(19) DANMARK

(10) **DK/EP 3860989 T3**

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: *C 07 D 401/14 (2006.01)* *A 61 K 31/4155 (2006.01)* *A 61 K 31/4439 (2006.01)*
A 61 P 25/00 (2006.01) *A 61 P 25/16 (2006.01)* *C 07 D 403/12 (2006.01)*
C 07 D 417/12 (2006.01) *C 07 D 417/14 (2006.01)* *C 07 D 487/08 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2023-05-01**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2023-04-05**

(86) Europæisk ansøgning nr.: **19791136.5**

(86) Europæisk indleveringsdag: **2019-10-04**

(87) Den europæiske ansøgnings publiceringsdag: **2021-08-11**

(86) International ansøgning nr.: **US2019054803**

(87) Internationalt publikationsnr.: **WO2020072964**

(30) Prioritet: **2018-10-05 US 201862741945 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **KONDENSEREDE PYRROLINER DER FUNGERER SOM INHIBITORER AF UBIQUITIN-SPECIFIK PROTEASE 30 (USP30)**

(56) Fremdragne publikationer:
WO-A1-2016/156816
WO-A1-2017/103614
WO-A1-2017/141036

Fortsættes ...

WO-A1-2017/163078
WO-A1-2018/060742

DESCRIPTION

TECHNICAL FIELD

[0001] This disclosure relates to inhibiting Ubiquitin-Specific Protease 30 (USP30), including novel compounds and methods for inhibiting USP30. The compounds and related methods are useful in the field of medicine including the development of new therapies (e.g., for the treatment of conditions related to the therapeutic inhibition of USP30 such as Parkinson's Disease (PD)). Any references to methods of treatment in the subsequent paragraphs of this description are to be interpreted as references to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy (or for diagnosis).

BACKGROUND

[0002] The ubiquitination system is a highly regulated process which affects a wide variety of cellular activities and physiological processes. Ubiquitination is a reversible process, facilitated by a group of proteins known as deubiquitinating enzymes (DUBs), which deconjugate ubiquitin (Ub) from the substrate. DUBs are encoded by approximately 100 human genes and are divided into six families, with the largest family being the ubiquitin-specific proteases (USPs) with more than 50 members.

[0003] Ubiquitination regulates mitochondrial dynamics and biogenesis, affecting the abundance and function of these organelles. Mitochondria serve many functions to maintain cell health in mammals, including generating ATP. As mitochondria age they become damaged, losing their metabolic functionality, and begin releasing pro-apoptotic proteins. Mitochondria self-regulate their quality via the mechanism of mitophagy, which is the selective removal of damaged mitochondria from the cell. Ubiquitination of mitochondrial proteins is believed to contribute to mitochondrial dynamics in mammalian cells, possibly by "flagging" those proteins for inactivation. Ubiquitin-Specific Protease 30 (USP30) is embedded in the outer membrane of mitochondria, where it participates in the maintenance of mitochondrial morphology. It is believed that over-expression of USP30 can lead to a decrease in mitophagