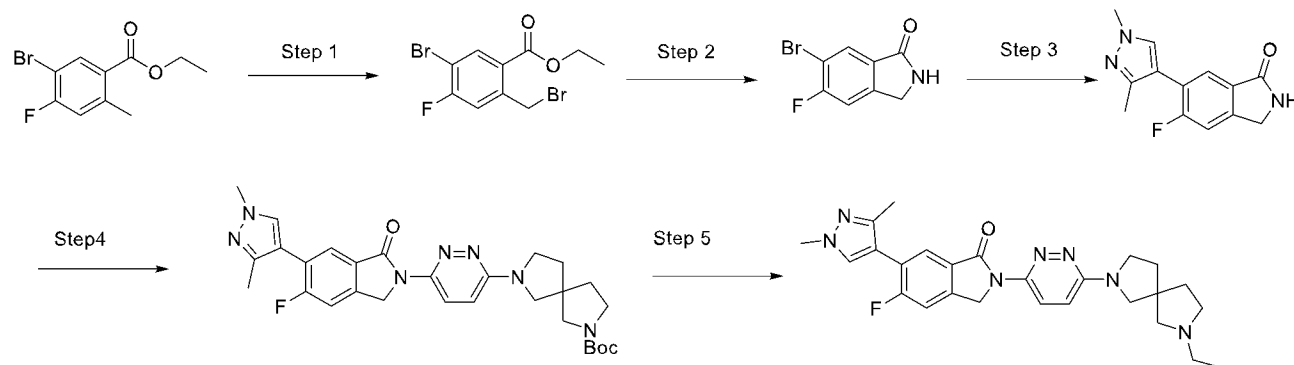
**[0381] Step 6:** To a round bottom flask charged with 4-chloro-6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (120 mg, 0.46 mmol), 2-methylpropan-2-yl (1S,3s,5R)-3-[(6-iodo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (230.80 mg, 0.50 mmol), Cs<sub>2</sub>CO<sub>3</sub> (446.50 mg, 1.37 mmol), and XantPhos Pd G4 (43.96 mg, 0.05 mmol) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 2-methylpropan-2-yl (1S,3s,5R)-3-[(6-[4-chloro-6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl]-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (40 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 4-chloro-6-(1,3-dimethylpyrazol-4-yl)-2-(6-[(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy]-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (10.3 mg, 0.02 mmol, 4.53%) as a white solid.

**[0382]** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ=8.96 (br d, J = 8.8 Hz, 1H), 8.85 (br d, J = 9.3 Hz, 1H), 8.70 (d, J = 9.6 Hz, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.41 (d, J = 9.6 Hz, 1H), 5.61 - 5.47 (m, 1H), 5.16 (s, 2H),

3.82 (s, 3H), 2.48 - 2.42 (m, 5H), 2.16 (br d,  $J = 8.0$  Hz, 2H), 1.95 - 1.75 (m, 4H), 1.45 (s, 6H); LC/MS (ESI): 494.1  $[M+H]^+$ .

**[0383] Example 30. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisindolin-1-one (Compound No. 414)**

**[0384] Scheme 30.**



**[0385] Step 1:** Ethyl 5-bromo-4-fluoro-2-methylbenzoate (2.60 g, 10.0 mmol, 1.0 eq), *N*-bromosuccinimide (2.49 g, 14.0 mmol, 1.4 eq) and benzoyl peroxide (242. mg, 1.0 mmol, 0.1 eq) were combined with carbon tetrachloride (150 mL). The reaction mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford ethyl 5-bromo-2-(bromomethyl)-4-fluorobenzoate (2.61 g, 77%) as a brown solid. LC/MS (ESI): 338.9, 340.9, 342.9  $[M+H]^+$ .

**[0386] Step 2:** Ethyl 5-bromo-2-(bromomethyl)-4-fluorobenzoate (2.61 g, 7.7 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 230.0, 232.0  $[M+H]^+$ .

**[0387] Step 3:** 6-Bromo-5-fluoroisindolin-1-one (456.0 mg, 2.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (488 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and  $PdCl_2(dppf).CH_2Cl_2$  adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. The mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisindolin-1-one (298.9 mg, 61%) as a brown solid. LC/MS (ESI): 246.1  $[M+H]^+$ .

**[0388] Step 4:** To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)isindolin-1-one (34.2 mg, 0.15 mmol, 1.0 eq), *tert*-butyl 7-(6-bromopyridazin-3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (57.3 mg, 0.15 mmol, 1.1 eq),  $Cs_2CO_3$  (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted

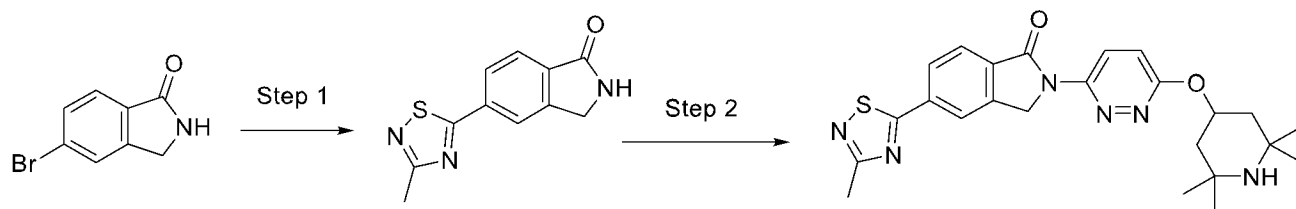
with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to afford *tert*-butyl 7-(6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-1-oxoisindolin-2-yl)pyridazin-3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (69 mg, 77%) as a brown solid. LC/MS (ESI): 578.3 [M+H]<sup>+</sup>.

**[0389] Step 5:** To a round bottom flask charged with *tert*-butyl 7-(6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-1-oxoisindolin-2-yl)pyridazin-3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (69 mg, 0.12 mmol, 1.0 eq) and acetaldehyde (0.3 mL, 1.52 mmol, 12.0 eq) was added MeOH (4 mL); and the reaction mixture was stirred at 0 °C for 1h. Then NaBH<sub>3</sub>CN (37.24 mg, 0.76 mmol, 6.0 eq) was added and the reaction mixture was stirred at RT for 1 h. The reaction was concentration and the resulting residue was purified by RP-HPLC using MeCN and H<sub>2</sub>O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisindolin-1-one (9.02 mg, 0.01 mmol, 12.6%) as a white solid.

**[0390]** <sup>1</sup>H NMR (400 MHz, METHANOL-*d*<sub>4</sub>) δ : 8.58 (d, J = 9.9 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.51 (d, J = 9.9 Hz, 1H), 7.07 (d, J = 9.9 Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.64 - 3.50 (m, 4H), 3.10 (br t, J = 6.8 Hz, 2H), 3.05 - 2.97 (m, 2H), 2.89 (q, J = 7.3 Hz, 2H), 2.33 (s, 3H), 2.20 - 2.10 (m, 2H), 2.04 (dt, J = 2.6, 7.1 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); LC/MS (ESI): 476.3 [M+H]<sup>+</sup>.

**[0391] Example 31. Synthesis of 5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isindolin-1-one (Compound No. 451)**

**[0392] Scheme 31.**



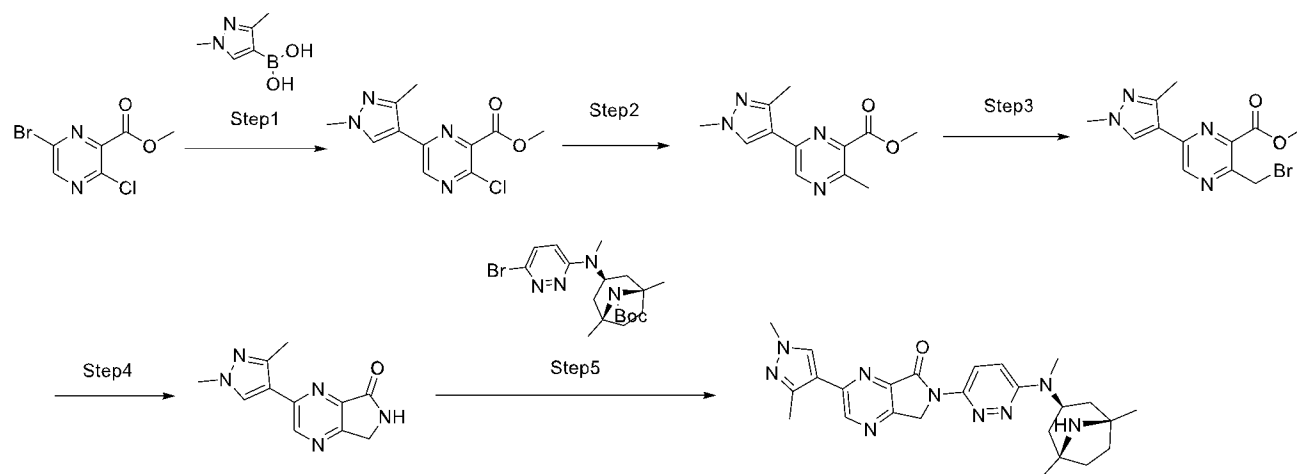
**[0393] Step 1:** 5-Bromoisindolin-1-one (315 mg, 1.5 mmol, 1.5 eq), 4,4,4',4'',5,5,5',5''-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Then 5-bromo-3-methyl-1,2,4-thiadiazole (177.3 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the reaction mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v* to afford 5-(3-methyl-1,2,4-thiadiazol-5-yl)isindolin-1-one (71.9 mg, 31%) as a brown solid. LC/MS (ESI): 232.1 [M+H]<sup>+</sup>.

**[0394] Step 2:** To a round bottom flask charged with 5-(3-methyl-1,2,4-thiadiazol-5-yl)isoindolin-1-one (34.8 mg, 0.15 mmol, 1.0 eq), 3-bromo-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazine (50.0 mg, 0.16 mmol, 1.1 eq), Cs<sub>2</sub>CO<sub>3</sub> (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v. The resulting residue was further purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one (20.68 mg, 29.7 %) as a white solid.

**[0395]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 9.16 (d, *J* = 1.9 Hz, 1H), 8.74 (dd, *J* = 2.6, 9.4 Hz, 1H), 8.71 - 8.67 (m, 1H), 8.47 - 8.44 (m, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.16 (s, 1H), 5.23 (d, *J* = 5.5 Hz, 2H), 4.13 (br s, 1H), 4.06 - 4.03 (m, 1H), 3.90 (s, 3H), 3.54 - 3.44 (m, 1H), 2.76 (br d, *J* = 14.6 Hz, 1H), 2.44 - 2.34 (m, 1H), 2.22 - 2.14 (m, 1H), 2.11 - 2.07 (m, 1H), 2.06 - 1.96 (m, 2H), 1.85 - 1.70 (m, 1H), 1.58 (br d, *J* = 8.0 Hz, 1H); LC/MS (ESI): 402.2 [M+H]<sup>+</sup>.

**[0396] Example 32. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (Compound No. 452)**

**[0397] Scheme 32.**



**[0398] Step 1:** Methyl 6-bromo-3-chloropyrazine-2-carboxylate (400 mg, 1.59 mmol, 1.0 eq), (2,5-dimethylpyrazol-3-yl)boranediol (222.52 mg, 1.59 mmol, 1.0 eq), sodium carbonate (505.57 mg, 4.77 mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (116.28 mg, 0.16 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) and water (1 mL) were added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 3-

chloro-6-(1,3-dimethylpyrazol-4-yl)pyrazine-2-carboxylate (300 mg, 70.72%) LC/MS (ESI): 267.0 [M+H]<sup>+</sup>.

**[0399] Step 2:** Methyl 3-chloro-6-(1,3-dimethylpyrazol-5-yl)pyrazine-2-carboxylate (500 mg, 1.87 mmol, 1.2 eq), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.29 mL, 2.25 mmol, 1.0 eq), potassium carbonate (777.31 mg, 5.62 mmol, 3.0 eq) and PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub> adduct (137.05 mg, 0.19 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (10 mL) was added and the reaction mixture was heated to 110 °C 3 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA(100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 6-(1,3-dimethylpyrazol-5-yl)-3-methylpyrazine-2-carboxylate (430 mg, 93.13%). LC/MS (ESI): 247.1 [M+H]<sup>+</sup>.

**[0400] Step 3:** Methyl 6-(1,3-dimethyl-1H-pyrazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 1.75 mmol, 1.0 eq), *N*-bromosuccinimide (371.67 mg, 2.10 mmol, 1.2 eq) and benzoyl peroxide (129.17 mg, 0.79 mmol, 0.45 eq) were combined with carbon tetrachloride (10 mL) and the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford methyl 3-(bromomethyl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyrazine-2-carboxylate (440 mg, 77.32%) as a brown solid. LC/MS (ESI): 325.1, 327.1 [M+H]<sup>+</sup>.

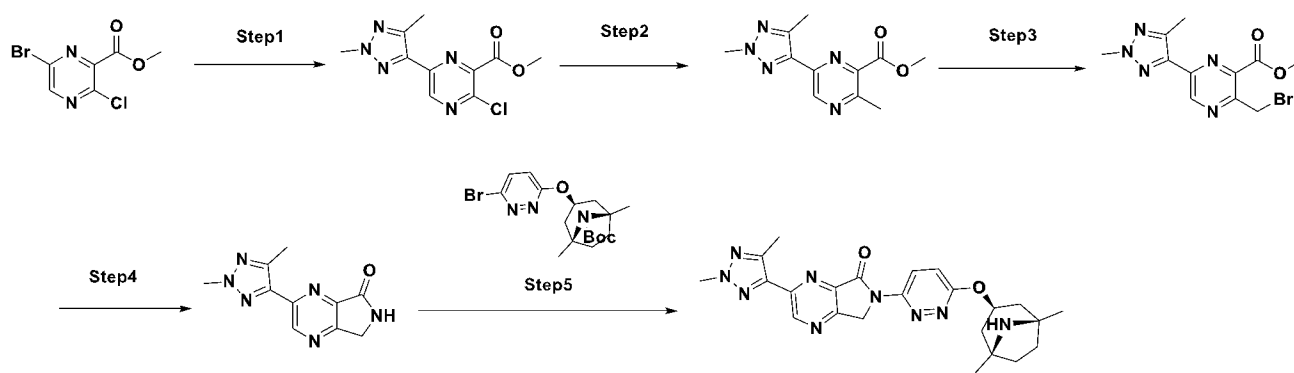
**[0401] Step 4:** Methyl 3-(bromomethyl)-6-(1,3-dimethylpyrazol-4-yl)pyrazine-2-carboxylate (440 mg, 1.35 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. The mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum, and used in the next step without further purification. LC/MS (ESI): 230.1 [M+H]<sup>+</sup>

**[0402] Step 5:** To a round bottom flask charged with 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-5-one (40 mg, 0.17 mmol, 1.0 eq), tert-butyl (1R,3s,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (71.95 mg, 0.17 mmol, 1.0 eq), Cs<sub>2</sub>CO<sub>3</sub> (170.13 mg, 0.52 mmol, 3.0 eq), and XantPhos Pd G4 (16.79 mg, 0.02 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 2-methylpropan-2-yl (1R,3s,5S)-3-({6-[2-(1,3-dimethylpyrazol-4-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (40.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(1,3-dimethylpyrazol-4-yl)-6-(6-{{(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl}oxy}}-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-5-one (25 mg, 30 %) as a white solid.

**[0403]**  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 9.10 (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d,  $J$  = 10.0 Hz, 1H), 5.16 (s, 2H), 5.02 (td,  $J$  = 5.6, 11.3 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d,  $J$  = 7.6 Hz, 2H), 1.79 (br t,  $J$  = 10.9 Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d,  $J$  = 5.1 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 474.3  $[\text{M}+\text{H}]^+$ .

**[0404]** Example 33. Synthesis of 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (Compound No. 453)

**[0405]** Scheme 33.



**[0406]** **Step 1:** 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 90  $^\circ\text{C}$ . When full conversion was achieved, the reaction mixture was cooled to room temperature. Then methyl 6-bromo-3-chloropyrazine-2-carboxylate (249.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90  $^\circ\text{C}$ . When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH, 20/1, v/v to obtain methyl 3-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (165.5 mg, 62%) as a brown solid. LC/MS (ESI): 268.1  $[\text{M}+\text{H}]^+$ .

**[0407]** **Step 2:** Methyl 3-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (500 mg, 1.87 mmol, 1.2 eq), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.29 mL, 2.25 mmol, 1.0 eq), potassium carbonate (777.31 mg, 5.62 mmol, 3.0 eq) and  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  adduct (137.05 mg, 0.19 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (10 mL) was added and the reaction mixture was heated to 110  $^\circ\text{C}$  3 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to

afford methyl 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 93.13%). LC/MS (ESI): 247.1 [M+H]<sup>+</sup>.

**[0408] Step 3:** Methyl 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 1.75 mmol, 1.0 eq), *N*-bromosuccinimide (371.67 mg, 2.10 mmol, 1.2 eq) and benzoyl peroxide (129.17 mg, 0.79 mmol, 0.45 eq) were combined with carbon tetrachloride (10 mL) and the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford methyl 3-(bromomethyl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (440 mg, 77.32%) as a brown solid. LC/MS (ESI): 325.1, 327.1 [M+H]<sup>+</sup>.

**[0409] Step 4:** Methyl 3-(bromomethyl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (440 mg, 1.35 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum, and used in the next step without further purification. LC/MS (ESI): 230.1 [M+H]<sup>+</sup>

**[0410] Step 5:** To a round bottom flask charged with 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (40 mg, 0.17 mmol, 1.0 eq), *tert*-butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (71.95 mg, 0.17 mmol, 1.0 eq), Cs<sub>2</sub>CO<sub>3</sub> (170.13 mg, 0.52 mmol, 3.0 eq), and XantPhos Pd G4 (16.79 mg, 0.02 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved in HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H<sub>2</sub>O as eluent to provide 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1*R*,3*S*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (25 mg, 30 %) as a white solid.

**[0411]** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 9.34 (s, 1H), 8.71 (d, *J* = 9.6 Hz, 1H), 7.35 (d, *J* = 9.6 Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, *J* = 5.8, 11.9 Hz, 2H), 1.80 (br d, *J* = 6.6 Hz, 2H), 1.53 (br d, *J* = 6.9 Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H); LC/MS (ESI): 462.2 [M+H]<sup>+</sup>.

**[0412]** In some embodiments, of the disclosure can be made by similar means according to the **Examples 1-33**. **Table 2** provides for physical data for the compounds disclosed herein.

**TABLE 2**

| No. | NMR/MS                                 |
|-----|----------------------------------------|
| 1   | LC/MS (ESI): 405.2 [M+H] <sup>+</sup>  |
| 2   | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>  |
| 3   | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>  |
| 4   | LC/MS (ESI): 402.20 [M+H] <sup>+</sup> |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5   | LC/MS (ESI): 390.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 6   | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 7   | LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 8   | LC/MS (ESI): 506.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 9   | LC/MS (ESI): 498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 10  | LC/MS (ESI): 488.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 11  | LC/MS (ESI): 386.17 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |
| 12  | LC/MS (ESI): 376.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 13  | LC/MS (ESI): 418.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 14  | LC/MS (ESI): 388.18 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |
| 15  | LC/MS (ESI): 434.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 16  | LC/MS (ESI): 428.18 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |
| 17  | <sup>1</sup> H NMR (C <sub>2</sub> DF <sub>3</sub> O <sub>2</sub> , 400MHz) δ 9.94 (d, <i>J</i> = 9.5 Hz, 1H), 9.38 (s, 1H), 9.08 (s, 1H), 9.00 (s, 1H), 8.90 (s, 1H), 8.80 (d, <i>J</i> = 9.5 Hz, 1H), 6.92-6.49 (m, 1H), 5.73 (s, 2H), 4.41 (s, 3H), 3.57 (br d, <i>J</i> = 7.0 Hz, 2H), 2.95 (br d, <i>J</i> = 3.4 Hz, 1H), 2.10 - 2.03 (m, 2H), 2.01-1.91 (m, 2H), 1.73 (s, 6H), 1.67 (s, 6H); LC/MS (ESI): 446.3 [M+H] <sup>+</sup> |
| 18  | LC/MS (ESI): 476.27 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                   |
| 19  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 8.92 (s, 1H), 8.45-8.40 (m, 2H), 8.13 (s, 1H), 7.99 (s, 1H), 7.26 (d, <i>J</i> = 10.0 Hz, 1H), 5.19 (s, 2H), 4.87-4.76 (m, 1H), 3.90 (s, 3H), 3.58-3.51 (m, 2H), 2.86 (s, 3H), 2.10 (br d, <i>J</i> = 12.9 Hz, 2H), 1.79-1.68 (m, 2H), 1.62 (br d, <i>J</i> = 7.0 Hz, 2H), 1.33 (br t, <i>J</i> = 12.2 Hz, 2H), 1H not observed (NH); LC/MS (ESI): 431.2 [M+H] <sup>+</sup> |
| 20  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 8.93 (s, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.21 (s, 2H), 5.07-4.94 (m, 1H), 3.90 (s, 3H), 2.91 (s, 3H), 2.05 - 1.92 (m, 2H), 1.68 (br s, 6H), 1.31 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 459.3 [M+H] <sup>+</sup>                                                                  |
| 21  | LC/MS (ESI): 506.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 22  | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 23  | LC/MS (ESI): 490.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 24  | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 25  | LC/MS (ESI): 430.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 26  | LC/MS (ESI): 492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 27  | LC/MS (ESI): 429.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 28  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 9.02 (d, <i>J</i> = 6.3 Hz, 2H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.52 (s, 1H), 8.28 (s, 1H), 8.04-7.72 (m, 1H), 7.34 (d, <i>J</i> = 9.5 Hz, 1H), 5.63 (br s, 1H), 5.28 (s, 2H), 2.28-2.07 (m, 2H), 1.58-1.34 (m, 2H), 1.27 (br s, 6H), 1.22-1.03 (m, 6H), 1H not observed (NH); LC/MS (ESI): 484.2 [M+H] <sup>+</sup>                                                      |
| 29  | LC/MS (ESI): 484.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 30  | LC/MS (ESI): 516.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 31  | LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 32  | LC/MS (ESI): 445.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 33  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.58 (s, 2H), 9.30 (s, 1H), 9.21 (s, 1H), 9.17 (br s, 1H), 8.65-8.51 (m, 2H), 7.67-7.52 (m, 1H), 5.32 (s, 2H), 3.93-3.89 (m, 2H), 3.79 (s, 2H), 3.40 (br s, 2H), 1.08-1.00 (m, 2H), 1.00-0.91 (m, 2H); LC/MS (ESI): 400.3 [M+H] <sup>+</sup>                                                                                                                                |
| 34  | LC/MS (ESI): 433.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 35  | LC/MS (ESI): 497.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 36  | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 37  | LC/MS (ESI): 453.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 38  | LC/MS (ESI): 403.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 39  | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |
| 40  | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                    |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 41  | LC/MS (ESI): 419.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 42  | LC/MS (ESI): 434.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 43  | LC/MS (ESI): 475.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 44  | LC/MS (ESI): 403.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 45  | LC/MS (ESI): 422.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 46  | LC/MS (ESI): 419.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 47  | LC/MS (ESI): 475.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 48  | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 49  | LC/MS (ESI): 464.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 50  | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 51  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.97 - 8.92 (m, 1H), 8.85 - 8.75 (m, 1H), 8.55 - 8.49 (m, 1H), 8.38 - 8.32 (m, 1H), 7.98 - 7.89 (m, 1H), 7.86 - 7.81 (m, 1H), 7.48 - 7.40 (m, 1H), 5.22 - 5.17 (m, 2H), 5.13 - 5.02 (m, 1H), 3.84 - 3.78 (m, 3H), 2.96 - 2.91 (m, 3H), 2.47 (s, 3H), 1.97 - 1.87 (m, 2H), 1.82 - 1.75 (m, 2H), 1.54 - 1.49 (m, 6H), 1.45 - 1.39 (m, 6H); LC/MS (ESI): 475.3 [M+H] <sup>+</sup>                                                                                           |
| 52  | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 53  | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 54  | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 55  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) $\delta$ = 9.33 (s, 1H), 8.97 (s, 1H), 8.37 (s, 1H), 7.88 (s, 1H), 5.17 (s, 2H), 5.07 (m, 1H), 3.81 (s, 3H), 3.03 (s, 3H), 2.48 (s, 3H), 1.81 (br d, <i>J</i> =7.4 Hz, 2H), 1.54-1.69 (m, 6H), 1.23 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3 [M+H] <sup>+</sup>                                                                                                                                                                                                             |
| 56  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 9.06 (s, 1H), 8.72 (s, 1H), 8.71 (d, 2H, <i>J</i> = 9.0 Hz), 8.2-8.3 (m, 1H), 7.99 (s, 1H), 7.35 (dd, 1H, <i>J</i> = 1.4, 9.6 Hz), 5.6-5.7 (m, 1H), 5.29 (s, 2H), 4.28 (d, 2H, <i>J</i> = 7.3 Hz), 2.13 (br dd, 2H, <i>J</i> = 3.9, 15.8 Hz), 1.48 (t, 3H, <i>J</i> = 7.3 Hz), 1.36 (br d, 2H, <i>J</i> = 11.9 Hz), 1.3-1.3 (s, 6H), 1.17 (s, 6H); 1H not observed (NH); LC/MS (ESI): 458.2 [M+H] <sup>+</sup>                                                           |
| 57  | LC/MS (ESI): 492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 58  | LC/MS (ESI): 515.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 59  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) $\delta$ = 8.98 (s, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.19 (br s, 1H), 7.88 (s, 1H), 7.32 (d, <i>J</i> = 9.6 Hz, 1H), 5.63 - 5.53 (m, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.11 (br dd, <i>J</i> = 3.6, 12.3 Hz, 1H), 1.88 - 1.80 (m, 1H), 1.63 (br dd, <i>J</i> = 4.3, 11.8 Hz, 1H), 1.37 (t, <i>J</i> = 11.6 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.59 - 0.52 (m, 2H), 0.51 - 0.44 (m, 1H), 0.40 - 0.33 (m, 1H); LC/MS (ESI): 460.1 [M+H] <sup>+</sup> |
| 60  | LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 61  | LC/MS (ESI): 527.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 62  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.03 (s, 1H), 8.46 (d, <i>J</i> = 9.8 Hz, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.34 (d, <i>J</i> = 9.9 Hz, 1H), 5.25 (s, 2H), 5.05 - 4.93 (m, 1H), 2.91 (s, 3H), 2.64 (s, 6H), 1.96 (br d, <i>J</i> = 7.8 Hz, 2H), 1.80 - 1.72 (m, 2H), 1.68 (br d, <i>J</i> = 7.5 Hz, 2H), 1.63 (br dd, <i>J</i> = 5.4, 12.9 Hz, 2H), 1.30 (s, 6H); LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                                   |
| 63  | LC/MS (ESI): 516.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 64  | LC/MS (ESI): 462.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 65  | LC/MS (ESI): 530.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 66  | LC/MS (ESI): 543.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 67  | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 68  | LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 69  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.06 (s, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (s, 1H), 7.92 (s, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 2H), 2.65 (s, 6H), 2.22 (br dd, <i>J</i> = 5.9, 12.3 Hz, 2H), 1.88 (br d, <i>J</i> = 7.4 Hz, 2H), 1.60 (br d, <i>J</i> = 6.9 Hz, 2H), 1.49 (br t, <i>J</i> = 11.4 Hz, 2H), 1.25 (s, 6H); LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                        |
| 70  | LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 71  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) δ = 9.03 (s, 1H), 8.63 (s, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.29 (s, 1H), 7.92 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.27 (s, 2H), 5.10 - 5.00 (m, 1H), 3.99 (s, 3H), 2.91 (s, 3H), 1.67 - 1.58 (m, 4H), 1.35 (s, 6H), 1.22 (s, 6H); LC/MS (ESI): 529.2 [M+H] <sup>+</sup>                                                                                                                                          |
| 72  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 8.98 (s, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.51 (br t, <i>J</i> = 5.7 Hz, 1H), 5.23 (s, 2H), 3.81 (s, 3H), 2.47-2.48 (s, 3H), 2.36 (br dd, <i>J</i> = 13.0, 5.9 Hz, 2H), 2.06 (br d, <i>J</i> = 7.8 Hz, 2H), 1.79 (br d, <i>J</i> = 8.0 Hz, 2H), 1.69 (br t, <i>J</i> = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 460.2 [M+H] <sup>+</sup> |
| 73  | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 74  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) δ : 9.28 (br d, <i>J</i> = 9.8 Hz, 1H), 9.13 (br d, <i>J</i> = 9.0 Hz, 1H), 9.06 (s, 1H), 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.64 (s, 1H), 7.96 (s, 1H), 7.40 (d, <i>J</i> = 9.6 Hz, 1H), 5.53 (td, <i>J</i> = 5.2, 10.9 Hz, 1H), 5.27 (s, 2H), 3.99 (s, 3H), 2.43 (br dd, <i>J</i> = 5.9, 13.1 Hz, 2H), 2.15 (br d, <i>J</i> = 8.1 Hz, 2H), 1.95 - 1.82 (m, 4H), 1.47 (s, 6H); LC/MS (ESI): 514.2 [M+H] <sup>+</sup>           |
| 75  | LC/MS (ESI): 498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 76  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) δ = 8.98 (s, 1H), 8.72 (d, <i>J</i> = 9.5 Hz, 1H), 8.38 (s, 1H), 7.89 (s, 1H), 7.38 (br d, <i>J</i> = 9.6 Hz, 1H), 5.74 - 5.58 (m, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.30 - 2.13 (m, 2H), 1.53 (br d, <i>J</i> = 6.5 Hz, 2H), 1.45 - 1.16 (m, 12H), <sup>1</sup> H not observed (NH); LC/MS (ESI): 462.3 [M+H] <sup>+</sup>                                                                                      |
| 77  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 9.07 (s, 1H), 8.94 (s, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.36 - 8.25 (m, 1H), 8.12 (s, 1H), 8.01 - 7.62 (m, 1H), 7.35 (d, <i>J</i> = 9.5 Hz, 1H), 5.57 - 5.45 (m, 1H), 5.28 (s, 2H), 2.57 (s, 3H), 2.22 (dd, <i>J</i> = 5.9, 12.3 Hz, 2H), 1.88 (br d, <i>J</i> = 7.5 Hz, 2H), 1.62 (br d, <i>J</i> = 7.6 Hz, 2H), 1.56 - 1.48 (m, 2H), 1.27 (s, 6H); LC/MS (ESI): 496.2 [M+H] <sup>+</sup>                          |
| 78  | LC/MS (ESI): 498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 79  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) δ: 8.87-8.97 (m, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.31 (s, 1H), 7.83 (d, <i>J</i> = 0.9 Hz, 1H), 7.41 (d, <i>J</i> = 9.6 Hz, 1H), 5.43-5.62 (m, 1H), 5.15 (s, 2H), 4.91-5.12 (m, 1H), 3.75 (s, 3H), 2.41 (s, 3H), 2.17-2.31 (m, 1H), 1.92-2.14 (m, 2H), 1.64-1.91 (m, 3H), 1.25-1.50 (m, 6H), 1H not observed (NH); LC/MS (ESI): 478.2 [M+H] <sup>+</sup>                                                                |
| 80  | LC/MS (ESI): 463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 81  | LC/MS (ESI): 434.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 82  | LC/MS (ESI): 496.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 83  | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 84  | LC/MS (ESI): 463.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 85  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400MHz) δ = 8.97 (s, 1H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.30 (s, 1H), 7.85 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.08 (td, <i>J</i> = 5.6, 11.6 Hz, 1H), 3.83 (s, 3H), 2.92 (s, 3H), 2.48 (s, 3H), 2.13 (br d, <i>J</i> = 8.1 Hz, 2H), 2.01 - 1.93 (m, 2H), 1.92 - 1.86 (m, 2H), 1.79 (br dd, <i>J</i> = 5.4, 13.4 Hz, 2H), 1.42 (s, 6H), 1H not observed (NH); LC/MS (ESI): 473.3 [M+H] <sup>+</sup>           |
| 86  | LC/MS (ESI): 479.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 88  | LC/MS (ESI): 477.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 89  | LC/MS (ESI): 473.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 90  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 8.47 - 8.41 (m, 2H), 8.35 (s, 1H), 7.89 (s, 1H), 7.32 (d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.07 - 4.93 (m, 1H), 3.82 (s, 3H), 2.90 (s, 3H), 2.48 (s, 3H), 1.95 - 1.89 (m, 2H), 1.77 - 1.58 (m, 6H), 1.28 (s, 6H); LC/MS (ESI): 507.2 [M+H] <sup>+</sup>                                                                                                                                                            |
| 91  | LC/MS (ESI): 466.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 92  | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 93  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ , 8.96 (br d, <i>J</i> = 8.8 Hz, 1H), 8.85 (br d, <i>J</i> = 9.3 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.41 (d, <i>J</i> = 9.6 Hz, 1H), 5.61 - 5.47 (m, 1H), 5.16 (s, 2H), 3.82 (s, 3H), 2.48 - 2.42 (m,                                                                                                                                                                                   |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | 5H), 2.16 (br d, $J = 8.0$ Hz, 2H), 1.95 - 1.75 (m, 4H), 1.45 (s, 6H); LC/MS (ESI): 494.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                          |
| 94  | LC/MS (ESI): 474.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 95  | LC/MS (ESI): 418.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 96  | $^1H$ NMR (METHANOL- $d_4$ , 400 MHz) $\delta$ : 9.02 (s, 1H), 8.85 (d, $J = 9.6$ Hz, 1H), 8.27 (s, 1H), 7.26 (d, $J = 9.6$ Hz, 1H), 5.69 - 5.57 (m, 1H), 5.29 (s, 2H), 4.19 (s, 3H), 2.61 (s, 3H), 2.61 - 2.56 (m, 2H), 2.38 - 2.29 (m, 2H), 2.08 - 2.00 (m, 2H), 1.86 (dd, $J = 11.4, 13.2$ Hz, 2H), 1.55 (s, 6H), $^1H$ not observed (NH); LC/MS (ESI): 461.2 $[M+H]^+$                                                                                   |
| 97  | LC/MS (ESI): 461.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 98  | $^1H$ NMR (DMSO- $d_6$ , 400 MHz) $\delta$ 8.98 (s, 1H), 8.70 (d, $J = 9.6$ Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.88 (s, 1H), 7.34 (d, $J = 9.6$ Hz, 1H), 5.51 (s, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.26 (br dd, $J = 5.6, 12.4$ Hz, 2H), 1.90 (br t, $J = 7.1$ Hz, 2H), 1.71 - 1.48 (m, 6H), 1.30 (s, 3H), 0.91 (t, $J = 7.4$ Hz, 3H); LC/MS (ESI): 474.2 $[M+H]^+$                                                                          |
| 99  | $^1H$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.96$ (s, 1H), 8.71 (d, $J = 9.5$ Hz, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.48 (br d, $J = 6.0$ Hz, 1H), 5.24 (s, 2H), 3.90 (s, 3H), 2.25 (br dd, $J = 6.1, 12.2$ Hz, 2H), 1.92 (br d, $J = 7.5$ Hz, 2H), 1.66 (br d, $J = 7.5$ Hz, 2H), 1.57 (br t, $J = 11.6$ Hz, 2H), 1.30 (s, 6H); LC/MS (ESI): 446.2 $[M+H]^+$                                         |
| 100 | $^1H$ NMR (METHANOL- $d_4$ , 400 MHz) $\delta$ : 8.97 (s, 1H), 8.88 (d, $J = 9.6$ Hz, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.28 (d, $J = 9.6$ Hz, 1H), 5.71 - 5.58 (m, 1H), 5.30 (s, 2H), 3.90 (s, 3H), 2.66 (dd, $J = 5.9, 13.9$ Hz, 2H), 2.54 (s, 3H), 2.39 - 2.30 (m, 2H), 1.99 (br d, $J = 8.5$ Hz, 2H), 1.92 - 1.80 (m, 6H), 1.08 (t, $J = 7.5$ Hz, 6H), $^1H$ not observed (NH); LC/MS (ESI): 488.3 $[M+H]^+$                                              |
| 101 | LC/MS (ESI): 486.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 102 | LC/MS (ESI): 474.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 103 | LC/MS (ESI): 542.4 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 104 | LC/MS (ESI): 486.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 105 | LC/MS (ESI): 511.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 106 | LC/MS (ESI): 481.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 107 | LC/MS (ESI): 464.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 108 | LC/MS (ESI): 478.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 109 | LC/MS (ESI): 490.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 110 | LC/MS (ESI): 495.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 111 | $^1H$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.32$ (s, 1H), 8.94 (br s, 1H), 8.86 (br s, 1H), 8.74 (dd, $J = 9.6, 0.9$ Hz, 1H), 7.43 (d, $J = 9.5$ Hz, 1H), 5.49-5.60 (m, 1H), 5.21 (s, 2H), 2.84 (s, 3H), 2.67 (s, 3H), 2.42-2.48 (m, 2H), 2.17 (br d, $J = 8.1$ Hz, 2H), 1.89 (br d, $J = 8.3$ Hz, 2H), 1.76-1.85 (m, 2H), 1.46 (s, 6H); LC/MS (ESI): 478.3 $[M+H]^+$                                                                                       |
| 112 | $^1H$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.15$ (br s, 1H), 9.00 (s, 1H), 8.74 (d, $J = 9.6$ Hz, 1H), 8.58 (s, 1H), 8.40 (s, 1H), 7.40 (d, $J = 9.6$ Hz, 1H), 5.58 - 5.48 (m, 1H), 5.26 (s, 2H), 2.72 - 2.68 (m, 3H), 2.48 - 2.38 (m, 2H), 2.21 - 2.08 (m, 2H), 1.94 - 1.77 (m, 4H), 1.46 (s, 6H); LC/MS (ESI): 463.1 $[M+H]^+$                                                                                                                            |
| 113 | LC/MS (ESI): 460.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 114 | LC/MS (ESI): 463.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 115 | $^1H$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.97$ (s, 1H), 8.70 (d, $J = 9.6$ Hz, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.88 (d, $J = 1.0$ Hz, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.51 (ddd, $J = 4.4, 6.8, 10.9$ Hz, 1H), 5.25 (s, 2H), 3.81 (s, 3H), 2.55 - 2.51 (m, 1H), 2.48 (s, 3H), 2.21 - 2.12 (m, 1H), 2.06 (q, $J = 10.0$ Hz, 3H), 1.91 - 1.83 (m, 1H), 1.79 - 1.63 (m, 2H), 1.51 - 1.37 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H); LC/MS (ESI): 474.2 $[M+H]^+$ |
| 116 | LC/MS (ESI): 478.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 117 | LC/MS (ESI): 461.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 120 | LC/MS (ESI): 405.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 123 | LC/MS (ESI): 417.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 124 | LC/MS (ESI): 433.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 134 | LC/MS (ESI): 445.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 135 | LC/MS (ESI): 462.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 136 | LC/MS (ESI): 376.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 137 | LC/MS (ESI): 390.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 138 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 139 | LC/MS (ESI): 488.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 140 | LC/MS (ESI): 484.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 141 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.22 - 8.13 (m, 2H), 7.32 (d, <i>J</i> = 9.5 Hz, 1H), 5.62 (ddd, <i>J</i> = 4.1, 7.1, 11.1 Hz, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 2.09 (br d, <i>J</i> = 9.9 Hz, 2H), 1.39 - 1.06 (m, 14H), 1H not observed (NH); LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                                     |
| 142 | LC/MS (ESI): 498.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 143 | LC/MS (ESI): 434.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 144 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 145 | LC/MS (ESI): 402.20 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 146 | LC/MS (ESI): 388.18 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 147 | LC/MS (ESI): 386.17 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 148 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 9.54 (br d, <i>J</i> = 10.6 Hz, 1H), 9.17 (d, <i>J</i> = 1.9 Hz, 1H), 8.81 (d, <i>J</i> = 10.3 Hz, 1H), 8.68 - 8.57 (m, 1H), 8.47 (s, 1H), 8.43 (d, <i>J</i> = 2.0 Hz, 1H), 8.17 - 8.14 (m, 1H), 8.05 (br s, 1H), 5.09 (s, 2H), 4.85 - 4.77 (m, 1H), 3.90 (s, 3H), 3.08 (s, 3H), 2.21 (br t, <i>J</i> = 12.8 Hz, 2H), 1.81 - 1.72 (m, 2H), 1.56 (s, 6H), 1.53 (s, 6H); LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                            |
| 149 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 9.17 (d, <i>J</i> = 1.9 Hz, 1H), 8.49 (d, <i>J</i> = 10.0 Hz, 1H), 8.42 (d, <i>J</i> = 2.0 Hz, 1H), 8.40 - 8.31 (m, 3H), 7.32 (d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.12 - 5.03 (m, 1H), 2.91 (s, 3H), 1.73 (br t, <i>J</i> = 12.4 Hz, 2H), 1.61 (dd, <i>J</i> = 3.1, 12.4 Hz, 2H), 1.39 (s, 6H), 1.28 (s, 6H), 1H not observed (NH); LC/MS (ESI): 447.3 [M+H] <sup>+</sup>                                                                                                        |
| 150 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 8.95 (d, <i>J</i> = 2.1 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (d, <i>J</i> = 2.0 Hz, 1H), 7.34 (d, <i>J</i> = 9.6 Hz, 1H), 5.69 - 5.58 (m, 1H), 5.24 (s, 2H), 2.68 (s, 3H), 2.43 (s, 3H), 2.19 - 2.02 (m, 2H), 1.36 - 1.06 (m, 14H), 1H not observed (NH); LC/MS (ESI): 479.2 [M+H] <sup>+</sup>                                                                                                                                                                                 |
| 151 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 152 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 153 | LC/MS (ESI): 445.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 154 | LC/MS (ESI): 433.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 155 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 9.12 (d, <i>J</i> = 1.6 Hz, 1H), 8.49 (d, <i>J</i> = 9.8 Hz, 1H), 8.44 (s, 1H), 8.36 (d, <i>J</i> = 1.8 Hz, 1H), 8.14 (s, 1H), 7.51 (d, <i>J</i> = 10.0 Hz, 1H), 5.13 (s, 2H), 4.27 (br d, <i>J</i> = 11.1 Hz, 1H), 4.15 (br d, <i>J</i> = 10.8 Hz, 1H), 3.89 (s, 3H), 3.14 - 3.03 (m, 2H), 2.95 (br t, <i>J</i> = 11.5 Hz, 1H), 2.84 - 2.74 (m, 2H), 0.84 (br d, <i>J</i> = 7.1 Hz, 1H), 0.48 (br s, 2H), 0.33 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 417.2 [M+H] <sup>+</sup> |
| 156 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.30 (br s, 1H), 8.17 (s, 1H), 8.14 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.17 (s, 2H), 5.06 (br t, <i>J</i> = 11.8 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.37 - 2.34 (m, 5H), 1.69 - 1.52 (m, 3H), 1.35 (s, 6H), 1.22 (s, 6H); LC/MS (ESI): 475.3 [M+H] <sup>+</sup>                                                                                                                          |
| 157 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 9.12 (d, 1H, <i>J</i> = 2.0 Hz), 8.48 (d, 1H, <i>J</i> = 10.0 Hz), 8.44 (s, 1H), 8.37 (d, 1H, <i>J</i> = 2.1 Hz), 8.18 (s, 1H), 8.14 (s, 1H), 7.48 (d, 1H, <i>J</i> = 9.9 Hz), 5.14 (s, 2H), 4.27-4.34 (m, 1H), 4.11-4.19 (m, 1H), 3.90 (s, 3H), 3.02-3.15 (m, 1H), 2.82-2.92 (m, 1H), 2.79-2.86 (m, 1H), 2.62-2.72 (m, 2H), 1.66-1.72 (m, 1H), 0.97 (d, 6H, <i>J</i> = 6.8 Hz); LC/MS (ESI): 419.2 [M+H] <sup>+</sup>                                                                    |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 158 | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 159 | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 160 | LC/MS (ESI): 497.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 161 | LC/MS (ESI): 464.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 162 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.41 (s, 1H), 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.22 - 8.14 (m, 2H), 5.14 (m, 3H), 3.83 (s, 3H), 3.09 (s, 3H), 2.35 (s, 3H), 1.99 - 1.82 (m, 4H), 1.51 (s, 6H), 1.43 (s, 6H), 1H not observed (NH); LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                          |
| 163 | LC/MS (ESI): 501.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 164 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.94 (s, 1H), 8.85 - 8.66 (m, 2H), 8.53 (d, <i>J</i> = 9.9 Hz, 1H), 8.19 - 8.13 (m, 2H), 7.44 (br d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.05 (td, <i>J</i> = 5.7, 11.5 Hz, 1H), 3.82 (s, 3H), 2.94 (s, 3H), 2.36 (s, 3H), 2.18 (br d, <i>J</i> = 8.3 Hz, 2H), 2.03 - 1.93 (m, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.83 (br dd, <i>J</i> = 5.4, 13.2 Hz, 2H), 1.44 (s, 6H); LC/MS (ESI): 473.2 [M+H] <sup>+</sup>         |
| 165 | LC/MS (ESI): 417.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 166 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.99 - 8.88 (m, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.40 - 8.26 (m, 1H), 8.20 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.21 (s, 2H), 5.02 (td, <i>J</i> = 5.7, 11.3 Hz, 1H), 2.90 (s, 3H), 2.68 (s, 3H), 2.43 (s, 3H), 1.98 (br d, <i>J</i> = 7.6 Hz, 2H), 1.85 - 1.74 (m, 2H), 1.73 - 1.59 (m, 4H), 1.31 (s, 6H); LC/MS (ESI): 490.3 [M+H] <sup>+</sup>                                                   |
| 167 | LC/MS (ESI): 492.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 168 | LC/MS (ESI): 501.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 169 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.26 (d, <i>J</i> = 2.1 Hz, 1H), 9.06 (s, 1H), 8.56 (s, 1H), 8.56 (d, <i>J</i> = 3.8 Hz, 2H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.38 (br s, 1H), 8.07 - 7.70 (m, 1H), 7.31 (d, <i>J</i> = 10.0 Hz, 1H), 5.17 (s, 2H), 5.10 - 4.95 (m, 1H), 2.90 (s, 3H), 1.95 (br d, <i>J</i> = 7.5 Hz, 2H), 1.84 - 1.73 (m, 2H), 1.73 - 1.57 (m, 4H), 1.31 (s, 6H); LC/MS (ESI): 495.3 [M+H] <sup>+</sup>                                         |
| 170 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 171 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.97 - 8.92 (m, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.40 (s, 1H), 8.19 (d, <i>J</i> = 1.9 Hz, 1H), 8.11 (s, 1H), 7.33 (d, <i>J</i> = 9.6 Hz, 1H), 5.54 - 5.43 (m, 1H), 5.18 (s, 2H), 3.84 (s, 3H), 2.37 (s, 5H), 2.06 (br d, <i>J</i> = 7.8 Hz, 2H), 1.82 (br d, <i>J</i> = 8.1 Hz, 2H), 1.70 (br t, <i>J</i> = 11.8 Hz, 2H), 1.39 (s, 6H); LC/MS (ESI): 460.3 [M+H] <sup>+</sup>                                               |
| 172 | LC/MS (ESI): 530.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 173 | LC/MS (ESI): 543.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 174 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.95 (d, <i>J</i> = 1.8 Hz, 1H), 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (d, <i>J</i> = 1.9 Hz, 1H), 7.32 (d, <i>J</i> = 9.6 Hz, 1H), 5.53 - 5.41 (m, 1H), 5.23 (s, 2H), 2.67 (s, 3H), 2.43 (s, 3H), 2.16 (dd, <i>J</i> = 5.9, 11.9 Hz, 2H), 1.80 (br d, <i>J</i> = 7.0 Hz, 2H), 1.53 (br d, <i>J</i> = 7.4 Hz, 2H), 1.41 (br t, <i>J</i> = 11.3 Hz, 2H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 477.2 [M+H] <sup>+</sup> |
| 175 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.34 (s, 1H), 8.94 (d, <i>J</i> = 1.6 Hz, 1H), 8.18 (s, 2H), 5.13 (s, 2H), 5.01-5.10 (m, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.36 (s, 3H), 1.78 (br d, <i>J</i> = 7.4 Hz, 2H), 1.51-1.65 (m, 6H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3 [M+H] <sup>+</sup>                                                                                                                                                          |
| 176 | LC/MS (ESI): 516.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 177 | LC/MS (ESI): 529.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 178 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 179 | LC/MS (ESI): 463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 180 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.14 (d, <i>J</i> = 2.0 Hz, 1H), 8.49 (d, <i>J</i> = 10.0 Hz, 1H), 8.33 (d, <i>J</i> = 1.9 Hz, 1H), 8.32 - 8.19 (m, 1H), 7.34 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.09 (br s, 1H), 4.18 (s, 3H), 2.91 (s, 3H), 2.49 (br s, 3H), 1.75 - 1.59 (m, 4H), 1.39 (s, 6H), 1.27 (s, 6H); LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                     |
| 181 | LC/MS (ESI): 478.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 182 | LC/MS (ESI): 515.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 183 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.91 (d, <i>J</i> = 1.8 Hz, 1H), 8.75 - 8.63 (m, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 7.71 (br d, <i>J</i> = 10.3 Hz, 1H), 5.17 (s, 2H), 4.85 (br s, 1H), 4.01 (br s, 3H), 3.00 (s, 3H), 2.23 (br d, <i>J</i> = 8.4 Hz, 2H), 2.06 - 1.84 (m, 6H), 1.46 (s, 6H), 1H not observed (NH); LC/MS (ESI): 527.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                   |
| 184 | LC/MS (ESI): 498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 185 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 186 | LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 187 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.98-9.05 (m, 1H), 8.45-8.51 (m, 1H), 8.40-8.44 (m, 1H), 8.31-8.36 (m, 1H), 8.20-8.25 (m, 1H), 7.21-7.41 (m, 1H), 5.16 (s, 2H), 5.03-5.09 (m, 1H), 3.80 (s, 3H), 2.91 (s, 3H), 1.55-1.70 (m, 4H), 1.33-1.40 (m, 6H), 1.23 (s, 6H); LC/MS (ESI): 479.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                  |
| 188 | LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 189 | LC/MS (ESI): 462.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 190 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.99-9.09 (m, 1H), 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.37-8.47 (m, 1H), 8.22-8.31 (m, 1H), 7.24-7.36 (m, 1H), 5.57-5.68 (m, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 2.05-2.07 (m, 2H), 1.24-1.29 (m, 2H), 1.23 (s, 6H), 1.08-1.13 (m, 6H), 1H not observed (NH); LC/MS (ESI): 466.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                            |
| 191 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.33 (s, 1H), 8.71 (br d, <i>J</i> = 9.5 Hz, 1H), 8.58 (br s, 1H), 8.53 (s, 1H), 7.35 (br d, <i>J</i> = 9.5 Hz, 1H), 5.64-5.67 (m, 1H), 5.21 (s, 2H), 4.25 (s, 3H), 2.12-2.22 (m, 2H), 1.53-1.57 (m, 2H), 1.41-1.5270m, 6H), 1.23 -1.32(m, 6H), 1H not observed (NH); LC/MS (ESI): 449.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                               |
| 193 | LC/MS (ESI): 492.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 194 | LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 195 | LC/MS (ESI): 493.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 196 | LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 197 | LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 198 | LC/MS (ESI): 511.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 199 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.34 (d, <i>J</i> = 1.3 Hz, 1H), 8.70 (d, <i>J</i> = 9.5 Hz, 1H), 8.60 (d, <i>J</i> = 1.3 Hz, 1H), 8.54 (s, 1H), 7.32 (br d, <i>J</i> = 9.6 Hz, 1H), 5.49 (br s, 1H), 5.22 (s, 2H), 4.25 (s, 3H), 2.10 (br d, <i>J</i> = 7.0 Hz, 2H), 1.89-1.99 (m, 2H), 1.74-1.85 (m, 2H), 1.50 (br d, <i>J</i> = 6.6 Hz, 2H), 1.13-1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                                                                                            |
| 200 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.35 (s, 1H), 8.94 (d, <i>J</i> = 2.1 Hz, 1H), 8.24 (d, <i>J</i> = 2.1 Hz, 1H), 5.18 (s, 2H), 5.01-5.12 (m, 1H), 3.03 (s, 3H), 2.68 (s, 3H), 2.43 (s, 3H), 1.83 (br d, <i>J</i> = 7.4 Hz, 2H), 1.56-1.70 (m, 6H), 1.24 (s, 6H), 1H not observed (NH); LC/MS (ESI): 491.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                               |
| 201 | LC/MS (ESI): 514.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 202 | LC/MS (ESI): 514.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 203 | LC/MS (ESI): 492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 205 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.95 (d, <i>J</i> = 2.1 Hz, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.19 - 8.15 (m, 2H), 7.31 (d, <i>J</i> = 9.6 Hz, 1H), 5.61 - 5.52 (m, 1H), 5.19 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 2.09 (br dd, <i>J</i> = 3.3, 11.9 Hz, 1H), 2.02 (br s, 1H), 1.80 (t, <i>J</i> = 11.4 Hz, 1H), 1.60 (dd, <i>J</i> = 3.9, 12.0 Hz, 1H), 1.32 (t, <i>J</i> = 11.6 Hz, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 0.55 - 0.48 (m, 2H), 0.46 - 0.39 (m, 1H), 0.36 - 0.27 (m, 1H); LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                           |
| 206 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.18 (d, <i>J</i> = 2.0 Hz, 1H), 8.87 (br d, <i>J</i> = 10.6 Hz, 1H), 8.79 (br s, 1H), 8.75 (d, <i>J</i> = 9.6 Hz, 1H), 8.39 (d, <i>J</i> = 2.0 Hz, 1H), 7.41 (d, <i>J</i> = 9.5 Hz, 1H), 5.55 (tt, <i>J</i> = 10.9, 5.6 Hz, 1H), 5.24 (s, 2H), 4.19 (s, 3H), 2.46 (br d, <i>J</i> = 6.1 Hz, 2H), 2.18 (br d, <i>J</i> = 8.0 Hz, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.80 (br t, <i>J</i> = 12.1 Hz, 2H), 1.46 (s, 6H), 3H not observed (triazole methyl overlapped with DMSO- <i>d</i> <sub>6</sub> residue); LC/MS (ESI): 461.2 [M+H] <sup>+</sup> |
| 207 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.91 (d, <i>J</i> = 2.0 Hz, 1H), 8.39 (d, <i>J</i> = 9.6 Hz, 2H), 8.09-8.16 (m, 2H), 6.99 (d, <i>J</i> = 9.6 Hz, 1H), 5.12 (s, 2H), 4.33-4.45                                                                                                                                                                                                                                                                                                                                                                                                             |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | (m, 1H), 3.82 (s, 3H), 2.35 (s, 3H), 2.07 (br dd, $J = 12.9, 2.9$ Hz, 2H), 1.34-1.44 (m, 8H), 1.32 (s, 6H), 1H not observed (NH); LC/MS (ESI): 461.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                            |
| 208 | LC/MS (ESI): 496.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 209 | LC/MS (ESI): 494.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 210 | LC/MS (ESI): 498.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 211 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.96$ (d, $J = 2.1$ Hz, 1H), 8.75 (d, $J = 9.6$ Hz, 1H), 8.19 (s, 2H), 7.44 (d, $J = 9.6$ Hz, 1H), 5.89 - 5.76 (m, 1H), 5.20 (s, 2H), 4.75 (d, $J = 52.0$ Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 2.00 - 1.88 (m, 1H), 1.77 - 1.66 (m, 1H), 1.30 (br s, 6H), 1.19 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 480.2 $[M+H]^+$                                                                                                          |
| 212 | LC/MS (ESI): 480.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 213 | LC/MS (ESI): 496.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 214 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400MHz) $\delta = 8.94$ -9.03 (m, 1H), 8.75 (d, $J = 9.6$ Hz, 1H), 8.19 (s, 2H), 7.43 (d, $J = 9.6$ Hz, 1H), 5.60 (s, 1H), 5.20 (s, 2H), 4.63-4.87 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.98-2.12 (m, 1H), 1.47-1.84 (m, 5H), 1.17-1.35 (s, 6H), 1H not observed (NH); LC/MS (ESI): 478.5 $[M+H]^+$                                                                                                                                                       |
| 215 | LC/MS (ESI): 478.5 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 216 | LC/MS (ESI): 492.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 217 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta$ : 9.35 (s, 1H), 9.04 (s, 1H), 8.43 (s, 1H), 8.34 (br s, 1H), 8.23-8.31 (m, 1H), 5.12-5.17 (m, 2H), 5.04-5.11 (m, 1H), 3.81 (s, 3H), 3.04 (s, 3H), 1.87 (br d, $J = 6.9$ Hz, 2H), 1.72-1.80 (m, 2H), 1.56-1.67 (m, 4H), 1.27-1.32 (m, 6H); LC/MS (ESI): 478.2 $[M+H]^+$                                                                                                                                                                  |
| 218 | LC/MS (ESI): 499.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 219 | LC/MS (ESI): 461.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 220 | LC/MS (ESI): 443.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 221 | LC/MS (ESI): 475.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 222 | LC/MS (ESI): 448.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 223 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.41$ (s, 1H), 9.05 (d, $J = 2.0$ Hz, 1H), 8.71 (br d, $J = 12.3$ Hz, 1H), 8.44 (d, $J = 2.1$ Hz, 1H), 8.28 (d, $J = 2.1$ Hz, 1H), 7.70-7.82 (m, 1H), 5.16-5.19 (m, 1H), 5.15 (s, 2H), 3.82 (s, 3H), 3.10 (s, 3H), 1.90-1.98 (m, 2H), 1.81-1.87 (m, 2H), 1.51 (s, 6H), 1.43 (s, 6H); LC/MS (ESI): 480.2 $[M+H]^+$                                                                                                                      |
| 224 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.70$ (s, 1H), 8.94 (d, $J = 1.0$ Hz, 1H), 8.17-8.17 (m, 1H), 8.07 (s, 1H), 5.48-5.62 (m, 1H), 5.16 (s, 2H), 3.83 (s, 3H), 2.36 (s, 3H), 2.27-2.33 (m, 2H), 1.49 (br s, 8H), 1.39-1.47 (m, 6H), 1H not observed (NH); LC/MS (ESI): 463.3 $[M+H]^+$                                                                                                                                                                                     |
| 225 | LC/MS (ESI): 505.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 226 | LC/MS (ESI): 434.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 227 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.50$ (d, $J = 1.9$ Hz, 1H), 9.36 - 9.25 (m, 1H), 9.16 - 9.07 (m, 1H), 8.77 - 8.73 (m, 2H), 7.41 (d, $J = 9.6$ Hz, 1H), 5.59 - 5.49 (m, 1H), 5.29 (s, 2H), 2.72 (s, 3H), 2.47 - 2.39 (m, 2H), 2.25 - 2.06 (m, 2H), 1.95 - 1.89 (m, 2H), 1.89 - 1.82 (m, 2H), 1.48 (s, 6H); LC/MS (ESI): 464.2 $[M+H]^+$                                                                                                                                |
| 228 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 9.10$ (d, $J = 2.0$ Hz, 2H), 8.68 (d, $J = 9.6$ Hz, 1H), 8.56 (br d, $J = 11.6$ Hz, 1H), 8.31 (d, $J = 2.0$ Hz, 1H), 7.33 (d, $J = 9.6$ Hz, 1H), 5.51-5.59 (m, 1H), 5.17 (s, 2H), 4.11 (s, 3H), 2.42 (br s, 3H), 2.29 (br dd, $J = 13.7, 3.6$ Hz, 1H), 2.00-2.12 (m, 1H), 1.94 (br d, $J = 3.5$ Hz, 1H), 1.68-1.83 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 0.84-1.01 (m, 3H), 0.77 (br d, $J = 3.3$ Hz, 1H); LC/MS (ESI): 461.2 $[M+H]^+$ |
| 230 | LC/MS (ESI): 462.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 231 | LC/MS (ESI): 477.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 232 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 9.03$ (s, 1H), 8.70 (s, 1H), 8.48 (d, 1H, $J = 9.9$ Hz), 8.3-8.3 (m, 1H), 7.96 (s, 1H), 7.33 (d, 1H, $J = 10.0$ Hz), 5.27 (s, 2H), 5.0-5.1 (m, 1H), 4.28 (d, 2H, $J = 7.4$ Hz), 2.91 (s, 3H), 1.59 (br d, 4H, $J = 5.5$                                                                                                                                                                                                                |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | Hz), 1.47 (t, 3H, $J = 7.3$ Hz), 1.34 (s, 6H), 1.21 (br s, 6H); 1H not observed (NH); LC/MS (ESI): 458.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                         |
| 233 | LC/MS (ESI): 464.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 234 | LC/MS (ESI): 448.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 235 | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 236 | LC/MS (ESI): 418.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 237 | LC/MS (ESI): 463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 238 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 239 | <sup>1</sup> H NMR (METHANOL- <i>d</i> <sub>4</sub> , 400 MHz) δ : 8.94 (d, $J = 2.0$ Hz, 1H), 8.88 (d, $J = 9.6$ Hz, 1H), 8.29 (d, $J = 1.9$ Hz, 1H), 7.98 (s, 1H), 7.28 (d, $J = 9.6$ Hz, 1H), 5.72 - 5.59 (m, 1H), 5.25 (s, 2H), 3.91 (s, 3H), 2.66 (dd, $J = 5.9, 13.9$ Hz, 2H), 2.44 (s, 3H), 2.39 - 2.31 (m, 2H), 1.99 (br d, $J = 8.4$ Hz, 2H), 1.92 - 1.86 (m, 4H), 1.82 (br d, $J = 13.3$ Hz, 2H), 1.08 (t, $J = 7.6$ Hz, 6H), 1H not observed (NH); LC/MS (ESI): 488.3 [M+H] <sup>+</sup> |
| 240 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 8.9-9.0 (m, 1H), 8.7-8.8 (m, 1H), 8.2-8.2 (m, 2H), 7.4-7.4 (m, 1H), 5.5-5.6 (m, 1H), 5.1-5.2 (m, 2H), 3.82 (s, 3H), 2.4-2.5 (m, 2H), 2.3-2.4 (m, 3H), 2.1-2.2 (m, 2H), 1.7-1.9 (m, 6H), 1.4-1.5 (m, 3H), 0.9-1.0 (m, 3H); LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                        |
| 241 | LC/MS (ESI): 486.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 242 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 243 | LC/MS (ESI): 542.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 244 | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 245 | LC/MS (ESI): 486.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 246 | LC/MS (ESI): 478.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 247 | LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 248 | LC/MS (ESI): 463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 249 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 8.95 (d, $J = 2.0$ Hz, 1H), 8.71 (d, $J = 9.6$ Hz, 1H), 8.22 (s, 1H), 8.19 - 8.15 (m, 2H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.57 - 5.46 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.57 - 2.52 (m, 1H), 2.36 (s, 3H), 2.21 - 2.07 (m, 4H), 1.94 - 1.85 (m, 1H), 1.83 - 1.65 (m, 2H), 1.55 - 1.40 (m, 2H), 1.21 (s, 3H), 1.16 (s, 3H); LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                     |
| 250 | LC/MS (ESI): 463.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 251 | <sup>1</sup> H NMR (C <sub>2</sub> DF <sub>3</sub> O <sub>2</sub> , 400 MHz) δ = 9.90 (s, 1H), 9.64 (s, 1H), 8.89 (br d, $J = 9.6$ Hz, 1H), 8.70 (s, 1H), 8.24 (br d, $J = 9.6$ Hz, 1H), 7.72 - 7.49 (m, 1H), 7.39 - 7.14 (m, 1H), 6.07 (br s, 2H), 5.79 (br d, $J = 5.1$ Hz, 1H), 4.59 (s, 3H), 2.79 (br dd, $J = 5.3, 13.8$ Hz, 2H), 2.52 - 2.37 (m, 6H), 1.82 (s, 6H); LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                     |
| 252 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 9.14 (d, $J = 1.9$ Hz, 1H), 8.47 (d, $J = 10.0$ Hz, 1H), 8.33 (d, $J = 1.5$ Hz, 1H), 8.18 (br s, 1H), 7.48 (d, $J = 10.0$ Hz, 1H), 5.20 (s, 2H), 4.37 (br d, $J = 12.1$ Hz, 1H), 4.18 (s, 3H), 4.12 (br d, $J = 12.1$ Hz, 1H), 3.09 - 3.05 (m, 1H), 2.87 - 2.80 (m, 1H), 2.78 - 2.70 (m, 1H), 2.60 (br t, $J = 11.6$ Hz, 1H), 2.49 (br s, 3H), 2.36 (br d, $J = 10.4$ Hz, 1H), 0.96 (s, 9H); LC/MS (ESI): 448.2 [M+H] <sup>+</sup>   |
| 253 | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 254 | LC/MS (ESI): 433.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 255 | LC/MS (ESI): 422.95 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 272 | LC/MS (ESI): 434.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 273 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 274 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 8.51 - 8.33 (m, 2H), 8.04 (s, 1H), 7.64 - 7.60 (m, 1H), 7.55 (d, $J = 10.3$ Hz, 1H), 7.31 (d, $J = 10.0$ Hz, 1H), 5.13 (s, 2H), 5.11 - 5.03 (m, 1H), 3.81 (s, 3H), 2.90 (s, 3H), 2.36 (s, 3H), 2.16 (br d, $J = 8.1$ Hz, 2H), 2.03 - 1.87 (m, 4H), 1.80 (br dd, $J = 5.4, 13.6$ Hz, 2H), 1.45 (s, 6H); LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                         |
| 275 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ = 8.48 - 8.39 (m, 1H), 8.36 (d, $J = 9.9$ Hz, 1H), 7.99 (s, 1H), 7.55 (s, 1H), 7.49 (d, $J = 10.4$ Hz, 1H), 7.23 (d, $J = 10.1$ Hz,                                                                                                                                                                                                                                                                                                    |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | <sup>1</sup> H), 5.14 (br t, <i>J</i> = 11.9 Hz, 1H), 5.02 (s, 2H), 3.79 (s, 3H), 2.89 (s, 3H), 2.33 (s, 3H), 1.95 - 1.82 (m, 2H), 1.75 (br d, <i>J</i> = 11.0 Hz, 2H), 1.54 (s, 6H), 1.43 (s, 6H); LC/MS (ESI): 492.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                       |
| 276 | <sup>1</sup> H NMR (METHANOL- <i>d</i> <sub>4</sub> , 400 MHz) $\delta$ = 8.84 (d, <i>J</i> = 9.6 Hz, 1H), 8.52 (br s, 1H), 7.90 (s, 1H), 7.75 - 7.72 (m, 1H), 7.53 (dd, <i>J</i> = 0.9, 10.2 Hz, 1H), 7.26 (d, <i>J</i> = 9.6 Hz, 1H), 5.77 (tt, <i>J</i> = 4.1, 10.5 Hz, 1H), 5.22 (s, 2H), 3.89 (s, 3H), 2.47 (dd, <i>J</i> = 4.1, 13.8 Hz, 2H), 2.43 (s, 3H), 1.84 (dd, <i>J</i> = 10.9, 13.3 Hz, 2H), 1.64 (s, 6H), 1.56 (s, 6H); LC/MS (ESI): 479.2 [M+H] <sup>+</sup>                                                                                                                    |
| 277 | LC/MS (ESI): 493.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 278 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.36 (s, 1H), 8.09 (s, 1H), 7.65 (s, 1H), 7.60 (d, <i>J</i> = 10.4 Hz, 1H), 7.33 (d, <i>J</i> = 9.8 Hz, 1H), 5.55 - 5.40 (m, 1H), 5.20 (s, 2H), 3.79 (s, 3H), 2.39 - 2.31 (m, 5H), 2.04 (br d, <i>J</i> = 7.9 Hz, 2H), 1.81 (br d, <i>J</i> = 8.0 Hz, 2H), 1.72 (br t, <i>J</i> = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                                                      |
| 279 | LC/MS (ESI): 497.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 280 | <sup>1</sup> H NMR (CHLOROFORM- <i>d</i> , 400 MHz) $\delta$ = 8.92 (d, <i>J</i> = 9.6 Hz, 1H), 8.31 (br s, 1H), 7.75 (d, <i>J</i> = 1.0 Hz, 1H), 7.56 (s, 1H), 7.37 (dd, <i>J</i> = 1.2, 9.8 Hz, 1H), 7.19 (d, <i>J</i> = 9.6 Hz, 1H), 6.02 - 5.86 (m, 1H), 5.28 (s, 2H), 4.87 - 4.67 (m, <i>J</i> = 52.8 Hz, 1H), 3.93 (s, 3H), 2.46 (s, 3H), 2.05 (br d, <i>J</i> = 7.8 Hz, 2H), 1.55 - 1.50 (m, 6H), 1.43 (s, 6H); LC/MS (ESI): 497.2 [M+H] <sup>+</sup>                                                                                                                                    |
| 281 | LC/MS (ESI): 495.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 282 | LC/MS (ESI): 480.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 283 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ : 9.42 (br d, <i>J</i> = 7.4 Hz, 1H), 9.31 - 9.17 (m, 1H), 8.72 (d, <i>J</i> = 9.6 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, <i>J</i> = 0.8, 9.9 Hz, 1H), 7.39 (d, <i>J</i> = 9.6 Hz, 1H), 5.52 (td, <i>J</i> = 5.3, 10.8 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 3H), 2.48 (s, 3H), 2.41 (br dd, <i>J</i> = 5.8, 13.3 Hz, 2H), 2.13 (br d, <i>J</i> = 8.0 Hz, 2H), 1.95 - 1.81 (m, 4H), 1.48 (s, 6H); LC/MS (ESI): 478.2 [M+H] <sup>+</sup>                                                                                                 |
| 284 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.14 (s, 1H), 7.67 (s, 1H), 7.62 (d, <i>J</i> = 10.4 Hz, 1H), 7.31 (d, <i>J</i> = 9.5 Hz, 1H), 5.62 - 5.52 (m, 1H), 5.23 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 2.11 (br dd, <i>J</i> = 3.3, 12.1 Hz, 1H), 1.83 (br t, <i>J</i> = 11.4 Hz, 1H), 1.67 - 1.58 (m, 1H), 1.36 (br t, <i>J</i> = 11.0 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.54 (br d, <i>J</i> = 6.4 Hz, 2H), 0.47 (br d, <i>J</i> = 4.8 Hz, 1H), 0.36 (br s, 1H), 1H not observed (NH); LC/MS (ESI): 477.2 [M+H] <sup>+</sup> |
| 285 | LC/MS (ESI): 515.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 286 | LC/MS (ESI): 494.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 287 | LC/MS (ESI): 496.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 288 | LC/MS (ESI): 497.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 289 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.45 (d, <i>J</i> = 9.9 Hz, 1H), 8.35 (s, 1H), 7.67 (d, <i>J</i> = 9.8 Hz, 1H), 7.64 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.25 (s, 2H), 5.06 - 4.95 (m, 1H), 2.91 (s, 3H), 2.66 (s, 3H), 2.45 - 2.42 (m, 3H), 1.96 (br d, <i>J</i> = 7.3 Hz, 2H), 1.77 (br d, <i>J</i> = 12.1 Hz, 2H), 1.69 (br d, <i>J</i> = 7.6 Hz, 2H), 1.63 (br dd, <i>J</i> = 5.7, 12.7 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 507.2 [M+H] <sup>+</sup>                                                                                           |
| 290 | LC/MS (ESI): 509.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 291 | <sup>1</sup> H NMR (METHANOL- <i>d</i> <sub>4</sub> , 400 MHz) $\delta$ = 9.57 - 9.47 (m, 1H), 8.60 - 8.48 (m, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 7.53 (d, <i>J</i> = 10.1 Hz, 1H), 5.29 - 5.21 (m, 1H), 5.19 (s, 2H), 3.92 - 3.85 (m, 3H), 3.15 (s, 3H), 2.42 (s, 3H), 2.27 (br d, <i>J</i> = 8.3 Hz, 2H), 2.05 - 1.92 (m, 6H), 1.52 (s, 6H); LC/MS (ESI): 491.3 [M+H] <sup>+</sup>                                                                                                                                                                                                              |
| 292 | LC/MS (ESI): 480.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 293 | LC/MS (ESI): 493.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 294 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.47 (d, <i>J</i> = 10.0 Hz, 1H), 8.27 (s, 1H), 7.88 (s, 1H), 7.81 (d, <i>J</i> = 9.9 Hz, 1H), 7.34 (d, <i>J</i> = 10.0 Hz, 1H), 5.26 (s, 2H), 5.08 - 4.95 (m, 1H), 4.16 (s, 3H), 2.91 (s, 3H), 2.49 (br s, 3H), 1.99 (br d, <i>J</i> = 7.8 Hz, 2H), 1.80 - 1.62 (m, 6H), 1.32 (s, 6H); LC/MS (ESI): 491.2 [M+H] <sup>+</sup>                                                                                                                                                                                             |
| 295 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.46 (d, <i>J</i> = 9.9 Hz, 1H), 8.13 (s, 1H), 7.64 (s, 1H), 7.61 - 7.56 (m, 1H), 7.47 (d, <i>J</i> = 10.0 Hz, 1H), 5.18 (s, 2H), 4.36 (br d,                                                                                                                                                                                                                                                                                                                                                                             |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | $J = 12.1$ Hz, 1H), 4.12 (br d, $J = 11.9$ Hz, 1H), 3.80 (s, 3H), 3.08 (br d, $J = 11.4$ Hz, 1H), 2.89 - 2.71 (m, 2H), 2.65 - 2.57 (m, 1H), 2.39 (dd, $J = 2.4$ , 10.8 Hz, 1H), 2.35 (s, 3H), 0.96 (s, 9H), 1H not observed (NH); LC/MS (ESI): 464.2 $[M+H]^+$                                                                                                                                                                                     |
| 296 | LC/MS (ESI): 450.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 297 | LC/MS (ESI): 434.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 298 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.46$ (d, $J = 9.9$ Hz, 1H), 7.88 (s, 1H), 7.81 (d, $J = 10.0$ Hz, 1H), 7.47 (d, $J = 10.0$ Hz, 1H), 5.25 (s, 2H), 4.35 (br d, $J = 11.3$ Hz, 1H), 4.16 (s, 3H), 4.11 (br d, $J = 12.0$ Hz, 1H), 3.05 (br d, $J = 11.4$ Hz, 1H), 2.66-2.84 (m, 2H), 2.53-2.61 (m, 1H), 2.49 (br s, 3H), 2.32 (br dd, $J = 10.9$ , 1.8 Hz, 1H), 0.96 (s, 9H); 1H not observed (NH); LC/MS (ESI): 465.2 $[M+H]^+$ |
| 299 | LC/MS (ESI): 467.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 300 | LC/MS (ESI): 451.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 301 | LC/MS (ESI): 437.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 302 | LC/MS (ESI): 451.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 308 | LC/MS (ESI): 447.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 309 | LC/MS (ESI): 433.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 310 | LC/MS (ESI): 434.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 311 | LC/MS (ESI): 475.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 312 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.72$ (br d, $J = 6.3$ Hz, 2H), 8.51-8.63 (m, 2H), 7.90 (br d, $J = 3.9$ Hz, 2H), 7.30 (br d, $J = 9.6$ Hz, 1H), 5.54-5.69 (m, 1H), 5.26 (s, 2H), 4.03 (s, 3H), 2.07 (br d, $J = 8.3$ Hz, 2H), 1.23 (m, 8H), 1.07-1.14 (s, 6H), 1H not observed (NH); LC/MS (ESI): 475.3 $[M+H]^+$                                                                                                              |
| 313 | LC/MS (ESI): 447.24 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 314 | LC/MS (ESI): 483.4 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 315 | LC/MS (ESI): 515.25 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 316 | LC/MS (ESI): 444.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 317 | LC/MS (ESI): 444.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 318 | LC/MS (ESI): 447.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 319 | LC/MS (ESI): 474.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 320 | LC/MS (ESI): 451.5 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 321 | LC/MS (ESI): 465.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 322 | LC/MS (ESI): 474.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 323 | LC/MS (ESI): 484.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 324 | $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz) $\delta = 8.77$ (d, $J = 9.6$ Hz, 1H), 8.69 (d, $J = 4.9$ Hz, 2H), 8.17-8.23 (m, 3H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 5.0$ Hz, 2H), 7.38 (d, $J = 9.6$ Hz, 1H), 5.62-5.70 (m, 1H), 5.25 (s, 2H), 2.27 (br dd, $J = 13.0$ , 3.9 Hz, 2H), 1.66 (br t, $J = 11.8$ Hz, 2H), 1.46 (s, 6H), 1.37-1.43 (m, 6H); LC/MS (ESI): 444.3 $[M+H]^+$                                                           |
| 325 | LC/MS (ESI): 512.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 326 | $^1\text{LC/MS}$ (ESI): 512.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                            |
| 327 | LC/MS (ESI): 445.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 328 | LC/MS (ESI): 512.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 329 | LC/MS (ESI): 505.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 330 | LC/MS (ESI): 445.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 331 | LC/MS (ESI): 450.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 332 | LC/MS (ESI): 450.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 333 | LC/MS (ESI): 462.24 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 334 | LC/MS (ESI): 475.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 335 | LC/MS (ESI): 497.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 336 | LC/MS (ESI): 483.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 337 | LC/MS (ESI): 433.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 338 | LC/MS (ESI): 447.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                                       |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 339 | LC/MS (ESI): 461.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 340 | LC/MS (ESI): 487.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 341 | LC/MS (ESI): 498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 342 | LC/MS (ESI): 461.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 343 | LC/MS (ESI): 497.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 344 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 345 | LC/MS (ESI):429.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 346 | LC/MS (ESI):478.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 347 | LC/MS (ESI):489.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 348 | LC/MS (ESI):502.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 349 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.72 (br d, <i>J</i> = 10.9 Hz, 1H), 8.58 (d, <i>J</i> = 9.9 Hz, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.96 (s, 1H), 7.92 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.87 - 7.77 (m, 1H), 7.69 (d, <i>J</i> = 7.9 Hz, 1H), 7.46 (d, <i>J</i> = 10.0 Hz, 1H), 5.12 (s, 2H), 5.11 - 5.02 (m, 1H), 3.88 (s, 3H), 2.94 (s, 3H), 1.95 - 1.85 (m, 2H), 1.83 - 1.76 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 460.2 [M+H] <sup>+</sup> |
| 350 | LC/MS (ESI):483.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 351 | LC/MS (ESI):486.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 352 | LC/MS (ESI):445.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 353 | LC/MS (ESI):431.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 354 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.84 - 8.69 (m, 1H), 8.62 - 8.56 (m, 1H), 8.23 (s, 2H), 8.03 (s, 1H), 7.98 (dd, <i>J</i> = 1.4, 7.9 Hz, 1H), 7.93 - 7.84 (m, 1H), 7.69 (d, <i>J</i> = 8.0 Hz, 1H), 7.54 - 7.42 (m, 1H), 5.12 (br d, <i>J</i> = 1.3 Hz, 2H), 5.10 - 5.00 (m, 1H), 2.95 (s, 3H), 1.96 - 1.87 (m, 2H), 1.83 - 1.77 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 446.2 [M+H] <sup>+</sup>                                                |
| 355 | LC/MS (ESI):475.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 356 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.74 (d, <i>J</i> = 9.2 Hz, 2H), 8.27 - 8.21 (m, 2H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.31 (d, <i>J</i> = 9.5 Hz, 1H), 5.67 - 5.59 (m, 1H), 5.21 (s, 2H), 4.12 (s, 3H), 2.16 - 2.07 (m, 2H), 1.35 - 1.30 (m, 2H), 1.28 - 1.24 (m, 6H), 1.15 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                      |
| 357 | LC/MS (ESI):473.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 358 | LC/MS (ESI):449.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 359 | LC/MS (ESI):515.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 360 | LC/MS (ESI):489.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 361 | LC/MS (ESI):416.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 362 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.26 (br d, <i>J</i> = 10.5 Hz, 1H), 8.76 (d, <i>J</i> = 9.6 Hz, 1H), 8.42 (s, 2H), 8.24 (s, 1H), 8.20 (d, <i>J</i> = 7.9 Hz, 1H), 7.82 (d, <i>J</i> = 7.9 Hz, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.71 - 5.60 (m, 1H), 5.20 (s, 2H), 4.23 (s, 3H), 2.31 (br dd, <i>J</i> = 3.1, 13.1 Hz, 2H), 1.80 (br t, <i>J</i> = 11.9 Hz, 2H), 1.52 (m, 12H); LC/MS (ESI):448.2 [M+H] <sup>+</sup>                                 |
| 363 | LC/MS (ESI):528.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 364 | LC/MS (ESI):504.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 365 | LC/MS (ESI):491.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 366 | LC/MS (ESI):430.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 367 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 10.02 (br dd, <i>J</i> = 3.4, 2.2 Hz, 1H), 9.07 (br d, <i>J</i> = 9.0 Hz, 1H), 8.71-8.79 (m, 1H), 8.32 (s, 1H), 8.01 (s, 1H), 7.92-8.00 (m, 2H), 7.71 (d, <i>J</i> = 8.0 Hz, 1H), 5.07 (s, 2H), 4.70-4.88 (m, 1H), 3.88 (s, 3H), 3.11 (s, 3H), 2.16-2.33 (m, 4H), 1.76-1.92 (m, 4H), 1.47 (s, 6H); LC/MS (ESI):458.2 [M+H] <sup>+</sup>                                                                                   |
| 368 | LC/MS (ESI):502.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 369 | LC/MS (ESI):448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 370 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.50 (d, <i>J</i> = 9.9 Hz, 1H), 8.42 (s, 1H), 8.23 (s, 1H), 8.17 (d, <i>J</i> = 7.5 Hz, 1H), 7.80 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (d, <i>J</i> = 10.0 Hz, 1H), 5.19 (s, 2H), 5.07 - 4.97 (m, 1H), 4.23 (s, 3H), 2.90 (s, 3H), 1.66 - 1.43                                                                                                                                                                               |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | (m, 4H), 1.30 (s, 6H), 1.15 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 371 | LC/MS (ESI): 505.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 372 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.55 (d, <i>J</i> = 9.9 Hz, 1H), 8.04 (s, 1H), 8.03 - 8.00 (m, 1H), 7.97 - 7.93 (m, 1H), 7.93 - 7.87 (m, 1H), 7.87 - 7.81 (m, 1H), 7.44 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.09 (br t, <i>J</i> = 12.2 Hz, 1H), 4.13 (s, 3H), 2.94 (s, 3H), 1.96 - 1.85 (m, 2H), 1.84 - 1.75 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 461.3 [M+H] <sup>+</sup>                                                                                            |
| 373 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.51 (d, <i>J</i> = 9.9 Hz, 1H), 8.41 - 8.32 (m, 2H), 7.92 (d, <i>J</i> = 7.9 Hz, 1H), 7.32 (br d, <i>J</i> = 9.6 Hz, 1H), 5.24 (s, 2H), 5.05 (br d, <i>J</i> = 5.8 Hz, 1H), 4.47 (s, 3H), 2.91 (s, 3H), 1.77 - 1.46 (m, 4H), 1.44 - 1.03 (m, 12H), 1H not observed (NH); LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                            |
| 374 | LC/MS (ESI): 416.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 375 | LC/MS (ESI): 488.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 376 | LC/MS (ESI): 498.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 377 | LC/MS (ESI): 428.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 378 | LC/MS (ESI): 462.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 379 | LC/MS (ESI): 418.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 380 | LC/MS (ESI): 402.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 381 | LC/MS (ESI): 478.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 382 | LC/MS (ESI): 465.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 383 | LC/MS (ESI): 463.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 384 | LC/MS (ESI): 457.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 385 | LC/MS (ESI): 488.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 386 | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 387 | LC/MS (ESI): 461.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 388 | LC/MS (ESI): 400.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 389 | LC/MS (ESI): 472.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 390 | LC/MS (ESI): 470.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 391 | LC/MS (ESI): 430.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 392 | LC/MS (ESI): 518.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 394 | LC/MS (ESI): 420.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 395 | LC/MS (ESI): 418.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 396 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 397 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 398 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 399 | LC/MS (ESI): 432.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 400 | LC/MS (ESI): 444.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 401 | LC/MS (ESI): 456.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 402 | LC/MS (ESI): 458.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 403 | LC/MS (ESI): 477.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 404 | LC/MS (ESI): 432.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 405 | LC/MS (ESI): 444.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 406 | LC/MS (ESI): 487.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 407 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.51 (d, <i>J</i> = 9.9 Hz, 1H), 8.31 (s, 1H), 8.00 (s, 1H), 7.96 - 7.89 (m, 2H), 7.70 (d, <i>J</i> = 7.9 Hz, 1H), 7.49 (d, <i>J</i> = 10.0 Hz, 1H), 5.11 (s, 2H), 4.33 - 4.23 (m, 1H), 4.17 - 4.08 (m, 1H), 3.88 (s, 3H), 3.13 - 3.05 (m, 1H), 2.99 - 2.90 (m, 1H), 2.84 - 2.77 (m, 1H), 2.77 - 2.71 (m, 1H), 2.14 - 1.97 (m, 1H), 0.87 - 0.77 (m, 1H), 0.52 - 0.43 (m, 2H), 0.32 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 416.2 [M+H] <sup>+</sup> |
| 408 | LC/MS (ESI): 448.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 409 | LC/MS (ESI): 446.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 410 | LC/MS (ESI): 490.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 411 | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 412 | LC/MS (ESI): 416.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 413 | LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 414 | LC/MS (ESI): 476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 415 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 416 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.20 (br d, <i>J</i> = 4.5 Hz, 1H), 8.06 (s, 1H), 7.81 - 7.77 (m, 2H), 7.76 - 7.73 (m, 1H), 7.33 (d, <i>J</i> = 9.5 Hz, 1H), 5.49 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 2.33 - 2.29 (m, 2H), 2.03 - 1.93 (m, 2H), 1.72 (br d, <i>J</i> = 2.5 Hz, 2H), 1.66 - 1.56 (m, 2H), 1.34 (br s, 6H); LC/MS (ESI): 459.3 [M+H] <sup>+</sup>                                                   |
| 417 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.40 (s, 1H), 8.03 (s, 1H), 7.68-7.81 (m, 3H), 5.11-5.18 (m, 1H), 5.09 (s, 2H), 3.80 (s, 3H), 3.07 (s, 3H), 2.33 (s, 3H), 1.86-1.97 (m, 2H), 1.75-1.85 (m, 2H), 1.49 (s, 6H), 1.41 (s, 6H), 1H not observed (NH); LC/MS (ESI): 475.3 [M+H] <sup>+</sup>                                                                                                                                                                           |
| 418 | LC/MS (ESI): 445.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 419 | LC/MS (ESI): 445.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 420 | LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 421 | LC/MS (ESI): 461.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 422 | LC/MS (ESI): 477.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 423 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.00 (s, 1H), 7.82 - 7.72 (m, 3H), 7.37 - 7.30 (m, 1H), 5.13 (s, 2H), 5.11 - 5.02 (m, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.35 (s, 3H), 2.15 (br d, <i>J</i> = 8.1 Hz, 2H), 2.00 - 1.87 (m, 4H), 1.79 (br dd, <i>J</i> = 5.4, 13.4 Hz, 2H), 1.44 (s, 6H), 1H not observed (NH); LC/MS (ESI): 472.2 [M+H] <sup>+</sup>                                                                               |
| 424 | LC/MS (ESI): 474.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 425 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.86 (br s, 1H), 8.72-8.83 (m, 2H), 8.43 (s, 1H), 8.26 (s, 1H), 8.22 (dd, <i>J</i> = 7.9, 1.3 Hz, 1H), 7.84 (d, <i>J</i> = 8.0 Hz, 1H), 7.38 (d, <i>J</i> = 9.6 Hz, 1H), 5.49-5.58 (m, 1H), 5.20 (s, 2H), 4.23 (s, 3H), 2.45 (br d, <i>J</i> = 5.9 Hz, 2H), 2.13-2.21 (m, 2H), 1.89 (br d, <i>J</i> = 8.3 Hz, 2H), 1.79 (br t, <i>J</i> = 12.1 Hz, 2H), 1.45 (s, 6H), 1H not observed (NH); LC/MS (ESI): 446.2 [M+H] <sup>+</sup> |
| 426 | LC/MS (ESI): 446.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 427 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.41 (s, 1H), 8.04 (s, 1H), 7.74-7.80 (m, 3H), 5.11-5.17 (m, 1H), 5.10 (s, 2H), 3.81 (s, 3H), 3.06 (s, 3H), 2.34 (s, 3H), 2.08-2.16 (m, 2H), 1.98-2.05 (m, 2H), 1.92 (br d, <i>J</i> = 8.3 Hz, 2H), 1.84 (dd, <i>J</i> = 13.6, 5.6 Hz, 2H), 1.45 (s, 6H), 1H not observed (NH); LC/MS (ESI): 473.3 [M+H] <sup>+</sup>                                                                                                             |
| 428 | LC/MS (ESI): 459.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 429 | LC/MS (ESI): 460.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 430 | LC/MS (ESI): 491.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 431 | LC/MS (ESI): 492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 432 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 8.51 (d, <i>J</i> = 9.9 Hz, 1H), 7.84 - 7.73 (m, 3H), 7.38 (d, <i>J</i> = 10.0 Hz, 1H), 5.17 (s, 2H), 5.12 - 5.00 (m, 1H), 2.92 (s, 3H), 2.65 (s, 3H), 2.44 - 2.39 (m, 3H), 2.25 - 2.12 (m, 2H), 2.01 - 1.87 (m, 4H), 1.80 (br dd, <i>J</i> = 5.4, 13.3 Hz, 2H), 1.43 (s, 6H), 1H not observed (NH); LC/MS (ESI): 489.1 [M+H] <sup>+</sup>                                                                                        |
| 433 | LC/MS (ESI): 479.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 434 | LC/MS (ESI): 476.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 435 | LC/MS (ESI): 508.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 436 | LC/MS (ESI): 489.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 437 | LC/MS (ESI): 490.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 438 | LC/MS (ESI): 459.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 439 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) $\delta$ = 9.26 (br d, <i>J</i> = 9.3 Hz, 1H), 9.11 (br d, <i>J</i> = 8.9 Hz, 1H), 8.67 (d, <i>J</i> = 9.6 Hz, 1H), 7.93-7.99 (m, 2H), 7.76 (d, <i>J</i> = 8.0 Hz, 1H), 7.29 (d, <i>J</i> = 9.5 Hz, 1H), 5.38-5.48 (m, 1H), 5.12 (s, 2H), 4.07 (s, 3H),                                                                                                                                                                                      |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | 2.38-2.40 (m, 3H), 2.34 (br dd, $J = 13.1, 5.8$ Hz, 2H), 2.06 (br d, $J = 8.0$ Hz, 2H), 1.72-1.89 (m, 4H), 1.39 (s, 6H);<br>LC/MS (ESI): 460.2 $[M+H]^+$                                                                                                                                                                                                                                                                      |
| 441 | LC/MS (ESI): 491.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 442 | LC/MS (ESI): 465.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 443 | LC/MS (ESI): 497.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 444 | LC/MS (ESI): 476.1 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 445 | LC/MS (ESI): 506.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 446 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 8.70$ (d, $J = 9.7$ Hz, 1H), 8.29 (br d, $J = 2.9$ Hz, 1H), 8.26 (s, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.52 - 5.44 (m, 1H), 5.35 (s, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 2.27 - 2.18 (m, 2H), 1.88 (br s, 2H), 1.67 - 1.60 (m, 2H), 1.60 - 1.46 (m, 2H), 1.26 (br s, 6H);<br>LC/MS (ESI): 484.2 $[M+H]^+$                                          |
| 447 | LC/MS (ESI): 493.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 448 | LC/MS (ESI): 460.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 449 | LC/MS (ESI): 457.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 451 | LC/MS (ESI): 465.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 452 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 9.10$ (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d, $J = 10.0$ Hz, 1H), 5.16 (s, 2H), 5.02 (td, $J = 5.6, 11.3$ Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d, $J = 7.6$ Hz, 2H), 1.79 (br t, $J = 10.9$ Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d, $J = 5.1$ Hz, 2H), 1.31 (s, 6H);<br>LC/MS (ESI): 474.3 $[M+H]^+$                                     |
| 453 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 9.34$ (s, 1H), 8.71 (d, $J = 9.6$ Hz, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, $J = 5.8, 11.9$ Hz, 2H), 1.80 (br d, $J = 6.6$ Hz, 2H), 1.53 (br d, $J = 6.9$ Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H), 1H not observed (NH);<br>LC/MS (ESI): 462.2 $[M+H]^+$                                         |
| 454 | LC/MS (ESI): 431.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 455 | LC/MS (ESI): 461.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 456 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 13.17 - 12.36$ (m, 1H), 8.99 (s, 1H), 8.71 (d, $J = 9.5$ Hz, 1H), 8.25 (s, 1H), 8.20 (br s, 1H), 7.96 (s, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 5.55 - 5.45 (m, 1H), 5.24 (s, 2H), 2.56 (s, 3H), 2.28 (br dd, $J = 5.9, 12.5$ Hz, 2H), 1.96 (br d, $J = 7.8$ Hz, 2H), 1.69 (br d, $J = 7.5$ Hz, 2H), 1.59 (br t, $J = 11.6$ Hz, 2H), 1.32 (s, 6H); LC/MS (ESI): 446.2 $[M+H]^+$ |
| 457 | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta = 9.02$ (s, 1H), 8.70 (d, $J = 9.5$ Hz, 1H), 8.35 (s, 1H), 7.92 (d, $J = 0.8$ Hz, 1H), 7.36 (d, $J = 9.6$ Hz, 1H), 5.48 (td, $J = 4.2, 8.1$ Hz, 1H), 5.26 (s, 2H), 3.84 (s, 3H), 2.48 (s, 3H), 2.38 - 2.19 (m, 3H), 2.05 - 1.87 (m, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.46 - 1.45 (m, 6H), NH not observed;<br>LC/MS (ESI): 238.6 $[M+H]^+$                                   |
| 458 | LC/MS (ESI): 481.0 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 459 | LC/MS (ESI): 462.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 460 | LC/MS (ESI): 481.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 461 | LC/MS (ESI): 247.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 462 | LC/MS (ESI): 434.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 463 | LC/MS (ESI): 448.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 464 | LC/MS (ESI): 489.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 465 | LC/MS (ESI): 463.3 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 466 | $^1\text{H}$ NMR (400 MHz, $\text{C}_2\text{DF}_3\text{O}_2$ ) $\delta = 9.33$ (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 7.05 - 6.51 (m, 1H), 5.43 (s, 2H), 4.70 - 4.54 (m, 1H), 4.23 (s, 3H), 4.13 (br t, $J = 7.6$ Hz, 2H), 3.46 (br t, $J = 6.8$ Hz, 2H), 2.72 (s, 3H), 2.33 - 2.14 (m, 4H), 1.67 (s, 6H), 1.55 (s, 6H);<br>LC/MS (ESI): 487.3 $[M+H]^+$                                                          |
| 467 | LC/MS (ESI): 477.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 468 | LC/MS (ESI): 503.2 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |
| 469 | LC/MS (ESI): 231.6 $[M+H]^+$                                                                                                                                                                                                                                                                                                                                                                                                  |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 470 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 471 | LC/MS (ESI):248.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 472 | LC/MS (ESI): 240.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 473 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.98 (s, 1H), 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.38 (s, 1H), 8.16 (br s, 2H), 7.89 (s, 1H), 7.37 (d, <i>J</i> = 9.5 Hz, 1H), 5.49 (br s, 1H), 5.24 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.29 - 2.16 (m, 3H), 2.03 - 1.86 (m, 3H), 1.52 (s, 3H), 1.49 - 1.37 (m, 9H); LC/MS (ESI): 238.7 [M+2H] <sup>2+</sup>                                                                                                                                       |
| 474 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.98 (s, 1H), 8.76 - 8.69 (m, 1H), 8.38 (s, 1H), 8.25 - 8.06 (m, 2H), 7.89 (s, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.49 (br s, 1H), 5.24 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.30 - 2.16 (m, 3H), 2.03 - 1.87 (m, 3H), 1.52 (s, 3H), 1.49 - 1.40 (m, 9H); LC/MS (ESI): 238.7 [M+2H] <sup>2+</sup>                                                                                                                                               |
| 475 | LC/MS (ESI): 499.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 476 | LC/MS (ESI): 485.27 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 477 | LC/MS (ESI):480.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 478 | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 479 | LC/MS (ESI): 238.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 480 | LC/MS (ESI): 481.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 481 | LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 482 | LC/MS (ESI): 247.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 483 | LC/MS (ESI): 489.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 484 | LC/MS (ESI): 526.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 485 | LC/MS (ESI): 463.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 486 | LC/MS (ESI): 448.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 487 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.94 (d, <i>J</i> = 2.1 Hz, 1H), 8.56 (d, <i>J</i> = 9.9 Hz, 1H), 8.17 (d, <i>J</i> = 2.1 Hz, 1H), 8.14 (s, 1H), 7.64 (d, <i>J</i> = 9.9 Hz, 1H), 5.17 (s, 2H), 4.89 - 4.79 (m, 1H), 3.83 (s, 3H), 2.63 - 2.58 (m, 1H), 2.37 (s, 3H), 2.25 (br t, <i>J</i> = 12.9 Hz, 2H), 1.96 (br dd, <i>J</i> = 2.6, 13.1 Hz, 2H), 1.49 (s, 6H), 1.41 (s, 6H), 1.08 - 0.99 (m, 2H), 0.71 - 0.57 (m, 2H), NH not observed; LC/MS (ESI): 501.1 [M+H] <sup>+</sup> |
| 488 | LC/MS (ESI): 249.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 489 | LC/MS (ESI): 231.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 490 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 491 | LC/MS (ESI): 480.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 492 | LC/MS (ESI): 248.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 493 | LC/MS (ESI): 483.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 494 | LC/MS (ESI): 487.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 495 | LC/MS (ESI): 449.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 496 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 9.10 (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 5.16 (s, 2H), 5.02 (td, <i>J</i> = 5.6, 11.3 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d, <i>J</i> = 7.6 Hz, 2H), 1.79 (br t, <i>J</i> = 10.9 Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d, <i>J</i> = 5.1 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 474.3 [M+H] <sup>+</sup>                                                                               |
| 497 | <sup>1</sup> H NMR (400MHz, METHANOL- <i>d</i> <sub>4</sub> ) $\delta$ = 8.96 (s, 1H), 8.78 (d, <i>J</i> = 9.6 Hz, 1H), 8.45 (s, 1H), 8.21 (s, 1H), 7.17 (d, <i>J</i> = 9.6 Hz, 1H), 5.71 - 5.59 (m, 1H), 5.14 (s, 2H), 3.82 (s, 3H), 2.51 (s, 3H), 2.26 (br dd, <i>J</i> = 2.4, 12.3 Hz, 2H), 1.53 (br t, <i>J</i> = 11.3 Hz, 2H), 1.40 (s, 6H), 1.31 (br s, 6H); LC/MS (ESI): 463.2 [M+H] <sup>+</sup>                                                                                                                 |
| 498 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 9.38 (br s, 1H), 8.75 (br d, <i>J</i> = 9.3 Hz, 1H), 8.47 (br s, 1H), 7.41 (br d, <i>J</i> = 9.4 Hz, 1H), 5.54 (m, 1H), 5.25 (br s, 2H), 4.31 (br s, 3H), 2.46 (br s, 2H), 2.17 (br d, <i>J</i> = 7.6 Hz, 2H), 1.74-1.99 (m, 4H), 1.46 (br s, 6H), 1H not observed (NH); LC/MS (ESI):448.3 [M+H] <sup>+</sup>                                                                                                                                               |
| 499 | LC/MS (ESI):476.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 500 | LC/MS (ESI): 476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 501 | LC/MS (ESI): 392.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 502 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.26 (s, 1H), 8.80-8.88 (m, 1H), 8.77 (d, <i>J</i> = 9.6 Hz, 2H), 8.62 (s, 1H), 7.42 (d, <i>J</i> = 9.6 Hz, 1H), 5.48-5.60 (m, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 2.16-2.21 (m, 2H), 1.75-1.94 (m, 6H), 1.45 (s, 6H); LC/MS (ESI): 481.2 [M+H] <sup>+</sup>                                                                                                                                                       |
| 503 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ = 9.35 (s, 1H), 8.91-8.99 (m, 1H), 8.84 (br d, <i>J</i> = 8.8 Hz, 1H), 8.77 (d, <i>J</i> = 9.5 Hz, 1H), 7.44 (d, <i>J</i> = 9.6 Hz, 1H), 5.55 (m, 1H), 5.26 (s, 2H), 4.31 (s, 3H), 2.46 (br d, <i>J</i> = 6.0 Hz, 2H), 2.17 (br d, <i>J</i> = 8.0 Hz, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.81 (br t, <i>J</i> = 12.1 Hz, 2H), 1.46 (s, 6H); LC/MS (ESI): 482.2 [M+H] <sup>+</sup>                                    |
| 504 | LC/MS (ESI): 239.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 505 | LC/MS (ESI): 249.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 506 | LC/MS (ESI): 232.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 507 | LC/MS (ESI): 247.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 508 | LC/MS (ESI): 241.1 [M+2H] <sup>2+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 509 | LC/MS (ESI): 249.6 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 510 | LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 511 | LC/MS (ESI): 445.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 512 | LC/MS (ESI): 433.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 513 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 514 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ : 9.02 (s, 1H), 8.47 (d, <i>J</i> = 9.8 Hz, 1H), 8.25 (br s, 1H), 7.87 (s, 1H), 7.22 (br d, <i>J</i> = 9.8 Hz, 1H), 5.23 (s, 2H), 4.87 (br s, 1H), 4.20 (br s, 1H), 3.65 - 3.59 (m, 1H), 3.53 (br s, 1H), 3.16 (br d, <i>J</i> = 10.8 Hz, 1H), 3.06 (br d, <i>J</i> = 10.5 Hz, 1H), 2.63 (s, 6H), 2.04 (br d, <i>J</i> = 10.4 Hz, 1H), 1.89 (br d, <i>J</i> = 10.3 Hz, 1H); LC/MS (ESI): 420.1 [M+H] <sup>+</sup> |
| 515 | LC/MS (ESI): 417.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 516 | LC/MS (ESI): 462.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 517 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 518 | LC/MS (ESI): 403.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 519 | LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 520 | LC/MS (ESI): 403.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 521 | LC/MS (ESI): 434.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 522 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 523 | LC/MS (ESI): 420.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 524 | LC/MS (ESI): 403.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 525 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 526 | LC/MS (ESI): 461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 527 | LC/MS (ESI): 419.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 528 | LC/MS (ESI): 433.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 529 | LC/MS (ESI): 403.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 530 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 531 | LC/MS (ESI): 405.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 532 | LC/MS (ESI): 431.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 533 | LC/MS (ESI): 419.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 534 | LC/MS (ESI): 447.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 535 | LC/MS (ESI): 434.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 536 | LC/MS (ESI): 447.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 537 | LC/MS (ESI): 420.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 538 | LC/MS (ESI): 433.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 539 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 540 | LC/MS (ESI): 445.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 541 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 542 | LC/MS (ESI): 403.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 543 | LC/MS (ESI): 417.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 544 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| No. | NMR/MS                                |
|-----|---------------------------------------|
| 545 | LC/MS (ESI): 447.2 [M+H] <sup>+</sup> |
| 546 | LC/MS (ESI): 403.2 [M+H] <sup>+</sup> |
| 547 | LC/MS (ESI):403.1 [M+H] <sup>+</sup>  |
| 548 | LC/MS (ESI): 420.2 [M+H] <sup>+</sup> |
| 549 | LC/MS (ESI): 464.2 [M+H] <sup>+</sup> |
| 550 | LC/MS (ESI): 403.1 [M+H] <sup>+</sup> |
| 551 | LC/MS (ESI): 461.3 [M+H] <sup>+</sup> |
| 552 | LC/MS (ESI): 406.2 [M+H] <sup>+</sup> |
| 553 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup> |
| 554 | LC/MS (ESI): 434.1 [M+H] <sup>+</sup> |
| 555 | LC/MS (ESI): 431.2 [M+H] <sup>+</sup> |
| 556 | LC/MS (ESI): 433.3 [M+H] <sup>+</sup> |
| 557 | LC/MS (ESI): 419.2 [M+H] <sup>+</sup> |
| 558 | LC/MS (ESI): 431.3 [M+H] <sup>+</sup> |
| 559 | LC/MS (ESI): 404.2 [M+H] <sup>+</sup> |
| 560 | LC/MS (ESI): 404.1 [M+H] <sup>+</sup> |
| 561 | LC/MS (ESI): 405.2 [M+H] <sup>+</sup> |
| 562 | LC/MS (ESI): 462.2 [M+H] <sup>+</sup> |
| 563 | LC/MS (ESI): 418.2 [M+H] <sup>+</sup> |
| 564 | LC/MS (ESI): 434.2 [M+H] <sup>+</sup> |
| 565 | LC/MS (ESI): 432.2 [M+H] <sup>+</sup> |
| 566 | LC/MS (ESI): 432.2 [M+H] <sup>+</sup> |
| 567 | LC/MS (ESI): 419.3 [M+H] <sup>+</sup> |
| 568 | LC/MS (ESI): 418.2 [M+H] <sup>+</sup> |
| 569 | LC/MS (ESI): 447.3 [M+H] <sup>+</sup> |
| 570 | LC/MS (ESI): 434.0 [M+H] <sup>+</sup> |
| 571 | LC/MS (ESI): 432.2 [M+H] <sup>+</sup> |
| 572 | LC/MS (ESI):404.1 [M+H] <sup>+</sup>  |
| 573 | LC/MS (ESI): 406.2 [M+H] <sup>+</sup> |
| 574 | LC/MS (ESI):404.2 [M+H] <sup>+</sup>  |
| 575 | LC/MS (ESI):432.2 [M+H] <sup>+</sup>  |
| 576 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup> |
| 577 | LC/MS (ESI): 422.1 [M+H] <sup>+</sup> |
| 578 | LC/MS (ESI): 450.2 [M+H] <sup>+</sup> |
| 579 | LC/MS (ESI): 434.2 [M+H] <sup>+</sup> |
| 580 | LC/MS (ESI): 420.1 [M+H] <sup>+</sup> |
| 581 | LC/MS (ESI): 450.3 [M+H] <sup>+</sup> |
| 582 | LC/MS (ESI): 462.3[M+H] <sup>+</sup>  |
| 583 | LC/MS (ESI): 420.2 [M+H] <sup>+</sup> |
| 584 | LC/MS (ESI): 420.1 [M+H] <sup>+</sup> |
| 585 | LC/MS (ESI): 448.3 [M+H] <sup>+</sup> |
| 586 | LC/MS (ESI): 448.2 [M+H] <sup>+</sup> |
| 587 | LC/MS (ESI): 434.2 [M+H] <sup>+</sup> |
| 588 | LC/MS (ESI): 436.2 [M+H] <sup>+</sup> |
| 589 | LC/MS (ESI):494.2 [M+H] <sup>+</sup>  |
| 590 | LC/MS (ESI): 475.2 [M+H] <sup>+</sup> |
| 591 | LC/MS (ESI): 471.2 [M+H] <sup>+</sup> |
| 592 | LC/MS (ESI):462.3 [M+H] <sup>+</sup>  |
| 593 | LC/MS (ESI):474.2 [M+H] <sup>+</sup>  |
| 594 | LC/MS (ESI):504.0 [M+H] <sup>+</sup>  |
| 595 | LC/MS (ESI):461.5 [M+H] <sup>+</sup>  |
| 596 | LC/MS (ESI):462.2 [M+H] <sup>+</sup>  |
| 597 | LC/MS (ESI):474.2 [M+H] <sup>+</sup>  |
| 598 | LC/MS (ESI):463.0 [M+H] <sup>+</sup>  |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 599 | LC/MS (ESI):447.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 600 | LC/MS (ESI):448.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 601 | LC/MS (ESI):461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 602 | LC/MS (ESI):433.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 603 | LC/MS (ESI):446.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 604 | LC/MS (ESI):517.0 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 605 | LC/MS (ESI):249.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 606 | LC/MS (ESI):463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 607 | LC/MS (ESI): [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                               |
| 608 | LC/MS (ESI):482.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 609 | LC/MS (ESI):493.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 610 | LC/MS (ESI):497.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 611 | LC/MS (ESI):477.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 612 | LC/MS (ESI):461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 613 | LC/MS (ESI):420.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 614 | LC/MS (ESI):440.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 615 | LC/MS (ESI):432.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 616 | LC/MS (ESI):462.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 617 | LC/MS (ESI):482.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 618 | LC/MS (ESI):454.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 619 | LC/MS (ESI):495.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 620 | LC/MS (ESI):452.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 621 | LC/MS (ESI):508.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 622 | LC/MS (ESI):461.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 623 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 9.34 (s, 1H), 8.71 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 9.6 Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, J = 5.8, 11.9 Hz, 2H), 1.80 (br d, J = 6.6 Hz, 2H), 1.53 (br d, J = 6.9 Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H), NH not observed; LC/MS (ESI):462.2 [M+H] <sup>+</sup> |
| 624 | LC/MS (ESI):464.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 625 | LC/MS (ESI):518.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 626 | LC/MS (ESI):509.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 627 | LC/MS (ESI):495.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 628 | LC/MS (ESI):496.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 629 | LC/MS (ESI):437.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 630 | LC/MS (ESI):451.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 631 | LC/MS (ESI):464.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 632 | LC/MS (ESI):534.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 633 | LC/MS (ESI):537.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 634 | LC/MS (ESI):535.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 635 | LC/MS (ESI):524.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 636 | LC/MS (ESI):457.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 637 | LC/MS (ESI):485.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 638 | LC/MS (ESI):471.1[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 639 | LC/MS (ESI):437.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 640 | LC/MS (ESI):451.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 641 | LC/MS (ESI):437.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 642 | LC/MS (ESI): 457.1[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 643 | LC/MS (ESI):437.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 644 | LC/MS (ESI):455.1[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 645 | LC/MS (ESI):469.1[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                           |
| 646 | LC/MS (ESI):449.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 647 | LC/MS (ESI):443.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |
| 648 | LC/MS (ESI):465.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                          |

| No. | NMR/MS                                                                                                                                                                                                                                                                                                                                                                                            |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 649 | LC/MS (ESI):557.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 650 | LC/MS (ESI):435.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                               |
| 651 | LC/MS (ESI):449.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 652 | LC/MS (ESI):469.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 653 | LC/MS (ESI):455.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 654 | LC/MS (ESI):483.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 655 | LC/MS (ESI):441.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 656 | LC/MS (ESI):485.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 657 | LC/MS (ESI):479.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 658 | LC/MS (ESI):435.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 659 | LC/MS (ESI):469.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 660 | LC/MS (ESI):507.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 661 | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ = 9.03 (s, 1H), 8.46 (d, J = 9.8 Hz, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.34 (d, J = 9.9 Hz, 1H), 5.25 (s, 2H), 5.05 - 4.93 (m, 1H), 2.91 (s, 3H), 2.64 (s, 6H), 1.96 (br d, J = 7.8 Hz, 2H), 1.80 - 1.72 (m, 2H), 1.68 (br d, J = 7.5 Hz, 2H), 1.63 (br dd, J = 5.4, 12.9 Hz, 2H), 1.30 (s, 6H); LC/MS (ESI):495.2 [M+H] <sup>+</sup> |
| 662 | LC/MS (ESI):421.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 663 | LC/MS (ESI):463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 664 | LC/MS (ESI):496.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 665 | LC/MS (ESI):449.21 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                             |
| 666 | LC/MS (ESI):421.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 667 | LC/MS (ESI):471.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 668 | LC/MS (ESI):457.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 669 | LC/MS (ESI):423.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 670 | LC/MS (ESI):441.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 671 | LC/MS (ESI):469.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                               |
| 672 | LC/MS (ESI):451.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 673 | LC/MS (ESI):463.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 674 | LC/MS (ESI):437.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 675 | LC/MS (ESI):479.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 676 | LC/MS (ESI):498.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 677 | LC/MS (ESI):517.4 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 678 | LC/MS (ESI):487.2[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                               |
| 679 | LC/MS (ESI):527.5 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 680 | LC/MS (ESI):507.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 681 | LC/MS (ESI):485.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 682 | LC/MS (ESI):520.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 683 | LC/MS (ESI):505.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 684 | LC/MS (ESI):510.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 685 | LC/MS (ESI):518.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 686 | LC/MS (ESI):524.1 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 687 | LC/MS (ESI): 503.3[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 688 | LC/MS (ESI):492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 689 | LC/MS (ESI): 509.3[M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 690 | LC/MS (ESI):464.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 691 | LC/MS (ESI):476.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 692 | LC/MS (ESI):492.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 693 | LC/MS (ESI):485.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                                                                              |
| 694 | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz) δ 9.11 (d, 1H, J=0.8 Hz), 8.83 (d, 1H, J=2.0 Hz), 8.62 (d, 1H, J=1.8 Hz), 8.48 (d, 1H, J=10.0 Hz), 8.35 (s, 1H), 8.08 (d, 1H, J=0.8 Hz), 7.36 (d, 1H, J=10.0 Hz), 5.41 (s, 2H), 5.0-5.1 (m, 1H), 2.93 (s, 3H), 2.00 (br d, 2H, J=7.5 Hz), 1.88 (br t, 2H, J=12.4 Hz), 1.75 (br d, 2H, J=7.8                                            |

| No.        | NMR/MS                                                                                                                                                                                                                                                                                                                                  |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|            | H <sub>z</sub> ), 1.67 (br dd, 2H, J=5.4, 12.9 Hz), 1.35 (s, 6H); LC/MS (ESI):470.2 [M+H] <sup>+</sup>                                                                                                                                                                                                                                  |
| <b>695</b> | <sup>1</sup> H NMR : (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ = 8.88 - 8.69 (m, 2H), 8.57 - 8.40 (m, 2H), 7.36 (br d, J = 9.0 Hz, 1H), 5.37 (br s, 2H), 5.08 (br s, 1H), 2.94 (br s, 3H), 2.36 (br s, 3H), 2.14 - 1.97 (m, 4H), 1.91 - 1.80 (m, 2H), 1.77 - 1.66 (m, 2H), 1.42 (br s, 6H); LC/MS (ESI):484.2 [M+H] <sup>+</sup> |
| <b>696</b> | LC/MS (ESI):510.3 [M+H] <sup>+</sup>                                                                                                                                                                                                                                                                                                    |

**[0413] Example B-1: Splicing assay for monitoring levels of splice variants upon compound treatment**

**[0414]** Real-time quantitative PCR (qPCR) was used to detect splicing change of HTT and determine potency of the compounds. qPCR assays were used to measure a change in HTT canonical splicing and a control housekeeping gene, GAPDH, was used as a normalization control.

**[0415]** AD-239 or SK-N-SH cells were seeded in fibronectin coated 96-well plates (Corning; catalog # 354409) at 5,000 cells/well and incubated overnight in the cell culture incubator maintained at 37 °C and 5% CO<sub>2</sub>. The following day, at ~70-80% confluency, cells were treated with compounds in a 10-point serial dilution and treated for 24-h. The final DMSO concentration was kept at 0.1%. After 24 h, the media was aspirated and the cells were washed with cold PBS. RNA extraction and RT-PCR was performed using Cells-to-C<sub>T</sub> kit (ThermoFisher; catalog # A35378) per manufacturer's recommendations.

**[0416]** Levels of HTT mRNA were quantified by performing qPCR on a ThermoFisher Quantstudio 6 Flex instrument using standard conditions (Holding stage at 95 °C for 10 min; 40 cycles at 95 °C for 15 sec and 60 °C for 60 sec). FAM labeled probe were used for HTT Exon 49-50 detection and purchased from ThermoFisher with forward primer: TCCTCCTGAGAAAGAGAAGGAC, Reverse primer: GCCTGGAGATCCAGACTCA, probe: TGGCAACCCTTGAGGCCCTGTCCT). VIC-GAPDH control TaqMan assay was purchased from ThermoFisher (Assay ID Hs02758991\_g1).

**[0417]** Data analysis was performed by determining the  $\Delta C_t$  relative to GAPDH. The  $\Delta C_t$  value was normalized to the DMSO control ( $\Delta \Delta C_t$ ) and converted to relative expression using the  $2^{(-\Delta \Delta C_t)}$  equation. Fold change in gene expression was fitted to the 4 parametric logistic equation using GraphPad Prism to evaluate EC<sub>50</sub> concentrations.

**[0418]** The results are shown in Table 3.

**TABLE 3.**

| No.      | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|----------|---------|-------------|-------------|---------|
| <b>1</b> | 0.95    | 1.05        |             |         |
| <b>2</b> | 0.47    | 0.07        |             |         |
| <b>4</b> |         | 1           | 1           |         |
| <b>5</b> |         | 1.2         | 1.14        |         |
| <b>6</b> |         | 1.21        | 0.79        |         |
| <b>7</b> |         | 0.97        | 0.9         |         |
| <b>8</b> |         | 1.3         | 1.42        |         |
| <b>9</b> |         | 3.06        | 0.9         |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 10  |         | 1.12        | 1.07        |         |
| 14  |         | 0.83        | 1.07        |         |
| 15  |         | 0.94        | 0.88        |         |
| 17  |         | 1.14        | 0.35        | 5972    |
| 18  |         | 1.13        | 1.15        |         |
| 19  |         | 1.08        | 0.76        | 11026   |
| 20  |         | 0.1         | 0.22        | 48.6    |
| 21  |         | 1.11        | 1.19        |         |
| 22  |         | 1.13        | 1.16        |         |
| 23  |         | 0.87        | 0.86        |         |
| 24  |         | 0.92        | 0.91        |         |
| 25  |         | 0.86        | 0.93        |         |
| 26  |         | 0.87        | 1.02        |         |
| 27  |         | 1.45        | 1.63        |         |
| 28  |         | 1.17        | 0.93        | 1176    |
| 29  |         | 0.85        | 0.85        |         |
| 30  |         | 0.97        | 1.05        |         |
| 31  |         | 1.15        | 1.15        |         |
| 32  |         | 1.7         | 1.23        |         |
| 33  |         | 1.18        | 1.3         |         |
| 34  |         | 0.56        | 0.14        |         |
| 35  |         | 1.07        | 0.62        |         |
| 36  | 1.04    | 0.96        |             |         |
| 37  |         | 1.12        | 1.01        |         |
| 38  |         | NT          |             |         |
| 39  |         | 0.82        | 0.11        |         |
| 40  |         | 0.96        | 0.64        |         |
| 41  |         | 0.81        | 0.11        |         |
| 42  |         | 0.99        | 1.07        |         |
| 43  |         | 1.11        | 0.9         |         |
| 44  |         | 1.47        | 1.21        |         |
| 45  |         | 0.86        | 0.11        |         |
| 46  |         | 1.19        | 1.2         |         |
| 47  |         | 1.12        | 1.01        |         |
| 48  |         | 1.13        | 0.68        |         |
| 49  |         | 0.19        | 0.07        |         |
| 50  |         | 1.04        | 1.31        |         |
| 51  |         | 0.06        | 0.14        | 43.88   |
| 52  |         | 1.02        | 0.92        |         |
| 53  | 1.05    | 0.9         |             |         |
| 54  | 0.5     | 0.07        |             |         |
| 55  | 0.11    | 0.1         |             | 20.56   |
| 56  | 0.73    | 0.1         |             | 190.5   |
| 58  | 1.06    | 0.97        |             |         |
| 59  | 0.23    | 0.06        |             | 66.4    |
| 60  |         | NT          |             |         |
| 61  | 0.15    | 0.16        |             |         |
| 62  | 0.13    | 0.3         |             | 10.49   |
| 63  | 0.56    | 0.08        |             |         |
| 64  | 1.06    | 0.54        |             |         |
| 65  | 1.67    | 1.4         |             |         |
| 66  | 1.38    | 1.27        |             |         |
| 67  | 1.03    | 0.96        |             |         |
| 68  | 0.97    | 0.56        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 69  | 0.08    | 0.16        |             | 22.21   |
| 70  | 0.46    | 0.06        |             |         |
| 71  | 0.63    | 0.07        |             | 129.6   |
| 72  | 0.1     | 0.08        |             | 19.86   |
| 73  | 1.09    | 0.13        |             |         |
| 74  | 0.35    | 0.06        |             | 53.61   |
| 75  | 0.99    | 0.92        |             |         |
| 76  | 0.24    | 0.06        |             | 37.01   |
| 77  | 0.86    | 0.22        |             | 495.7   |
| 78  | 0.87    | 0.44        |             |         |
| 79  | 0.33    | 0.05        |             | 51.83   |
| 80  | 1.09    | 0.28        |             |         |
| 81  | 0.58    | 0.08        |             |         |
| 82  | 0.77    | 0.51        |             |         |
| 83  | 0.87    | 0.24        |             |         |
| 84  | 0.87    | 0.38        |             |         |
| 85  | 0.12    | 0.23        |             | 11.98   |
| 88  | 0.12    | 0.09        |             |         |
| 89  | 1.25    | 1           |             |         |
| 90  | 0.16    | 0.15        |             | 15.05   |
| 91  | 0.48    | 0.1         |             |         |
| 92  | 1.03    | 0.21        |             |         |
| 93  | 0.51    | 0.11        |             | 63.50   |
| 94  | 0.95    | 0.47        |             |         |
| 95  | 1.1     | 0.93        |             |         |
| 96  | 0.84    | 0.2         |             | 497.60  |
| 97  | 1.03    | 0.44        |             |         |
| 98  | 0.15    | 0.07        |             | 24.13   |
| 99  | 0.52    | 0.08        |             | 109.70  |
| 100 | 0.27    | 0.06        |             | 65.71   |
| 101 | 0.81    | 0.72        |             |         |
| 102 | 0.91    | 0.79        |             |         |
| 103 | 0.83    | 0.75        |             |         |
| 104 | 1.00    | 0.78        |             |         |
| 105 | 0.54    | 0.08        |             |         |
| 106 | 0.94    | 0.64        |             |         |
| 108 | 1.21    | 0.26        |             |         |
| 109 | 0.95    | 0.88        |             |         |
| 110 | 1.31    | 0.55        |             |         |
| 111 |         | 0.22        | 0.06        | 44.71   |
| 112 |         | 0.31        | 0.07        | 64.42   |
| 113 |         | 0.70        | 0.10        |         |
| 114 | 0.68    | 0.11        |             |         |
| 115 | 0.48    | 0.08        |             | 50.85   |
| 116 | 0.79    | 0.14        |             |         |
| 117 | 1.33    | 1.23        |             |         |
| 118 | 1.08    | 1.34        |             |         |
| 119 | 1.23    | 1.08        |             |         |
| 120 | 1.09    | 0.69        |             |         |
| 121 | 1.22    | 0.74        |             |         |
| 122 | 1.29    | 0.71        |             |         |
| 123 | 1.13    | 0.83        |             |         |
| 124 | 0.95    | 0.08        |             |         |
| 125 | 0.78    | 0.11        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 126 | 1.08    | 0.28        |             |         |
| 127 | 1.20    | 1.48        |             |         |
| 128 | 1.15    | 0.61        |             |         |
| 129 | 0.94    | 0.29        |             |         |
| 130 | 0.98    | 0.64        |             |         |
| 131 | 1.04    | 0.88        |             |         |
| 132 | 0.94    | 0.78        |             |         |
| 134 |         | 1.21        | 0.94        |         |
| 135 |         | 1.09        | 1.12        |         |
| 136 |         | 0.99        | 1.01        |         |
| 137 |         | 0.96        | 0.8         |         |
| 138 |         | 1.35        | 1.25        |         |
| 139 | 1.02    | 1.02        |             |         |
| 140 |         | 1.1         | 0.94        |         |
| 141 |         | 0.04        | 0.14        | 89      |
| 142 |         | 1.16        | 1.04        |         |
| 143 |         | 1.16        | 0.9         |         |
| 144 | 0.94    | 0.90        |             |         |
| 145 |         | 1.07        | 1.05        |         |
| 148 |         | 0.08        | 0.13        | 95.7    |
| 149 |         | 0.55        | 0.08        | 1346    |
| 150 |         | 0.16        | 0.12        | 233.8   |
| 152 |         | 1.09        | 0.74        |         |
| 153 |         | 1.47        | 0.88        |         |
| 154 |         | 0.46        | 0.08        |         |
| 155 |         | 0.5         | 0.07        | 1074    |
| 156 |         | 0.1         | 0.25        | 64.48   |
| 157 |         | 0.55        | 0.09        | 1093    |
| 158 |         | 1.23        | 0.59        |         |
| 159 |         | 1.07        | 0.28        |         |
| 160 |         | 1.09        | 0.36        |         |
| 161 |         | 0.1         | 0.11        |         |
| 162 |         | 0.09        | 0.07        | 101.3   |
| 163 |         | 0.89        | 0.86        |         |
| 164 |         | 0.13        | 0.26        | 18.03   |
| 165 |         | 0.87        | 0.63        |         |
| 166 | 0.09    | 0.13        |             | 11.02   |
| 167 | 0.45    | 0.06        |             |         |
| 168 | 1.05    | 1.07        |             |         |
| 169 | 0.85    | 0.18        |             | 348.30  |
| 170 | 1.05    | 0.85        |             |         |
| 171 | 0.13    | 0.1         |             | 15.41   |
| 172 | 0.96    | 1.22        |             |         |
| 173 | 1.11    | 1.03        |             |         |
| 174 | 0.56    | 0.07        |             | 62.77   |
| 175 | 0.1     | 0.07        |             | 42.14   |
| 176 | 1.01    | 0.54        |             |         |
| 177 | 1.06    | 0.47        |             |         |
| 178 | 0.12    | 0.25        |             |         |
| 179 |         | NT          |             |         |
| 180 | 0.1     | 0.15        |             | 14.11   |
| 181 | 0.99    | 0.97        |             |         |
| 182 | 1.01    | 1.02        |             |         |
| 183 | 0.47    | 0.06        |             | 120     |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 184 | 0.69    | 0.09        |             |         |
| 185 | 0.88    | 0.77        |             |         |
| 186 | 0.75    | 0.14        |             |         |
| 187 | 0.21    | 0.05        |             | 43.64   |
| 188 | 0.07    | 0.16        |             |         |
| 189 | 0.19    | 0.06        |             |         |
| 190 | 0.3     | 0.04        |             | 45.61   |
| 191 | 0.29    | 0.08        |             | 51.78   |
| 193 | 1.47    | 1.14        |             |         |
| 194 | 1.04    | 0.75        |             |         |
| 195 | 0.83    | 0.1         |             |         |
| 196 | 0.99    | 0.59        |             |         |
| 197 | 0.9     | 0.91        |             |         |
| 198 | 0.96    | 0.1         |             |         |
| 199 | 0.76    | 0.27        |             | 435.90  |
| 200 | 0.24    | 0.06        |             | 45.88   |
| 201 | 0.85    | 0.21        |             |         |
| 202 | 0.88    | 0.95        |             |         |
| 203 | 1.04    | 1.09        |             |         |
| 205 | 0.19    | 0.07        |             | 24.11   |
| 206 | 0.08    | 0.22        |             | 7.707   |
| 207 | 0.36    | 0.1         |             | 31.04   |
| 208 | 1.09    | 1.15        |             |         |
| 209 | 1       | 0.86        |             |         |
| 210 | 1.12    | 1.11        |             |         |
| 211 | 0.55    | 0.06        |             | 93.1    |
| 212 | 1.09    | 0.17        |             |         |
| 213 | 0.96    | 0.5         |             |         |
| 214 | 0.22    | 0.06        |             | 37.83   |
| 215 | 0.7     | 0.07        |             |         |
| 216 | 0.79    | 0.95        |             |         |
| 217 | 0.19    | 0.06        |             | 50.16   |
| 218 | 1.18    | 0.99        |             |         |
| 219 | 1       | 0.92        |             |         |
| 220 | 0.93    | 0.6         |             |         |
| 221 | 0.97    | 0.96        |             |         |
| 222 | 1.37    | 0.98        |             |         |
| 223 | 0.7     | 0.1         |             | 259.00  |
| 224 | 0.82    | 0.29        |             | 688.00  |
| 225 | 0.93    | 0.65        |             |         |
| 226 | 0.65    | 0.12        |             |         |
| 227 | 0.45    | 0.07        |             | 100.3   |
| 228 | 0.11    | 0.15        |             | 17.37   |
| 230 | 1.02    | 1           |             |         |
| 231 | 0.25    | 0.05        |             |         |
| 232 | 0.69    | 0.27        |             | 133.90  |
| 234 | 1.34    | 1.38        |             |         |
| 235 | 1.15    | 0.22        |             |         |
| 236 | 1.11    | 0.92        |             |         |
| 237 | 0.65    | 0.12        |             |         |
| 238 | 0.81    | 0.49        |             |         |
| 239 | 0.29    | 0.06        |             | 59.62   |
| 240 | 0.22    | 0.06        |             | 31.61   |
| 241 | 0.87    | 0.69        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 242 | 0.85    | 0.67        |             |         |
| 243 | 0.87    | 0.70        |             |         |
| 244 | 0.79    | 0.19        |             |         |
| 245 | 1.18    | 0.81        |             |         |
| 246 | 0.74    | 0.15        |             |         |
| 247 | 0.86    | 0.79        |             |         |
| 248 |         | 1.33        | 0.56        |         |
| 249 |         | 0.31        | 0.07        | 66.63   |
| 250 |         | 0.67        | 0.08        |         |
| 251 |         | 0.13        | 0.07        | 29.55   |
| 252 | 0.24    | 0.11        |             | 43.60   |
| 253 | 0.31    | 0.08        |             | 60.33   |
| 254 | 0.67    | 0.08        |             |         |
| 255 | 1.04    | 1.11        |             |         |
| 256 | 0.77    | 0.20        |             |         |
| 257 | 1.32    | 0.64        |             |         |
| 258 | 0.84    | 0.88        |             |         |
| 259 | 0.99    | 0.31        |             |         |
| 260 | 1.08    | 0.94        |             |         |
| 261 | 0.10    | 0.08        |             |         |
| 263 | 1.11    | 0.88        |             |         |
| 264 | 1.08    | 0.77        |             |         |
| 265 | 0.94    | 0.51        |             |         |
| 266 | 0.99    | 0.74        |             |         |
| 272 | 1       | 0.93        |             |         |
| 273 | 1.09    | 0.41        |             |         |
| 274 | 0.07    | 0.16        |             | 12.59   |
| 275 | 0.14    | 0.06        |             | 23.02   |
| 276 | 0.23    | 0.06        |             | 38.48   |
| 277 | 0.5     | 0.07        |             |         |
| 278 | 0.12    | 0.09        |             | 20.05   |
| 279 | 0.8     | 0.12        |             |         |
| 280 | 0.38    | 0.05        |             | 90.24   |
| 281 | 0.24    | 0.05        |             |         |
| 282 | 0.17    | 0.11        |             |         |
| 283 | 0.08    | 0.17        |             | 15.18   |
| 284 | 0.16    | 0.06        |             | 35.79   |
| 285 | 0.94    | 0.7         |             |         |
| 286 | 0.59    | 0.05        |             |         |
| 287 | 0.7     | 0.07        |             |         |
| 288 | 1.03    | 0.17        |             |         |
| 289 | 0.24    | 0.08        |             | 39.75   |
| 290 | 0.67    | 0.09        |             |         |
| 291 | 0.17    | 0.08        |             | 39.35   |
| 292 | 0.95    | 0.28        |             |         |
| 293 | 0.18    | 0.23        |             |         |
| 294 | 0.19    | 0.4         |             | 14.03   |
| 295 | 0.47    | 0.05        |             | 76.59   |
| 296 | 0.73    | 0.09        |             |         |
| 297 | 0.81    | 0.72        |             |         |
| 298 | 0.15    | 0.07        |             | 42.08   |
| 299 | 1.13    | 0.69        |             |         |
| 300 | 0.99    | 1.11        |             |         |
| 301 | 1.09    | 0.26        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 302 | 1.04    | 0.12        |             |         |
| 303 | 0.9     | 0.26        |             |         |
| 304 | 0.98    | 0.98        |             |         |
| 305 | 0.85    | 0.73        |             |         |
| 306 | 1.16    | 0.62        |             |         |
| 308 | 0.79    | 0.25        |             |         |
| 309 |         | 1.05        | 0.82        |         |
| 310 |         | 1.2         | 0.82        |         |
| 311 |         | 0.78        | 0.82        |         |
| 312 |         | 0.38        | 0.14        | 6239    |
| 313 |         | 0.99        | 0.77        |         |
| 314 | 0.9     | 0.88        |             |         |
| 315 | 0.91    | 1.04        |             |         |
| 316 |         | 0.9         | 1.02        |         |
| 317 |         | 2.36        | 2.66        |         |
| 318 |         | 0.73        | 0.91        |         |
| 319 |         | 0.91        | 0.95        |         |
| 320 |         | 2.26        | 2.7         |         |
| 321 |         | 1.05        | 0.93        |         |
| 322 |         | 0.92        | 0.77        |         |
| 323 |         | 2.09        | 3.38        |         |
| 324 |         | 0.67        | 0.3         | 2785    |
| 325 |         | 1.19        | 1.41        |         |
| 326 |         | 1.06        | 1.05        |         |
| 327 |         | 1.25        | 1.38        |         |
| 328 |         | 0.93        | 0.89        |         |
| 329 |         | 1.01        | 0.97        |         |
| 330 |         | 0.92        | 0.75        |         |
| 331 | 1.06    | 1.04        |             |         |
| 332 |         | 0.98        | 0.65        |         |
| 333 |         | 0.88        | 0.59        |         |
| 334 |         | 1.44        | 1.33        |         |
| 335 | 0.96    | 0.99        |             |         |
| 336 |         | 0.87        | 0.67        |         |
| 337 |         | 0.7         | 0.61        |         |
| 338 |         | 1.04        | 0.74        |         |
| 339 |         | 1.09        | 0.78        |         |
| 340 | 1.02    | 1.04        |             |         |
| 341 |         | 0.8         | 1.14        |         |
| 342 |         | 0.86        | 1.17        |         |
| 343 | 0.94    | 0.95        |             |         |
| 344 |         | 0.9         | 1.05        |         |
| 345 |         | 1.04        | 1.05        |         |
| 346 |         | 0.41        | 0.1         |         |
| 347 |         | 1.06        | 0.76        |         |
| 348 |         | 0.78        | 1.01        |         |
| 349 |         | 0.27        | 0.08        | 450.9   |
| 350 |         | 0.84        | 0.92        |         |
| 351 |         | 0.88        | 0.94        |         |
| 352 |         | 0.9         | 0.62        |         |
| 353 |         | 0.78        | 0.77        |         |
| 354 |         | 0.62        | 0.34        |         |
| 355 |         | 0.9         | 1           |         |
| 356 |         | 1.04        | 0.65        | >10000  |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 357 |         | 1.01        | 1           |         |
| 358 |         | 1.14        | 1.17        |         |
| 359 |         | 0.99        | 1.07        |         |
| 360 |         | 1.14        | 1.01        |         |
| 361 |         | 1.15        | 1.04        |         |
| 362 |         | 0.17        | 0.09        | 235     |
| 363 |         | 1.14        | 0.97        |         |
| 364 |         | 0.89        | 0.87        |         |
| 365 |         | 1.03        | 1.09        |         |
| 366 |         | 0.81        | 0.78        |         |
| 367 |         | 0.09        | 0.12        | 62.6    |
| 368 |         | 0.72        | 0.77        |         |
| 369 |         | 1.15        | 0.38        |         |
| 370 |         | 0.13        | 0.09        | 237.2   |
| 371 |         | 1.1         | 0.86        |         |
| 372 |         | 1.16        | 0.69        | >10000  |
| 373 |         | 0.45        | 0.1         | 665.9   |
| 375 |         | 0.9         | 1.07        |         |
| 376 |         | 1.06        | 1.21        |         |
| 377 |         | 1.03        | 1.23        |         |
| 378 |         | 0.75        | 0.95        |         |
| 379 |         | 0.91        | 0.42        |         |
| 380 |         | 1.51        | 0.9         |         |
| 381 |         | 1.05        | 0.98        |         |
| 382 |         | 1.58        | 1.62        |         |
| 383 |         | 0.24        | 0.09        |         |
| 384 |         | 0.89        | 1.04        |         |
| 385 |         | 1.23        | 1.4         |         |
| 386 |         | 1.12        | 0.91        |         |
| 387 |         | 0.11        | 0.12        |         |
| 388 |         | 1.34        | 1.49        |         |
| 389 |         | 1.15        | 1.09        |         |
| 390 |         | 1.16        | 1.2         |         |
| 391 |         | 1.13        | 0.97        |         |
| 392 |         | 1.4         | 1.6         |         |
| 394 |         | 0.98        | 1.16        |         |
| 395 |         | 1.08        | 1.1         |         |
| 396 |         | 1.16        | 1.22        |         |
| 397 |         | 1.14        | 1.28        |         |
| 398 |         | 1.16        | 1.19        |         |
| 399 |         | 0.77        | 0.14        |         |
| 400 |         | 1.21        | 1.07        |         |
| 401 |         | 1.05        | 1.04        |         |
| 402 |         | 1.36        | 1.07        |         |
| 403 |         | 1.2         | 1.3         |         |
| 404 |         | 1.14        | 0.89        |         |
| 405 |         | 1.14        | 1.02        |         |
| 406 |         | 0.95        | 1.06        |         |
| 407 |         | 0.78        | 0.41        | 2064    |
| 408 |         | 0.89        | 0.88        |         |
| 409 |         | 1.01        | 1.08        |         |
| 411 | 1.12    | 0.98        |             |         |
| 412 | 1.09    | 1.04        |             |         |
| 413 | 0.98    | 0.88        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 414 | 0.97    | 0.69        |             |         |
| 415 | 1       | 0.17        |             |         |
| 416 | 0.24    | 0.05        |             | 61.05   |
| 417 | 0.67    | 0.16        |             | 427.4   |
| 418 | 0.75    | 0.15        |             |         |
| 419 | 1.51    | 1.25        |             |         |
| 420 | 1.32    | 0.32        |             |         |
| 421 | 0.69    | 0.09        |             |         |
| 422 | 1.46    | 1.47        |             |         |
| 423 | 0.1     | 0.1         |             | 19.9    |
| 424 | 0.76    | 0.1         |             |         |
| 425 | 0.83    | 0.1         |             | 128.90  |
| 426 | 1.4     | 1.4         |             |         |
| 427 | 0.55    | 0.1         |             | 130.9   |
| 428 | 0.98    | 0.75        |             |         |
| 429 | 0.71    | 0.09        |             |         |
| 430 | 1.32    | 0.6         |             |         |
| 431 | 0.96    | 0.91        |             |         |
| 432 | 0.55    | 0.05        |             | 75.77   |
| 433 | 0.96    | 0.87        |             |         |
| 434 | 1.06    | 0.97        |             |         |
| 435 | 0.96    | 1.03        |             |         |
| 436 | 0.9     | 0.86        |             |         |
| 437 | 0.92    | 0.29        |             |         |
| 438 | 0.48    | 0.06        |             |         |
| 439 | 0.18    | 0.09        |             | 22.16   |
| 441 | 1.2     | 1.16        |             |         |
| 442 | 0.82    | 0.25        |             |         |
| 443 | 1.02    | 1.05        |             |         |
| 444 | 0.74    | 0.43        |             |         |
| 445 | 0.67    | 0.09        |             |         |
| 446 | 0.72    | 0.14        |             | 259.50  |
| 447 | 1.12    | 0.3         |             |         |
| 448 | 0.99    | 1.11        |             |         |
| 449 | 0.99    | 0.63        |             |         |
| 451 |         | 0.68        | 0.18        |         |
| 452 | 0.12    | 0.07        |             | 17.25   |
| 453 | 0.2     | 0.12        |             | 17.97   |
| 454 | 0.87    | 0.67        |             |         |
| 455 | 0.57    | 0.06        |             |         |
| 456 | 0.92    | 0.17        |             | 300.7   |
| 457 | 0.56    | 0.07        |             | 123.8   |
| 458 | 0.08    | 0.09        |             | 10.66   |
| 459 | 1.29    | 0.98        |             |         |
| 460 | 0.22    | 0.06        |             | 44.95   |
| 461 | 0.95    | 0.1         |             |         |
| 462 | 1.31    | 1.33        |             |         |
| 463 | 1.2     | 1.16        |             |         |
| 464 | 0.76    | 0.08        |             |         |
| 465 | 0.89    | 0.914       |             |         |
| 466 | 0.17    | 0.089       |             | 40.04   |
| 467 | 0.099   | 0.12        |             |         |
| 468 | 0.91    | 0.82        |             |         |
| 469 | 1.15    | 0.35        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 470 | 0.48    | 0.06        |             | 105.4   |
| 471 | 0.54    | 0.09        |             |         |
| 472 | 0.68    | 0.1         |             | 230.4   |
| 473 |         |             |             | 172     |
| 474 |         |             |             | >1000   |
| 475 | 1.19    | 1.32        |             |         |
| 476 | 0.28    | 0.09        |             |         |
| 477 | 0.10    | 0.08        |             |         |
| 479 | 0.59    | 0.06        |             |         |
| 480 | 0.08    | 0.22        |             | 9.429   |
| 481 | 1.13    | 1           |             |         |
| 482 | 0.93    | 0.25        |             |         |
| 483 | 0.87    | 0.08        |             |         |
| 484 | 1.20    | 1.27        |             |         |
| 485 | 0.92    | 0.13        |             |         |
| 486 | 0.76    | 0.71        |             |         |
| 487 | 0.45    | 0.05        |             | 74.11   |
| 488 | 0.30    | 0.08        |             | 37.48   |
| 489 | 0.94    | 0.26        |             |         |
| 490 | 0.39    | 0.08        |             | 88.67   |
| 491 | 0.64    | 0.21        |             |         |
| 492 | 0.63    | 0.07        |             |         |
| 493 |         |             |             | 22.83   |
| 494 | 0.33    | 0.04        |             |         |
| 495 | 1.02    | 0.77        |             |         |
| 496 | 0.12    | 0.07        |             | 17.25   |
| 497 | 0.63    | 0.09        |             | 146.6   |
| 498 | 0.76    | 0.16        |             | 394.9   |
| 499 | 0.48    | 0.05        |             | 112.8   |
| 500 | 0.41    | 0.05        |             | 97.03   |
| 501 | 1.03    | 0.91        |             |         |
| 502 | 0.85    | 0.31        |             | 947.6   |
| 503 | 0.19    | 0.05        |             | 28.44   |
| 504 | 1.23    | 0.46        |             |         |
| 505 | 1.1     | 0.92        |             |         |
| 506 | 0.9     | 0.76        |             |         |
| 507 | 0.93    | 0.7         |             |         |
| 508 | 0.93    | 0.99        |             |         |
| 509 | 0.71    | 0.09        |             |         |
| 510 | 0.78    | 0.11        |             |         |
| 511 | 1.08    | 0.28        |             |         |
| 512 | 1.20    | 1.48        |             |         |
| 513 | 1.15    | 0.61        |             |         |
| 514 | 0.94    | 0.29        |             |         |
| 515 | 0.98    | 0.64        |             |         |
| 516 | 1.04    | 0.88        |             |         |
| 517 | 0.94    | 0.78        |             |         |
| 518 | 0.74    | 0.60        |             |         |
| 519 | 0.82    | 0.26        |             |         |
| 520 | 1.02    | 0.84        |             |         |
| 521 | 0.97    | 0.83        |             |         |
| 522 | 0.94    | 0.85        |             |         |
| 523 | 0.88    | 0.78        |             |         |
| 524 | 0.92    | 0.78        |             |         |

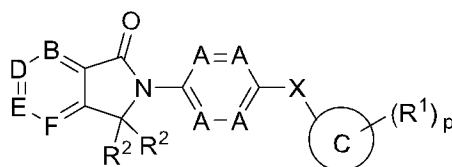
| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 525 | 0.96    | 0.79        |             |         |
| 526 | 0.99    | 0.95        |             |         |
| 527 | 0.96    | 0.91        |             |         |
| 528 | 0.94    | 0.41        |             |         |
| 529 | 0.96    | 0.68        |             |         |
| 530 | 0.91    | 0.73        |             |         |
| 531 | 1.23    | 1.12        |             |         |
| 532 | 1.12    | 0.6         |             |         |
| 533 | 0.72    | 0.26        |             |         |
| 534 | 1.26    | 1.24        |             |         |
| 535 | 1.29    | 1.10        |             |         |
| 536 | 0.77    | 0.20        |             |         |
| 537 | 1.32    | 0.64        |             |         |
| 538 | 0.84    | 0.88        |             |         |
| 539 | 0.99    | 0.31        |             |         |
| 540 | 1.08    | 0.94        |             |         |
| 541 | 1.11    | 0.88        |             |         |
| 542 | 1.08    | 0.77        |             |         |
| 543 | 0.94    | 0.51        |             |         |
| 544 | 0.99    | 0.74        |             |         |
| 549 | 1       | 0.58        |             |         |
| 550 | 0.91    | 0.97        |             |         |
| 551 | 0.84    | 0.82        |             |         |
| 552 | 0.93    | 0.69        |             |         |
| 553 | 0.95    | 0.82        |             |         |
| 554 | 0.87    | 0.84        |             |         |
| 555 | 0.95    | 0.87        |             |         |
| 556 | 0.86    | 0.4         |             |         |
| 557 | 0.95    | 0.9         |             |         |
| 558 | 0.95    | 0.6         |             |         |
| 559 | 1.16    | 0.28        |             |         |
| 560 | 0.96    | 0.13        |             |         |
| 561 | 1.22    | 1.35        |             |         |
| 562 | 1.1     | 0.97        |             |         |
| 563 | 0.77    | 0.1         |             |         |
| 564 | 1.09    | 0.99        |             |         |
| 565 | 1.04    | 0.88        |             |         |
| 566 | 0.88    | 0.18        |             |         |
| 567 | 0.91    | 0.17        |             |         |
| 568 | 0.9     | 0.08        |             |         |
| 569 | 1.38    | 1.21        |             |         |
| 570 | 0.95    | 0.99        |             |         |
| 571 | 0.98    | 0.99        |             |         |
| 572 | 0.88    | 1.02        |             |         |
| 573 | 0.92    | 1.03        |             |         |
| 574 | 0.95    | 0.94        |             |         |
| 575 | 1.16    | 0.99        |             |         |
| 576 | 0.97    | 1           |             |         |
| 577 | 0.98    | 0.98        |             |         |
| 578 | 0.85    | 0.73        |             |         |
| 579 | 1.16    | 0.62        |             |         |
| 580 | 0.96    | 0.5         |             |         |
| 581 | 1.38    | 0.42        |             |         |
| 582 | 1.17    | 0.86        |             |         |

| No. | <100 nM | < 1 $\mu$ M | <10 $\mu$ M | EC50 nM |
|-----|---------|-------------|-------------|---------|
| 583 | 1.2     | 0.35        |             |         |
| 584 | 1.11    | 0.83        |             |         |
| 585 | 0.95    | 0.73        |             |         |
| 586 | 1.11    | 0.94        |             |         |
| 587 | 1.02    | 0.23        |             |         |
| 588 | 0.95    | 0.21        |             |         |

[0419] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

### NUMBERED EMBODIMENTS

[0420] Embodiment 1. In some embodiments, is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I),

wherein,

ring C is 6 membered heterocycloalkyl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

each A is independently N or CR<sup>4</sup>;

each  $R^4$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

one of R<sup>6</sup> and R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents

independently selected from R<sup>10</sup>; and the other of R<sup>6</sup> or R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; wherein

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

R<sup>5</sup> and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>,

C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

p is an integer from 1-9.

**[0421]** Embodiment 2. The compound embodiment of 1, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>2</sup> is independently hydrogen.

**[0422]** Embodiment 3. The compound of embodiments 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein D is CR<sup>6</sup> or E is CR<sup>7</sup>.

**[0423]** Embodiment 4. The compound of any one of embodiments 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and

R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl.

**[0424]** Embodiment 5. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0425]** Embodiment 6. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen.

**[0426]** Embodiment 7. The compound of any one of embodiments 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl; and

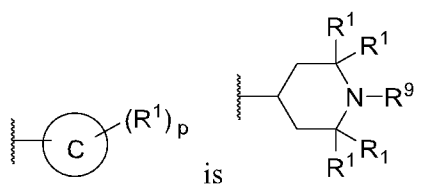
R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>.

**[0427]** Embodiment 8. The compound of Embodiment 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>6</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0428]** Embodiment 9. The compound of embodiment 8, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>6</sup> is hydrogen.

**[0429]** Embodiment 10. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine, piperazine, or morpholine.

**[0430]** Embodiment 11. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein:



wherein,

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; and

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl.

**[0431]** Embodiment 12. The compound of embodiment 11, or a pharmaceutically acceptable salt or solvate thereof, wherein:

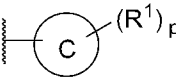
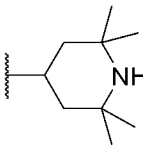
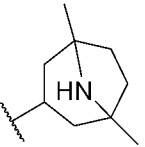
each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

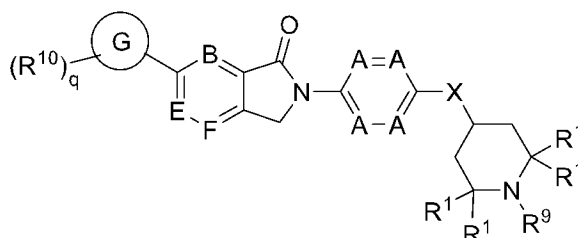
two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

R<sup>9</sup> is hydrogen.

**[0432]** Embodiment 13. The compound of embodiment 11 or 12, or a pharmaceutically acceptable salt

or solvate thereof, wherein  is  or .

**[0433]** Embodiment 14. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa),

wherein,

ring G is a 5 to 8-membered heteroaryl;

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

X is -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

each A is independently N or CR<sup>4</sup>;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

$R^5$ ,  $R^7$ , and  $R^8$  are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

$R^9$  is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

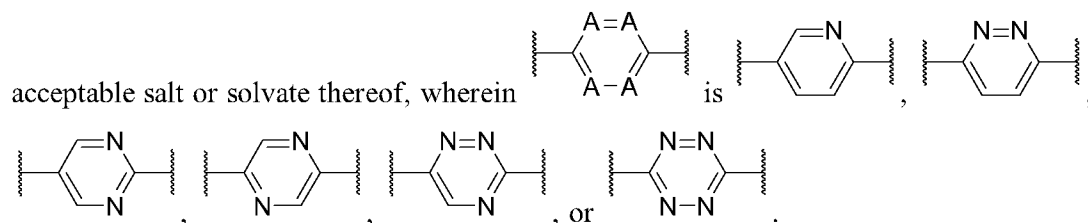
R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

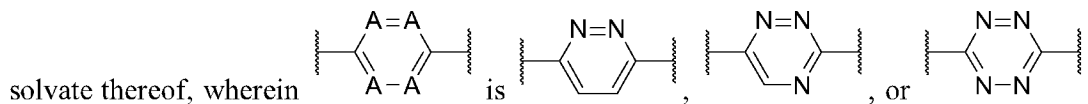
q is 0, 1, 2, or 3.

**[0434]** Embodiment 15. The compound of any one of embodiments 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein each A is independently N or CH.

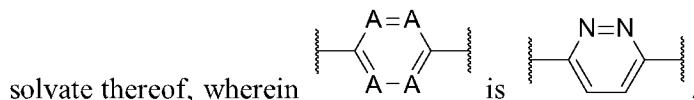
**[0435]** Embodiment 16. The compound of any one of embodiments 1-14, or a pharmaceutically



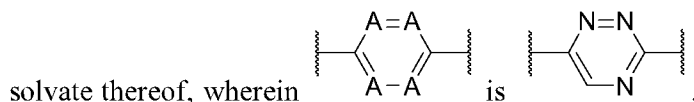
[0436] Embodiment 17. The compound of embodiment 16, or a pharmaceutically acceptable salt or



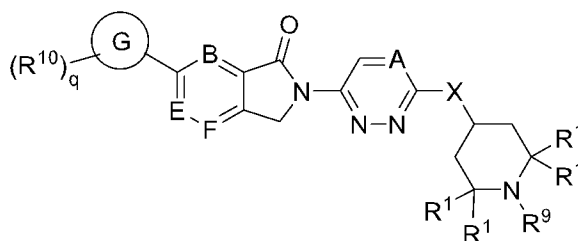
[0437] Embodiment 18. The compound of embodiment 16, or a pharmaceutically acceptable salt or



[0438] Embodiment 19. The compound of embodiment 16, or a pharmaceutically acceptable salt or



[0439] Embodiment 20. The compound of embodiment 17, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III),

wherein,

ring G is a 5 to 8-membered heteroaryl;

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the

alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl,

wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

X is -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>c</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

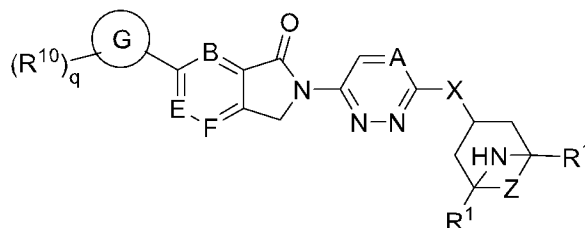
q is 0, 1, 2, or 3.

**[0440]** Embodiment 21. The compound of any one of embodiments 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>9</sup> is hydrogen.

**[0441]** Embodiment 22. The compound of any one of embodiments 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

[0442] Embodiment 23. The compound of embodiment 22, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene.

[0443] Embodiment 24. The compound of embodiment 20, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof:

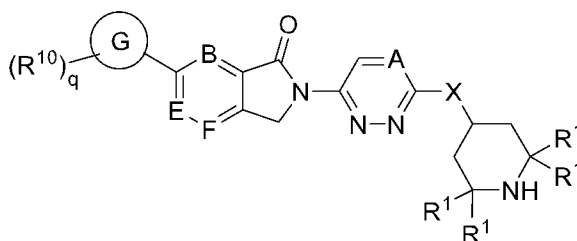


Formula (IVa),

wherein Z is C<sub>1</sub>-C<sub>3</sub>alkylene.

[0444] Embodiment 25. The compound of embodiment 24, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is -CH<sub>2</sub>CH<sub>2</sub>-.

[0445] Embodiment 26. The compound of embodiment 20, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IVb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IVb).

[0446] Embodiment 27. The compound of embodiment 26, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl.

[0447] Embodiment 28. The compound of embodiment 27, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a cyclopropyl.

[0448] Embodiment 29. The compound of any one of embodiments 1-26, or a pharmaceutically acceptable salt or solvate thereof, each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

[0449] Embodiment 30. The compound of embodiment 29, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl.

[0450] Embodiment 31. The compound of embodiment 29, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen or methyl.

[0451] Embodiment 32. The compound of any one of embodiments 20-31, or a pharmaceutically acceptable salt or solvate thereof, wherein A is N.

**[0452]** Embodiment 33. The compound of any one of embodiments 20-31, or a pharmaceutically acceptable salt or solvate thereof, wherein A is CH.

**[0453]** Embodiment 34. The compound of any one of embodiments 1-33, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O-.

**[0454]** Embodiment 35. The compound of any one of embodiments 1-33, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -NR<sup>3</sup>-.

**[0455]** Embodiment 36. The compound of embodiment 35, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>3</sup> is hydrogen or C<sub>1</sub>-C<sub>3</sub>alkyl.

**[0456]** Embodiment 37. The compound of embodiment 35, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>3</sup> is hydrogen or methyl.

**[0457]** Embodiment 38. The compound of any one of embodiments 1-37, or a pharmaceutically acceptable salt or solvate thereof, wherein B is CR<sup>5</sup>.

**[0458]** Embodiment 39. The compound of any one of embodiments 1-37, or a pharmaceutically acceptable salt or solvate thereof, wherein B is N.

**[0459]** Embodiment 40. The compound of any one of embodiments 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

**[0460]** Embodiment 41. The compound of embodiment 40, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0461]** Embodiment 42. The compound of any one of embodiments 1-37, or a pharmaceutically acceptable salt or solvate thereof wherein B is CH.

**[0462]** Embodiment 43. The compound of any one of embodiments 1-42, or a pharmaceutically acceptable salt or solvate thereof, wherein F is CR<sup>8</sup>.

**[0463]** Embodiment 44. The compound of any one of embodiments 1-42, or a pharmaceutically acceptable salt or solvate thereof, wherein F is N.

**[0464]** Embodiment 45. The compound of any one of embodiments 1-43, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

**[0465]** Embodiment 46. The compound of embodiment 45, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0466]** Embodiment 47. The compound of any one of embodiments 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CR<sup>7</sup>.

[0467] Embodiment 48. The compound of any one of embodiments 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein E is N.

[0468] Embodiment 49. The compound of any one of embodiments 1-48, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^7$  is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

[0469] Embodiment 50. The compound of embodiment 49, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^7$  is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

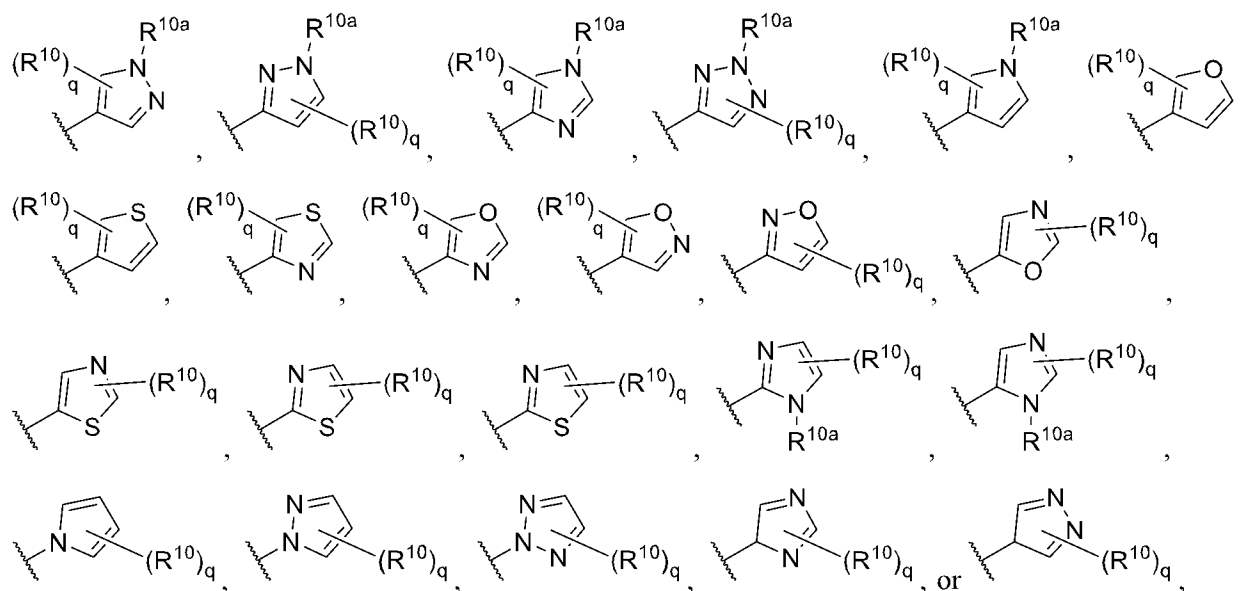
[0470] Embodiment 51. The compound of any one of embodiments 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CH.

[0471] Embodiment 52. The compound of any one of embodiments 14-51, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R<sup>c</sup>.

[0472] Embodiment 53. The compound of embodiment 52, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from R<sup>c</sup>.

[0473] Embodiment 54. The compound of embodiment 53, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, oxadiazole, thiazole, or thiadiazole.

[0474] Embodiment 55. The compound of any one of embodiments 14-51, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



wherein,

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

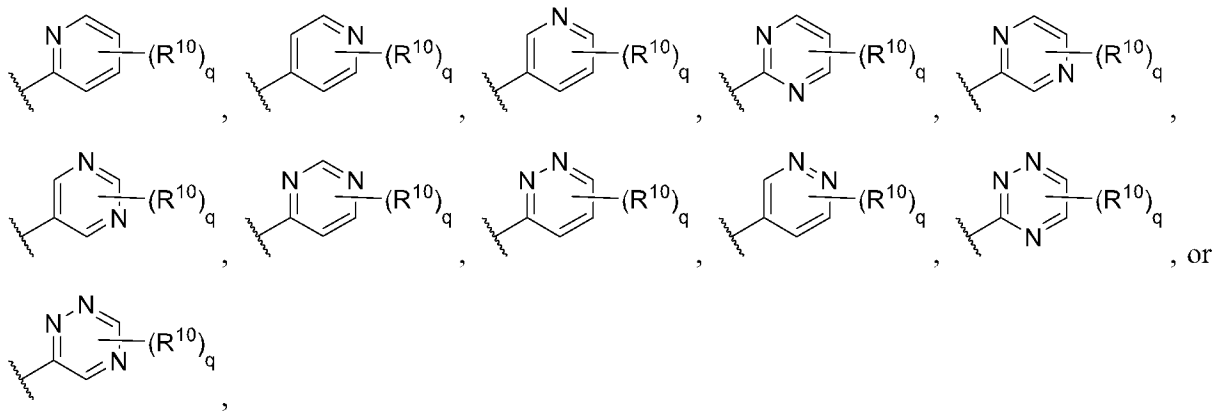
each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

q is 0, 1, 2, or 3.

**[0475]** Embodiment 56. The compound of embodiment 52, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R<sup>e</sup>.

**[0476]** Embodiment 57. The compound of embodiment 56, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyridine, pyrimidine, or triazine.

**[0477]** Embodiment 58. The compound of any one of embodiments 14-51, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



wherein,

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>e</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

q is 0, 1, 2, or 3.

**[0478]** Embodiment 59. The compound of any one of embodiments 14-51, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>e</sup>.

**[0479]** Embodiment 60. The compound of embodiment 59, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R<sup>e</sup>.

**[0480]** Embodiment 61. The compound of any one of embodiments 1-60, wherein the compound is selected from: Table 1.

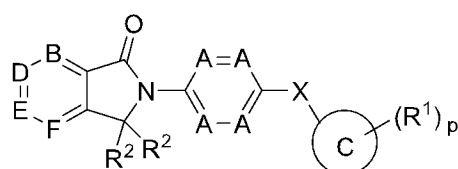
**[0481]** Embodiment 62. A pharmaceutically composition comprising a compound of any one of claims 1-61, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

**[0482]** Embodiment 63. A method of treating a neurodegenerative disease or disorder in a patient in need thereof, the method comprising administering to the patient a compound of any one of embodiments 1-61, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 62.

[0483] Embodiment 64. The method of embodiment 63, wherein the neurodegenerative disease or disorder is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Prion disease, and spinocerebellar ataxias.

[0484] Embodiment 65. The method of embodiment 64, wherein the neurodegenerative disease or disorder is Huntington's disease (HD).

[0485] Embodiment 1. A compound having the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is absent, -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least one of A is N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

one of R<sup>6</sup> and R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and the other of R<sup>6</sup> or R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -

$C(=O)NR^cR^d$ ,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_3$ - $C_6$ cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^{10}$ ; wherein  $R^7$  is not pyridyl substituted with two methoxy groups; each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_3$ - $C_6$ cycloalkyl, or 4 to 6-membered heterocycloalkyl; or

two  $R^{10}$  are taken together to form an oxo;

$R^5$  and  $R^8$  are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl, or  $C_1$ - $C_6$ aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

each  $R^a$  is independently  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

each  $R^b$  is independently hydrogen,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

$R^c$  and  $R^d$  are each independently hydrogen,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ hydroxyalkyl,  $C_1$ - $C_6$ aminoalkyl,  $C_1$ - $C_6$ heteroalkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ;

each  $R^e$  is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>,  $C_1$ - $C_6$ 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; and

p is an integer from 1-9.

**[0486]** Embodiment 2. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^2$  is independently hydrogen.

**[0487]** Embodiment 3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein D is CR<sup>6</sup> or E is CR<sup>7</sup>.

**[0488]** Embodiment 4. The compound of any one of embodiments 1-3, or a pharmaceutically acceptable

salt or solvate thereof, wherein:

R<sup>6</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and

R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl.

**[0489]** Embodiment 5. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0490]** Embodiment 6. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen.

**[0491]** Embodiment 7. The compound of any one of embodiments 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R<sup>6</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl; and

R<sup>7</sup> is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>.

**[0492]** Embodiment 8. The compound of embodiment 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>6</sup> is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0493]** Embodiment 9. The compound of embodiment 8, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>6</sup> is hydrogen.

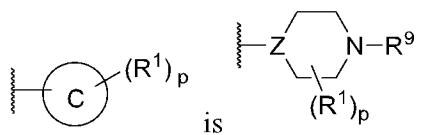
**[0494]** Embodiment 10. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is a 6-membered heterocycloalkyl.

**[0495]** Embodiment 11. The compound of any one of embodiments 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine, piperazine, or morpholine.

**[0496]** Embodiment 12. The compound of embodiment 11, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperazine.

**[0497]** Embodiment 13. The compound of embodiment 11, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine.

**[0498]** Embodiment 14. The compound of any one of embodiments 1-13, or a pharmaceutically acceptable salt or solvate thereof, wherein:



wherein,

Z is N or CH;

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>e</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

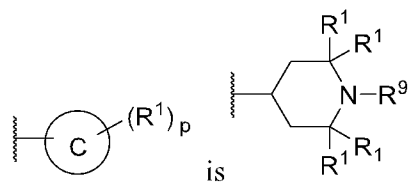
R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; and

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl.

**[0499]** Embodiment 15. The compound of embodiment 14, or a pharmaceutically acceptable salt or solvate thereof, wherein:

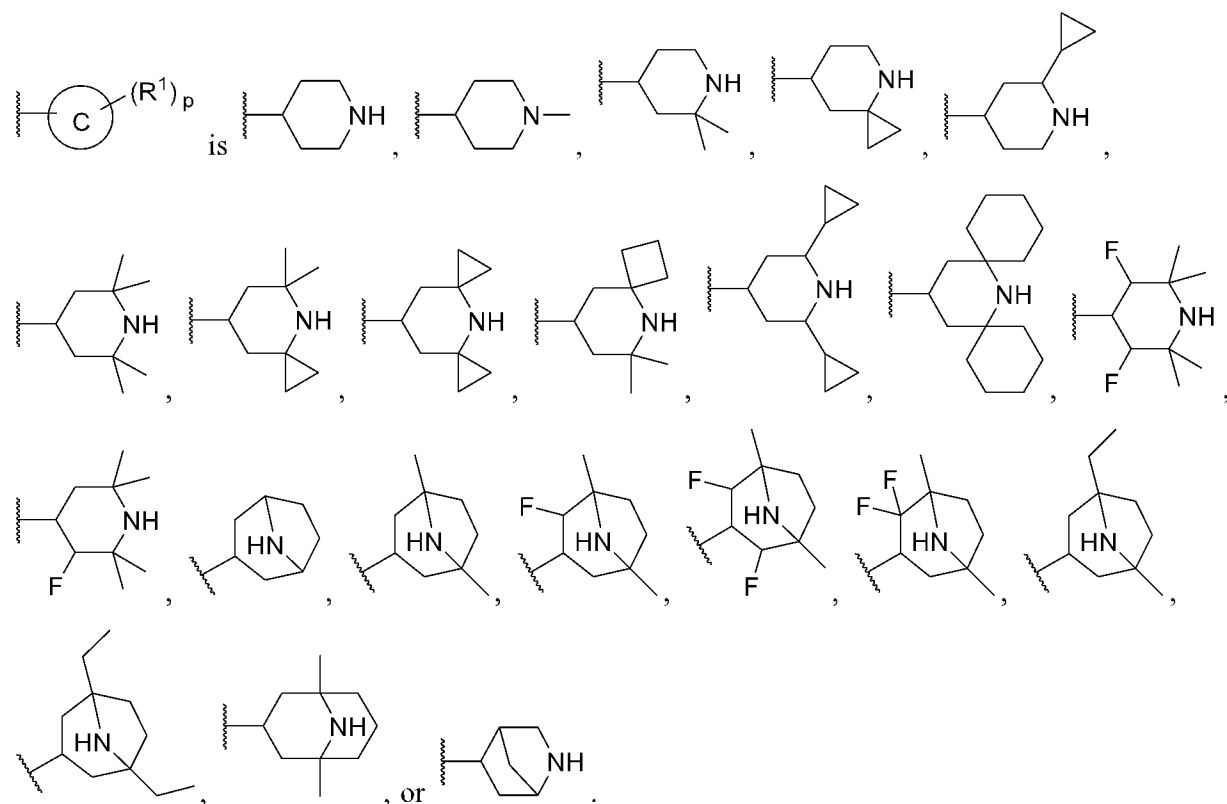


wherein,

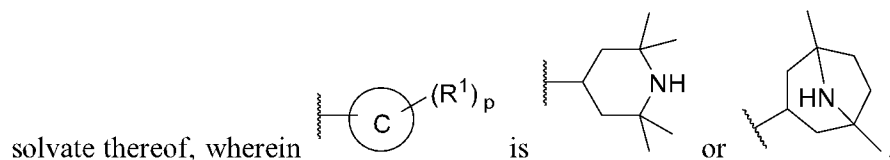
each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form a  $C_1$ - $C_3$ alkylene, or a  $C_1$ - $C_3$ heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from  $R^e$ ; or two  $R^1$  are taken together to form a  $C_3$ - $C_6$ cycloalkyl; and  $R^9$  is hydrogen.

**[0500]** Embodiment 16. The compound of any one of embodiments 1-11 or 13-15, or a pharmaceutically acceptable salt or solvate thereof, wherein:

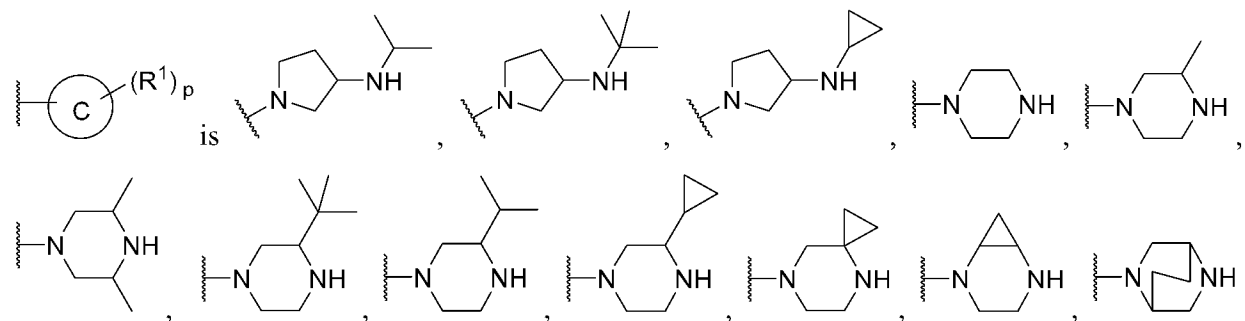


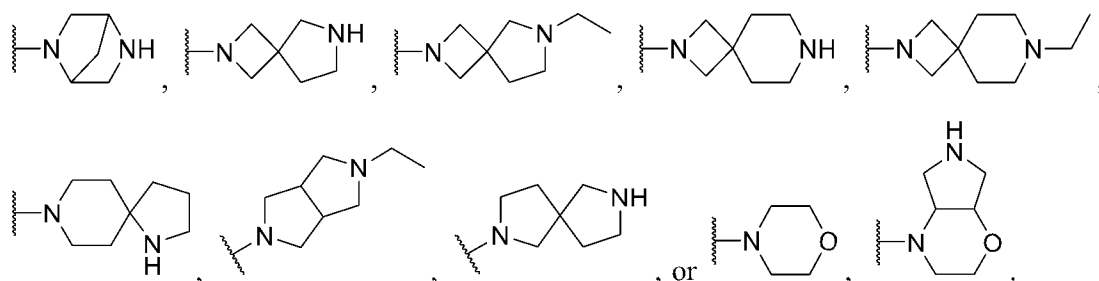
**[0501]** Embodiment 17. The compound of embodiment 16, or a pharmaceutically acceptable salt or



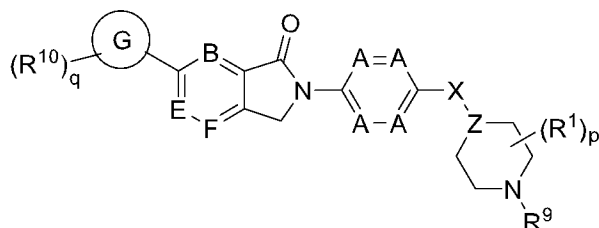
**[0502]** Embodiment 18. The compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O- or -NR<sup>3</sup>-.

**[0503]** Embodiment 19. The compound of any one of embodiments 1-11, or a pharmaceutically acceptable salt thereof, wherein X is absent; and





[0504] Embodiment 20. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II),

wherein,

ring G is a 5 to 8 membered heteroaryl;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl,

wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

X is bond, -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

Z is CH or N, wherein when X is -O- or -NR<sup>3</sup>- then Z is N;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least one of A is N;

each  $R^4$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

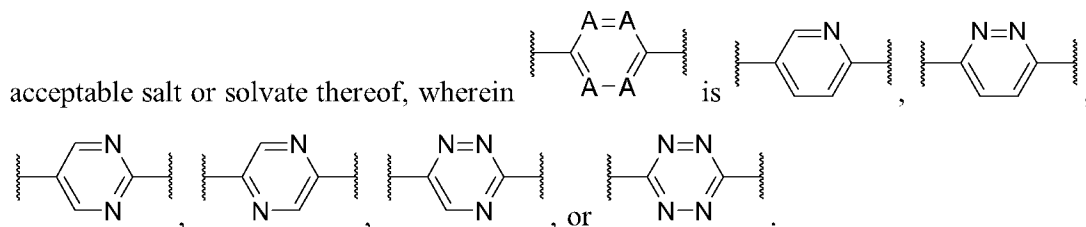
each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

p is 8; and

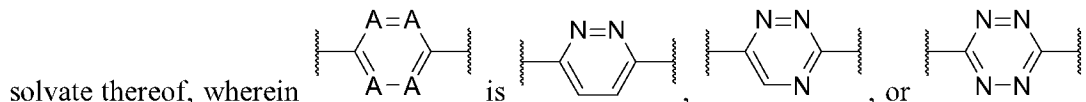
q is 0, 1, 2, or 3.

**[0505]** Embodiment 21. The compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein each A is independently N or CH, wherein one of A is N.

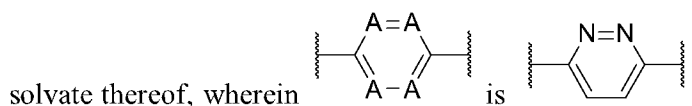
[0506] Embodiment 22. The compound of any one of embodiments 1-20, or a pharmaceutically



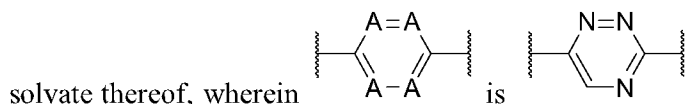
[0507] Embodiment 23. The compound of embodiment 22, or a pharmaceutically acceptable salt or



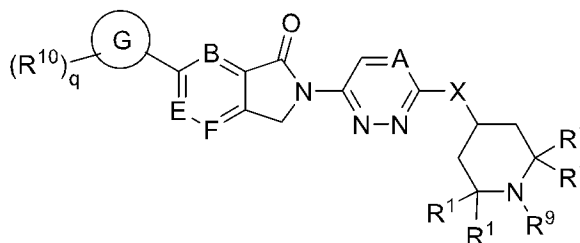
[0508] Embodiment 24. The compound of embodiment 22, or a pharmaceutically acceptable salt or



[0509] Embodiment 25. The compound of embodiment 22, or a pharmaceutically acceptable salt or



[0510] Embodiment 26. The compound of embodiment 20, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III),

wherein,

ring G is a 5 to 8 membered heteroaryl;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

X is -CH<sub>2</sub>-, -O-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>3</sub>haloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>c</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

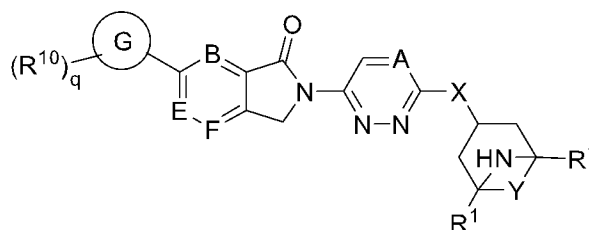
each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

q is 0, 1, 2, or 3.

**[0511]** Embodiment 27. The compound of any one of embodiments 20-26, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.

**[0512]** Embodiment 28. The compound of embodiment 27, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene.

**[0513]** Embodiment 29. The compound of embodiment 26, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof:

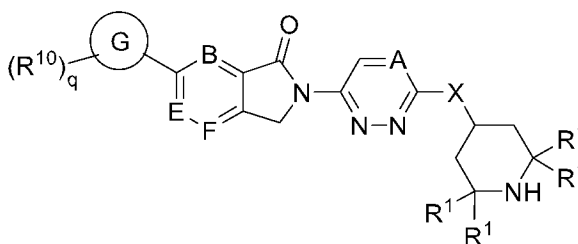


Formula (IIIa),

wherein Y is C<sub>1</sub>-C<sub>3</sub>alkylene.

**[0514]** Embodiment 30. The compound of embodiment 29, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH<sub>2</sub>CH<sub>2</sub>-.

**[0515]** Embodiment 31. The compound of embodiment 26, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IIIb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb).

**[0516]** Embodiment 32. The compound of embodiment 31, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl.

**[0517]** Embodiment 33. The compound of claim 32, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a cyclopropyl.

**[0518]** Embodiment 34. The compound of any one of embodiments 20-33, or a pharmaceutically acceptable salt or solvate thereof, each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.

**[0519]** Embodiment 35. The compound of embodiment 34, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl.

[0520] Embodiment 36. The compound of embodiment 34, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^1$  is independently hydrogen or methyl.

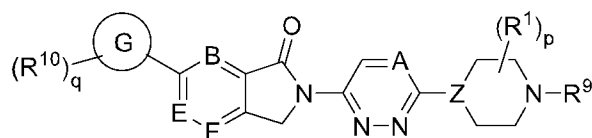
[0521] Embodiment 37. The compound of any one of embodiments 20-36, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O-.

[0522] Embodiment 38. The compound of any one of embodiments 20-36, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -NR<sup>3</sup>-.

[0523] Embodiment 39. The compound of embodiment 38, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>3</sup> is hydrogen or C<sub>1</sub>-C<sub>3</sub>alkyl.

[0524] Embodiment 40. The compound of embodiment 39, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>3</sup> is hydrogen or methyl.

[0525] Embodiment 41. The compound of embodiment 20, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV)

wherein,

ring G is a 5 to 8 membered heteroaryl;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl,

C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl,

hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the

alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

Z is CH or N;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with one or more R<sup>e</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

p is 8; and

q is 0, 1, 2, or 3.

**[0526]** Embodiment 42. The compound of embodiment 41, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is CH.

**[0527]** Embodiment 43. The compound of embodiment 41, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is N.

**[0528]** Embodiment 44. The compound of any one of embodiments 41-43, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene, or a C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.

**[0529]** Embodiment 45. The compound of embodiment 44, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene.

**[0530]** Embodiment 46. The compound of any one of embodiments 41-43, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl.

**[0531]** Embodiment 47. The compound of any one of embodiments 41-45, or a pharmaceutically acceptable salt or solvate thereof, each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.

**[0532]** Embodiment 48. The compound of embodiment 47, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl.

**[0533]** Embodiment 49. The compound of embodiment 47, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen or methyl.

**[0534]** Embodiment 50. The compound of any one of embodiments 20-49, or a pharmaceutically acceptable salt or solvate thereof, wherein A is N.

**[0535]** Embodiment 51. The compound of any one of embodiments 20-49, or a pharmaceutically acceptable salt or solvate thereof, wherein A is CH.

**[0536]** Embodiment 52. The compound of any one of embodiments 1-51, or a pharmaceutically acceptable salt or solvate thereof, wherein B is CR<sup>5</sup>.

**[0537]** Embodiment 53. The compound of any one of embodiments 1-51, or a pharmaceutically acceptable salt or solvate thereof, wherein B is N.

**[0538]** Embodiment 54. The compound of any one of embodiments 1-53, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.

**[0539]** Embodiment 55. The compound of embodiment 54, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0540]** Embodiment 56. The compound of any one of embodiments 1-52, or a pharmaceutically acceptable salt or solvate thereof wherein B is CH.

**[0541]** Embodiment 57. The compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, wherein F is CR<sup>8</sup>.

**[0542]** Embodiment 58. The compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, wherein F is N.

**[0543]** Embodiment 59. The compound of any one of embodiments 1-57, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl,

hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

**[0544]** Embodiment 60. The compound of embodiment 59, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

**[0545]** Embodiment 61. The compound of any one of embodiments 1-60, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CR<sup>7</sup>.

**[0546]** Embodiment 62. The compound of any one of embodiments 1-60, or a pharmaceutically acceptable salt or solvate thereof, wherein E is N.

**[0547]** Embodiment 63. The compound of any one of embodiments 1-61, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.

**[0548]** Embodiment 64. The compound of embodiment 63, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.

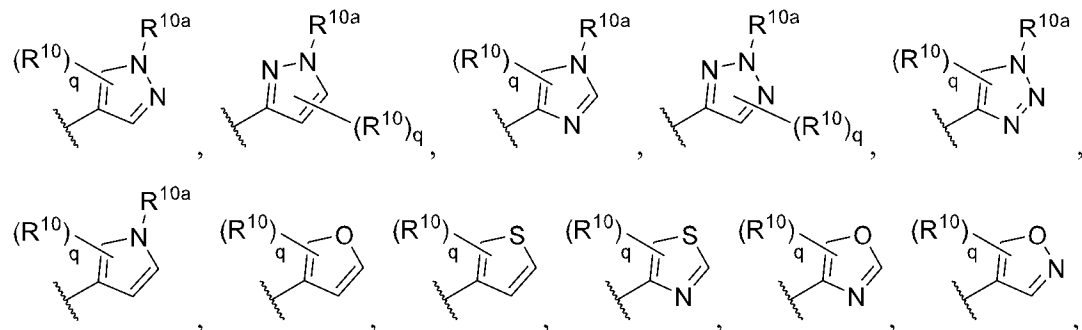
**[0549]** Embodiment 65. The compound of any one of embodiments 1-61, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CH.

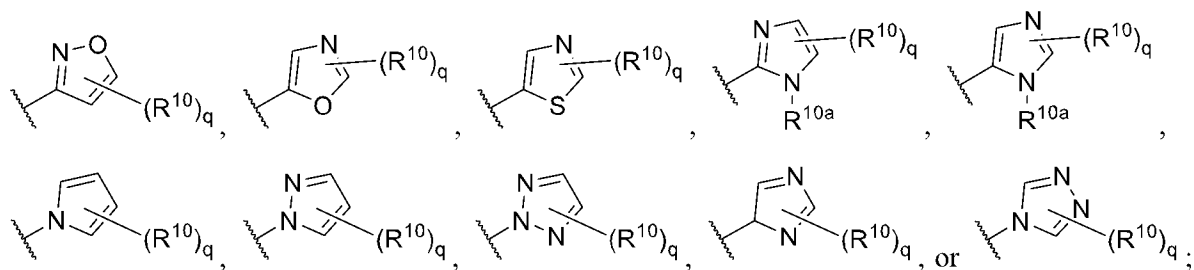
**[0550]** Embodiment 66. The compound of any one of embodiments 20-65, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 5- to 6-membered heteroaryl optionally substituted with 1 or 4 substituents selected from R<sup>c</sup>.

**[0551]** Embodiment 67. The compound of embodiment 66, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 5-membered heteroaryl optionally substituted with 1 or 2 substituents selected from R<sup>c</sup>.

**[0552]** Embodiment 68. The compound of embodiment 67, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole.

**[0553]** Embodiment 69. The compound of any one of embodiments 20-66, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:





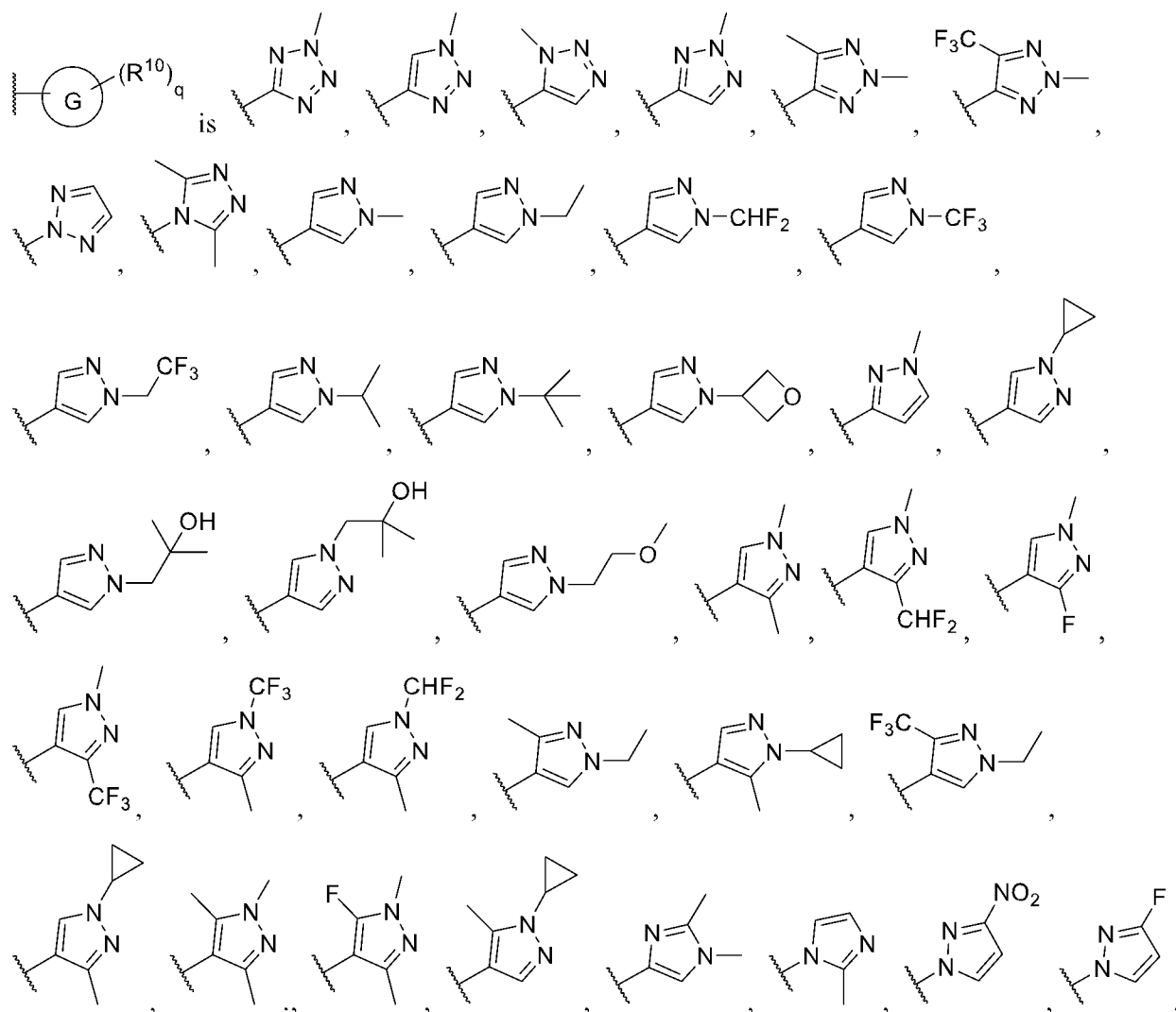
wherein,

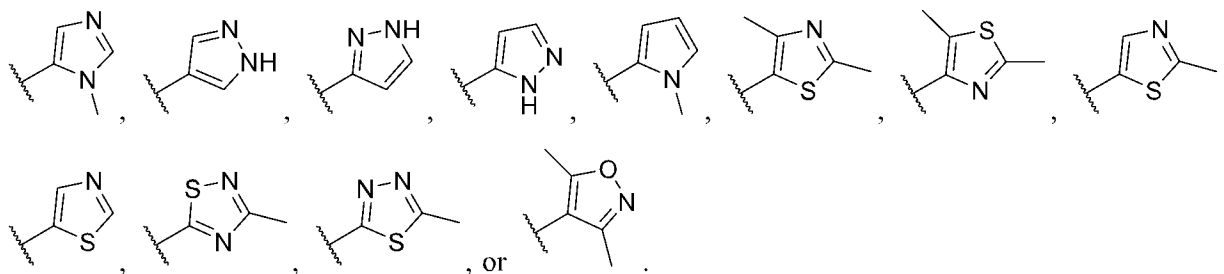
each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

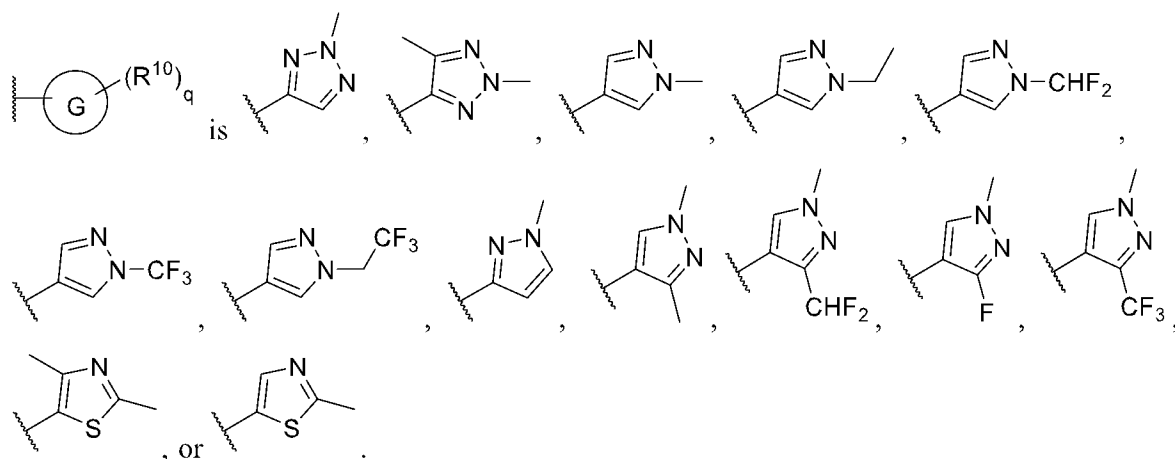
$q$  is 0, 1, 2, or 3.

**[0554]** Embodiment 70. The compound of any one of embodiments 20-66, or a pharmaceutically acceptable salt or solvate thereof, wherein:





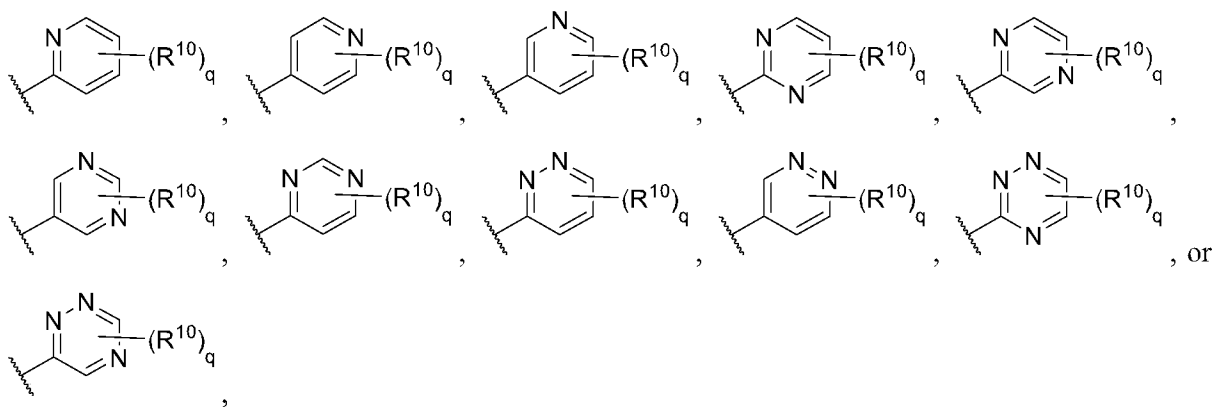
**[0555]** Embodiment 71. The compound of embodiment 70, or a pharmaceutically acceptable salt or solvate thereof, wherein:



**[0556]** Embodiment 72. The compound of embodiment 66, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R<sup>c</sup>.

**[0557]** Embodiment 73. The compound of embodiment 72, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyridine, pyrimidine, or triazine.

**[0558]** Embodiment 74. The compound of any one of embodiments 20-66, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



wherein,

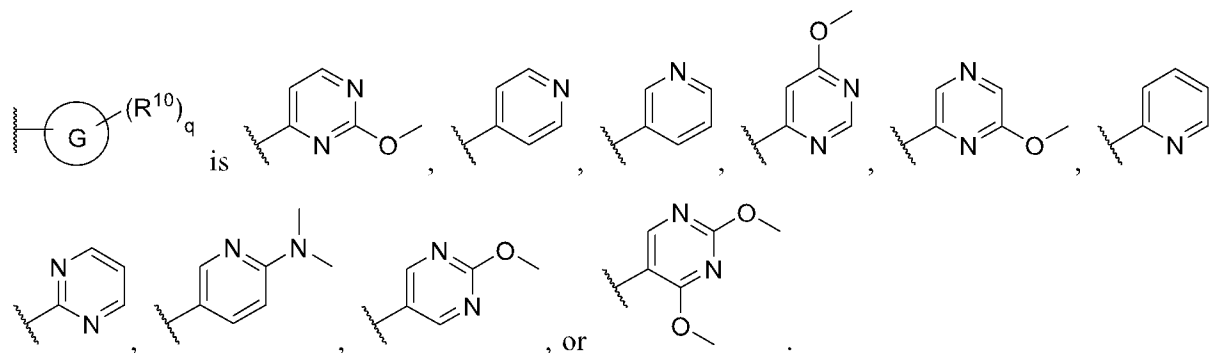
each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl,

C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and

q is 0, 1, 2, or 3.

**[0559]** Embodiment 75. The compound of embodiment 74, or a pharmaceutically acceptable salt

thereof, wherein:



**[0560]** Embodiment 76. The compound of any one of embodiments 20-66, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>c</sup>.

**[0561]** Embodiment 77. The compound of embodiment 76, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R<sup>c</sup>.

**[0562]** Embodiment 78. The compound of any one of embodiments 1-77, wherein the compound is selected from a compound of Table 1A, Table 1B, or Table 1C, or a pharmaceutically acceptable salt thereof.

**[0563]** Embodiment 79. A pharmaceutically composition comprising a compound of any one of embodiments 1-78, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

**[0564]** Embodiment 80. A method of treating a neurodegenerative disease or disorder in a patient in need thereof, the method comprising administering to the patient a compound of any one of embodiments 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 79.

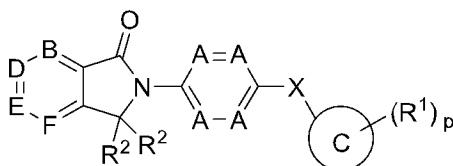
**[0565]** Embodiment 81. The method of embodiment 80, wherein the neurodegenerative disease or disorder is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Prion disease, and spinocerebellar ataxias.

**[0566]** Embodiment 82. The method of embodiment 81, wherein the neurodegenerative disease or disorder is Huntington's disease (HD).

## CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I''), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I''),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>2</sup> is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is absent, -CH<sub>2</sub>-, -O-, -OCH<sub>2</sub>-, -S-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each R<sup>4</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

or R<sup>3</sup> and one of R<sup>4</sup> are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -OCH<sub>2</sub>R<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-

(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

wherein at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> is C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C<sub>1</sub>-C<sub>6</sub>alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R<sup>c</sup>;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

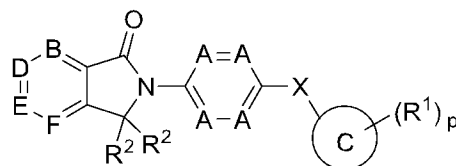
each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

2. A compound having the structure of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form an oxo; or

two  $R^1$  are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each  $R^2$  is independently hydrogen, halogen, -OH, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; or

X is absent, -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-;

$R^3$  is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub>cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each  $R^4$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

D is N or CR<sup>6</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

$R^5$  and  $R^8$  are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

one of  $R^6$  or  $R^7$  is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and the other of  $R^6$  or  $R^7$  is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; wherein  $R^7$  is not pyridyl substituted with two methoxy groups;

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and

heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

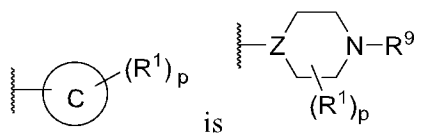
p is an integer from 1-9.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>2</sup> is independently hydrogen.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein D is CR<sup>6</sup> or E is CR<sup>7</sup>.
5. The compound of any one of claims 2-4, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R<sup>6</sup> is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>; and

R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>.

6. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^7$  is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^7$  is hydrogen.
8. The compound of any one of claims 2-4, or a pharmaceutically acceptable salt or solvate thereof, wherein:  
 $R^6$  is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl, wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; and  
 $R^7$  is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R<sup>10</sup>.
9. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^6$  is hydrogen, halogen, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
10. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^6$  is hydrogen.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is a 6-membered heterocycloalkyl.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine, piperazine, or morpholine.
13. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperazine.
14. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein



wherein,

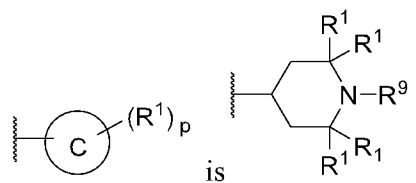
Z is N or CH;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>,

C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

- two R<sup>1</sup> are taken together to form an oxo; or
- two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or
- two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;
- R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;
- each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;
- R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; and
- each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heteroaryl.

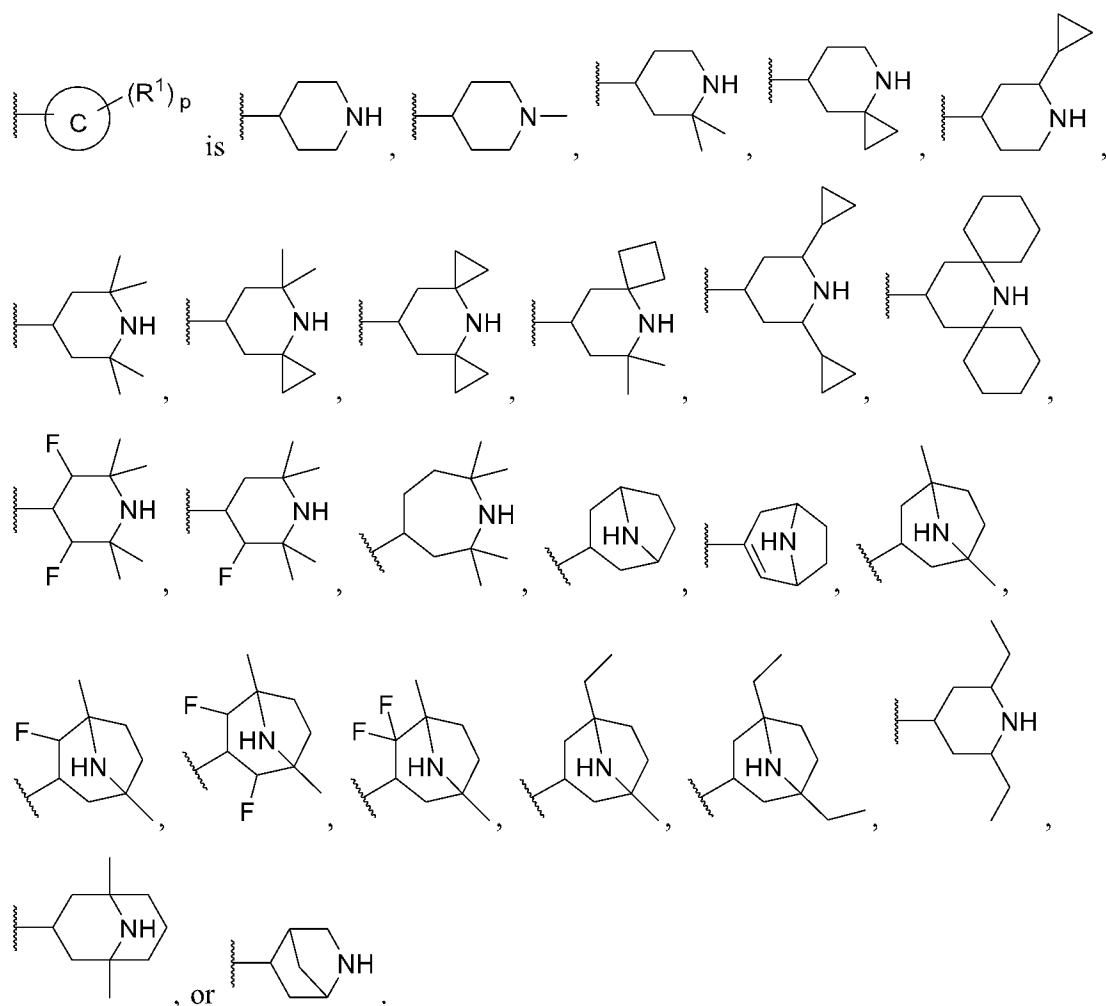
16. The compound of claim 14, or a pharmaceutically acceptable salt or solvate thereof, wherein



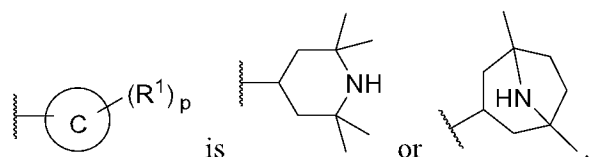
wherein,

- each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or
- two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or
- two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl; and
- R<sup>9</sup> is hydrogen.

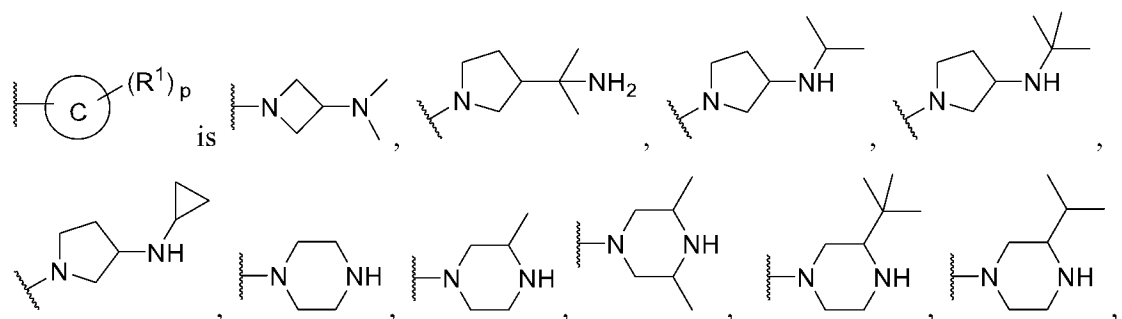
17. The compound of any one of claims 1-12 or 14-16, or a pharmaceutically acceptable salt or solvate thereof, wherein

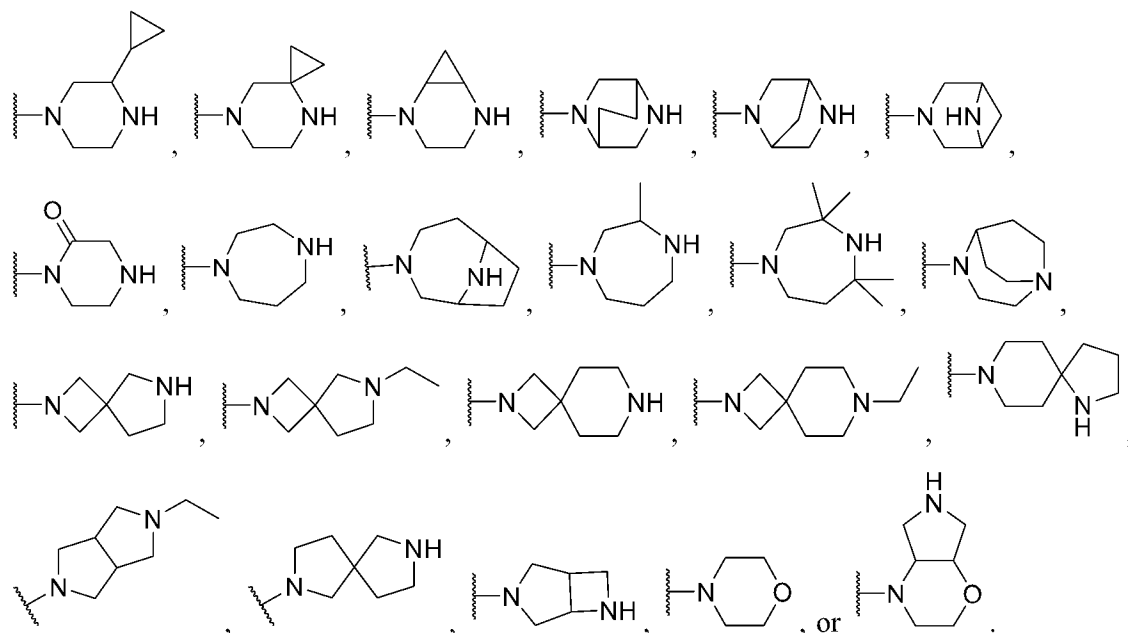


18. The compound of claim 17, or a pharmaceutically acceptable salt or solvate thereof, wherein

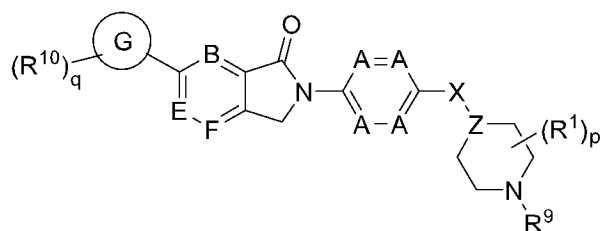


19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O- or -NR<sup>3</sup>-.
20. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein X is absent; and





21. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (II'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>,

C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form an oxo; or

two  $R^1$  are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

X is bond, -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-;

Z is CH or N, wherein when X is -O-, -S-, or -NR<sup>3</sup>-, then Z is CH;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

each A is independently N or CR<sup>4</sup>, wherein at least two of A are N;

each  $R^4$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, alkene, alkyne, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-

C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heteroaryl; and

p is 8;

$q$  is 0, 1, 2, or 3.

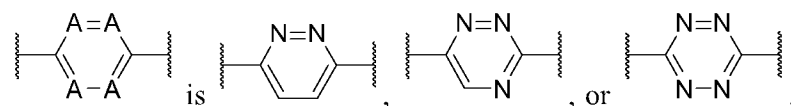
22. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-; and Z is CH.
23. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein X is bond and Z is N.
24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate thereof, wherein each A is independently N or CH, wherein two of A are N.
25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate

thereof, wherein

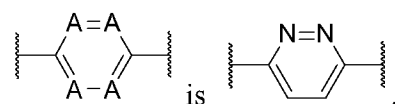
is

or

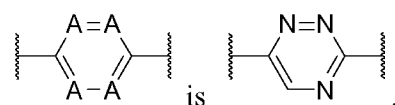
26. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein



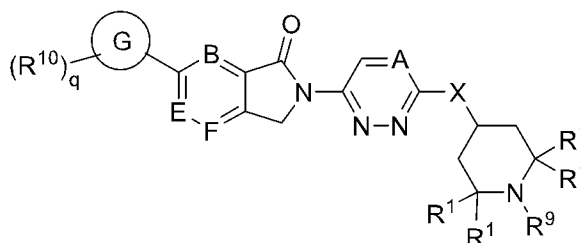
27. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein



28. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein



29. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (III'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each  $R^1$  is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two  $R^1$  are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

X is -CH<sub>2</sub>-, -O-, -S-, or -NR<sup>3</sup>-;

R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl,

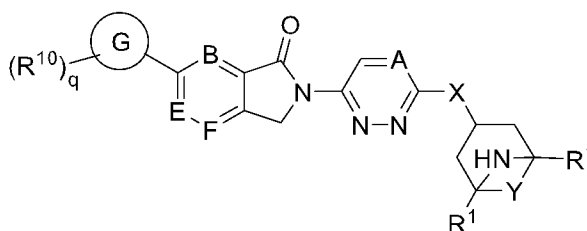
alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;

each R<sup>c</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

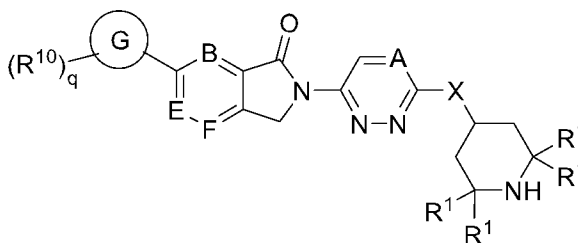
30. The compound of any one of claims 21-29, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.
31. The compound of claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene.
32. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of Formula (III') has the structure of Formula (IIIa'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa'),

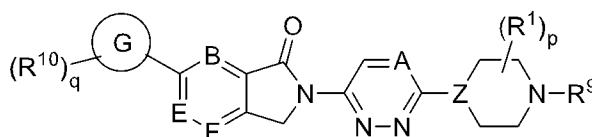
wherein Y is C<sub>1</sub>-C<sub>3</sub>alkylene.

33. The compound of claim 32, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH<sub>2</sub>CH<sub>2</sub>-.
34. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of Formula (III') has the structure of Formula (IIIb'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb').

35. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, wherein two  $R^1$  are taken together to form a  $C_3$ - $C_6$ cycloalkyl.
36. The compound of claim 35, or a pharmaceutically acceptable salt or solvate thereof, wherein two  $R^1$  are taken together to form a cyclopropyl.
37. The compound of any one of claims 21-36, or a pharmaceutically acceptable salt or solvate thereof, each  $R^1$  is independently hydrogen, halogen,  $C_1$ - $C_6$ alkyl, or  $C_1$ - $C_6$ haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from  $R^c$ .
38. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^1$  is independently hydrogen, halogen, or  $C_1$ - $C_6$ alkyl.
39. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^1$  is independently hydrogen or methyl.
40. The compound of any one of claims 21-39, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O- or - $NR^3$ -.
41. The compound of claim 40, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O-.
42. The compound of claim 40, or a pharmaceutically acceptable salt or solvate thereof, wherein X is - $NR^3$ -.
43. The compound of claim 42, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^3$  is hydrogen,  $C_1$ - $C_3$ alkyl or  $C_3$ - $C_6$ cycloalkyl.
44. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^3$  is hydrogen, methyl, ethyl, or cyclopropyl.
45. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein  $R^3$  is hydrogen or methyl.
46. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IV'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R<sup>1</sup> is independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form an oxo; or

two R<sup>1</sup> are taken together to form a bond, C<sub>1</sub>-C<sub>3</sub>alkylene, or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>; or

two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

Z is CH or N;

A is N or CH;

B is N or CR<sup>5</sup>;

E is N or CR<sup>7</sup>;

F is N or CR<sup>8</sup>;

R<sup>5</sup>, R<sup>7</sup>, and R<sup>8</sup> are each independently hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -SH, -SR<sup>a</sup>, -S(=O)R<sup>a</sup>, -S(=O)<sub>2</sub>R<sup>a</sup>, -S(=O)<sub>2</sub>NR<sup>c</sup>R<sup>d</sup>, -NR<sup>c</sup>R<sup>d</sup>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>b</sup>, -C(=O)NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkene, C<sub>2</sub>-C<sub>6</sub>alkyne, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>9</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R<sup>e</sup>;

each R<sup>10</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>c</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>e</sup>; or

two R<sup>10</sup> are taken together to form an oxo;

each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl,

alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>2</sub>-C<sub>6</sub>alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>;

each R<sup>e</sup> is independently halogen, oxo, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -S(=O)<sub>2</sub>NH<sub>2</sub>, -S(=O)<sub>2</sub>NHCH<sub>3</sub>, -S(=O)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)NH<sub>2</sub>, -C(=O)NHCH<sub>3</sub>, -C(=O)N(CH<sub>3</sub>)<sub>2</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>1</sub>-C<sub>6</sub>heteroalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl;

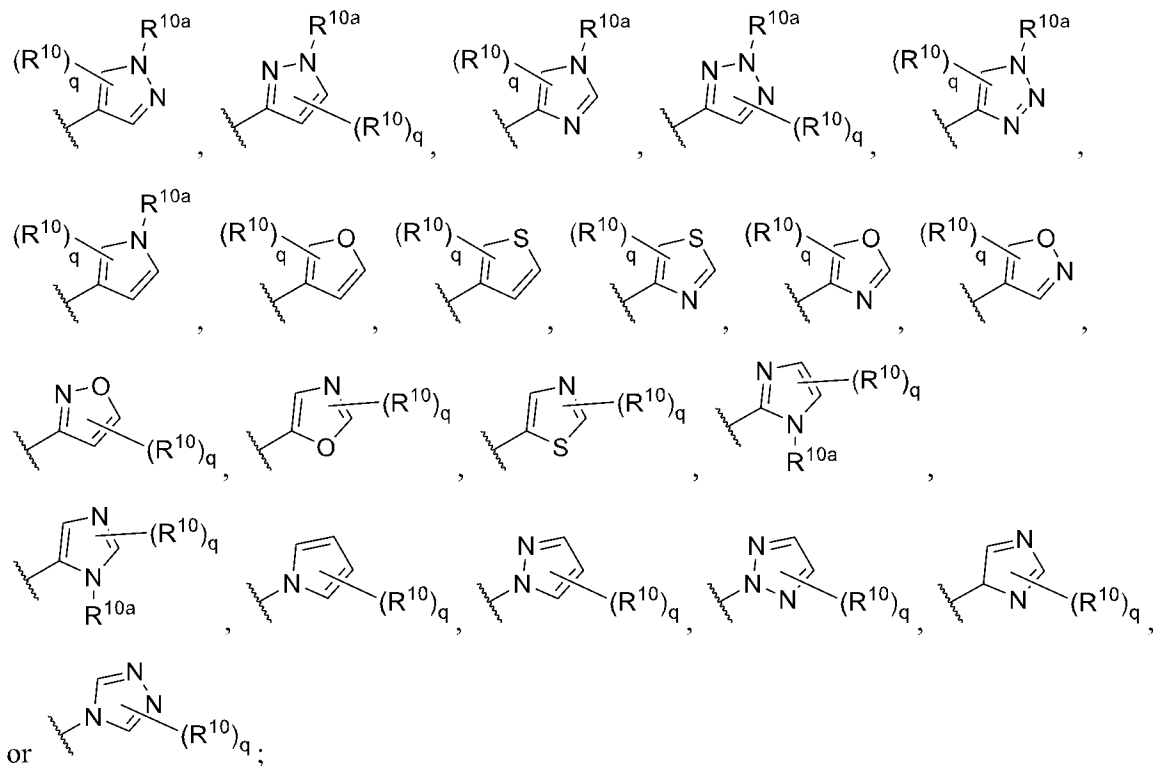
p is 8; and

q is 0, 1, 2, or 3.

47. The compound of claim 46, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is CH.
48. The compound of claim 46, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is N.
49. The compound of any one of claims 46-48, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene or C<sub>1</sub>-C<sub>3</sub>heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.
50. The compound of claim 49, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>1</sub>-C<sub>3</sub>alkylene.
51. The compound of any one of claims 46-48, or a pharmaceutically acceptable salt or solvate thereof, wherein two R<sup>1</sup> are taken together to form a C<sub>3</sub>-C<sub>6</sub>cycloalkyl.
52. The compound of any one of claims 46-48, or a pharmaceutically acceptable salt or solvate thereof, each R<sup>1</sup> is independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, haloalkyl, or hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>e</sup>.
53. The compound of claim 52, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub>alkyl.
54. The compound of claim 52, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>1</sup> is independently hydrogen or methyl.
55. The compound of any one of claims 21-54, or a pharmaceutically acceptable salt or solvate thereof, wherein A is N.
56. The compound of any one of claims 21-54, or a pharmaceutically acceptable salt or solvate thereof, wherein A is CH.

57. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt or solvate thereof, wherein B is CR<sup>5</sup>.
58. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt or solvate thereof, wherein B is N.
59. The compound of any one of claims 1-57, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.
60. The compound of claim 59, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
61. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt or solvate thereof wherein B is CH.
62. The compound of any one of claims 1-61, or a pharmaceutically acceptable salt or solvate thereof, wherein F is CR<sup>8</sup>.
63. The compound of any one of claims 1-61, or a pharmaceutically acceptable salt or solvate thereof, wherein F is N.
64. The compound of any one of claims 1-62, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.
65. The compound of claim 64, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>8</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
66. The compound of any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CR<sup>7</sup>.
67. The compound of any one of claims 1-65, or a pharmaceutically acceptable salt or solvate thereof, wherein E is N.
68. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, or C<sub>1</sub>-C<sub>6</sub>aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.
69. The compound of claim 68, or a pharmaceutically acceptable salt or solvate thereof, wherein R<sup>7</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl.
70. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CH.
71. The compound of any one of claims 21-70, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R<sup>c</sup>.

72. The compound of claim 71, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from  $R^e$ .
73. The compound of claim 72, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole.
74. The compound of any one of claims 21-70, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



wherein,

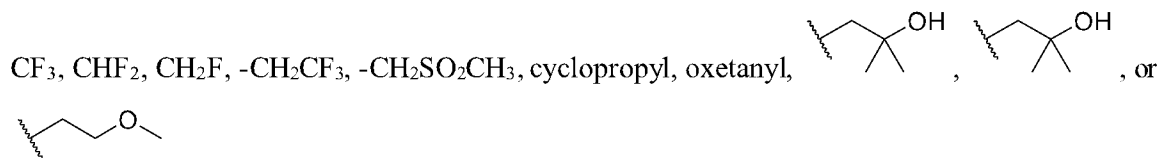
each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>e</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from  $R^e$ ;

each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from  $R^e$ ; and

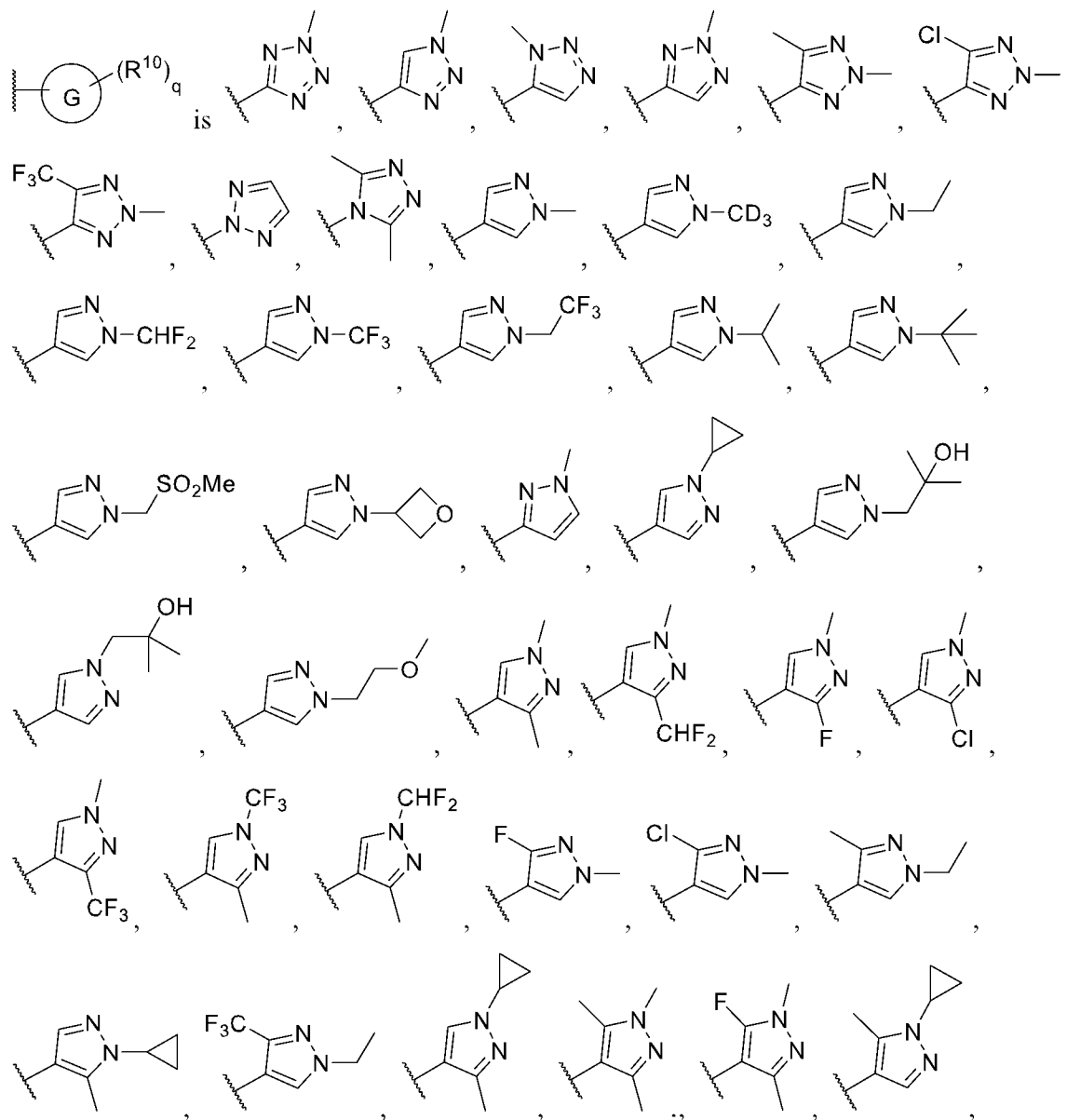
$q$  is 0, 1, 2, or 3.

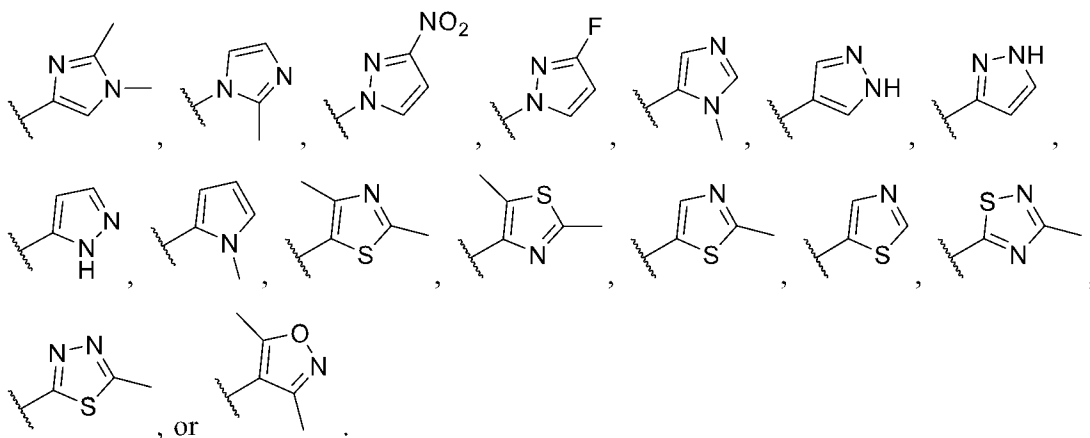
75. The compound of claim 74, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl;
- each  $R^{10a}$  is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl; and
- $q$  is 0, 1, or 2.

76. The compound of claim 74 or 75, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^{10}$  is independently -F, -Cl, methyl, ethyl, -OCH<sub>3</sub>, -CF<sub>3</sub>, -CHF<sub>2</sub>, or -CH<sub>2</sub>F.
77. The compound of any one of claims 74-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^{10a}$  is independently C<sub>1</sub>-C<sub>6</sub>alkyl which is optionally substituted with 1 to 4-substituents independently selected from halogen, -OH, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, and C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl.
78. The compound of any one of claims 74-77, or a pharmaceutically acceptable salt or solvate thereof, wherein each  $R^{10a}$  is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, -CD<sub>3</sub>, -

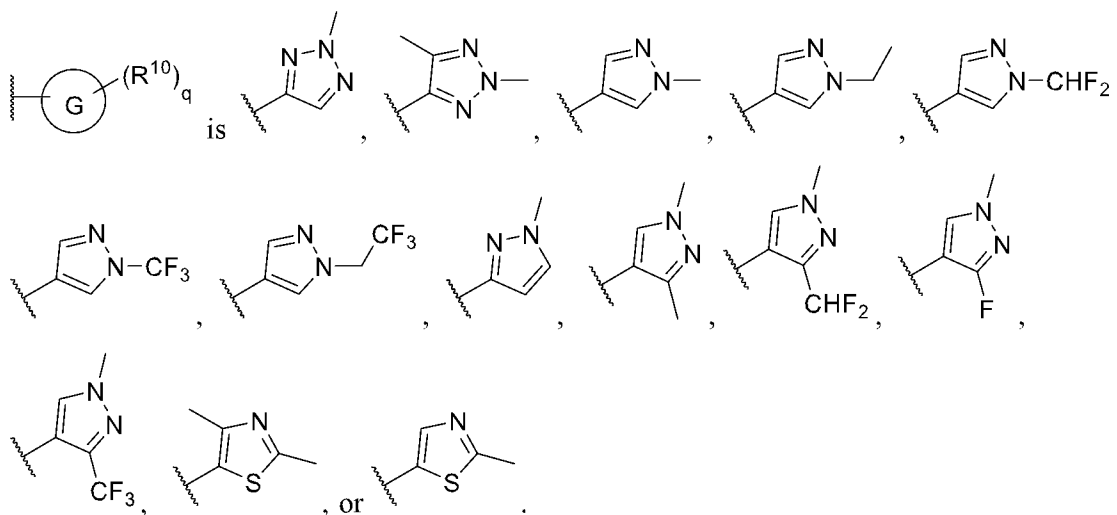


79. The compound of any one of claims 21-70, or a pharmaceutically acceptable salt or solvate thereof, wherein:

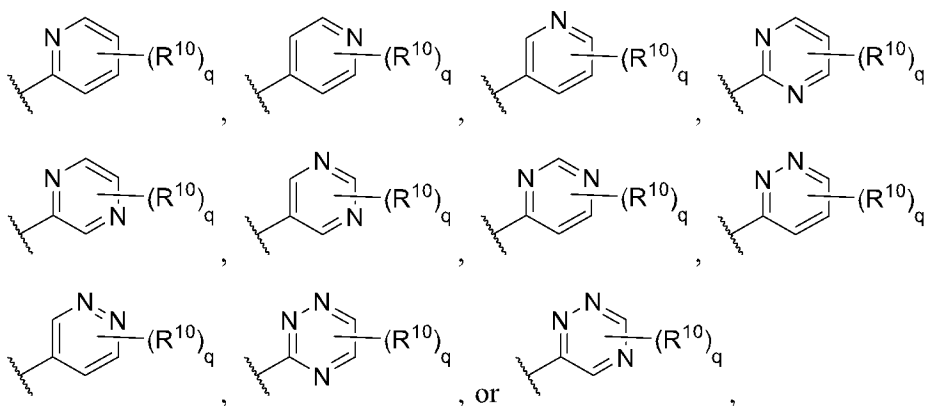




80. The compound of claim 79, or a pharmaceutically acceptable salt or solvate thereof, wherein



81. The compound of claim 71, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from  $R^e$ .
82. The compound of claim 81, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyridine, pyrimidine, or triazine.
83. The compound of any one of claims 21-70, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



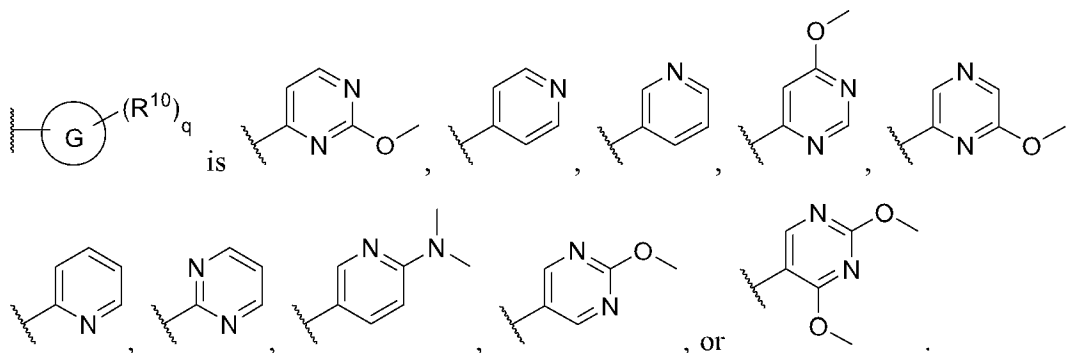
wherein,

each  $R^{10}$  is independently halogen, -CN, -NO<sub>2</sub>, -OH, -OR<sup>a</sup>, -NR<sup>e</sup>R<sup>d</sup>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>aminoalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered

heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R<sup>c</sup>; and

q is 0, 1, 2, or 3.

84. The compound of claim 83, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>10</sup> is independently -OCH<sub>3</sub> or -N(CH<sub>3</sub>)<sub>2</sub>; and q is 0, 1, or 2.
85. The compound of claim 79, or a pharmaceutically acceptable salt thereof, wherein



86. The compound of any one of claims 21-70, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 9 or 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R<sup>c</sup>.
87. The compound of claim 86, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 9-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R<sup>c</sup>.
88. The compound of any one of claims 1-87, or a pharmaceutically acceptable salt or solvate thereof, wherein:
- each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>;
- each R<sup>b</sup> is independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, or C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>; and
- R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or C<sub>1</sub>-C<sub>6</sub>haloalkyl, wherein each of the alkyl, and haloalkyl is optionally substituted with 1 to 4 substituents independently selected from R<sup>c</sup>.
89. The compound of claim 88, or a pharmaceutically acceptable salt or solvate thereof, wherein:
- each R<sup>a</sup> is independently C<sub>1</sub>-C<sub>6</sub>alkyl;
- each R<sup>b</sup> is independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl; and
- R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl.
90. The compound of claim 89, or a pharmaceutically acceptable salt or solvate thereof, wherein:
- each R<sup>a</sup> is independently methyl, ethyl, isopropyl, or tert-butyl;
- each R<sup>b</sup> is independently hydrogen, methyl or ethyl; and

R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, methyl, or ethyl.

91. The compound of any one of claims 1-90, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>c</sup> is independently halogen, -CN, -OH, -S(=O)CH<sub>3</sub>, -S(=O)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, -NH<sub>2</sub>, -NHCH<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -C(=O)CH<sub>3</sub>, -C(=O)OH, -C(=O)OCH<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>hydroxyalkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or 4 to 6-membered heterocycloalkyl.
92. The compound of claim 91, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>c</sup> is independently -F, -Cl, -OH, -CH<sub>2</sub>S(=O)<sub>2</sub>CH<sub>3</sub>, methyl, ethyl, isopropyl, tertbutyl, -OCH<sub>3</sub>, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or azetidine, oxytane, piperidine, piperazine, or morpholine.
93. The compound of claim 90, or a pharmaceutically acceptable salt or solvate thereof, wherein each R<sup>c</sup> is independently -F, -OH, -CF<sub>3</sub>, -CHF<sub>2</sub>, -OCH<sub>3</sub>, or methyl.
94. The compound of any one of claims 1-93, a pharmaceutically acceptable salt or solvate thereof, wherein the compound is selected from a compound of Table 1A, Table 1B, or Table 1C, or a pharmaceutically acceptable salt or solvate thereof.
95. A pharmaceutically composition comprising a compound of any one of claims 1-94, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.
96. A method of treating a neurodegenerative disease or disorder in a patient in need thereof, the method comprising administering to the patient a compound of any one of claims 1-94, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 95.
97. The method of claim 96, wherein the neurodegenerative disease or disorder is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, Prion disease, and spinocerebellar ataxias.
98. The method of claims 86, wherein the neurodegenerative disease or disorder is Huntington's disease (HD).

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/097833

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                     |                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>C07D 471/04(2006.01)i; C07D 401/04(2006.01)i; C07D 401/14(2006.01)i; C07D 405/14(2006.01)i; A61K 31/395(2006.01)i; A61P 25/00(2006.01)i; A61P 25/28(2006.01)i<br>According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                     |                                                                                   |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC: C07D A61K A61P<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>CNTXT,ENTXT,VEN,STN(Registry,Caplus),CNKI: ispindolinone,Huntington disease,HD,neurological disorder,neuro degenerative,structure search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                     |                                                                                   |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                     |                                                                                   |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Citation of document, with indication, where appropriate, of the relevant passages                                  | Relevant to claim No.                                                             |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | CN 102762548 A (沃泰克斯药物股份有限公司) 31 October 2012 (2012-10-31)<br>claims 1,32,35 and description paragraph 0031,Table 1 | 1-98                                                                              |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | WO 2022216947 A1 (CHDI FOUNDATION INC) 13 October 2022 (2022-10-13)<br>the whole document                           | 1-98                                                                              |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | CN 113396145 A (盖罗发现有限责任公司) 14 September 2021 (2021-09-14)<br>the whole document                                    | 1-98                                                                              |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | WO 2023081845 A1 (GEORGIAMUNE LLC) 11 May 2023 (2023-05-11)<br>the whole document                                   | 1-98                                                                              |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | WO 2023081854 A1 (GEORGIAMUNE LLC) 11 May 2023 (2023-05-11)<br>the whole document                                   | 1-98                                                                              |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                     |                                                                                   |
| <p>* Special categories of cited documents:</p> <p>“A” document defining the general state of the art which is not considered to be of particular relevance</p> <p>“D” document cited by the applicant in the international application</p> <p>“E” earlier application or patent but published on or after the international filing date</p> <p>“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>“O” document referring to an oral disclosure, use, exhibition or other means</p> <p>“P” document published prior to the international filing date but later than the priority date claimed</p> <p>“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>“&amp;” document member of the same patent family</p> |                                                                                                                     |                                                                                   |
| Date of the actual completion of the international search<br><b>26 September 2024</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                     | Date of mailing of the international search report<br><b>29 September 2024</b>    |
| Name and mailing address of the ISA/CN<br><b>CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION<br/>6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing<br/>100088, China</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                     | Authorized officer<br><b>ZHAN,YueChen</b><br><br>Telephone No. (+86) 010-62086307 |

# INTERNATIONAL SEARCH REPORT

International application No.

**PCT/CN2024/097833**

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **96-98**  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Claims 96-98 are directed to a method for the treatment of the human/animal body by therapy (Rule 39.1(iv) PCT). Nonetheless, the search of claims 96-98 is carried out based on the use of the compounds or compositions in the manufacture of medicaments for the diseases.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**INTERNATIONAL SEARCH REPORT**  
**Information on patent family members**

International application No.

**PCT/CN2024/097833**

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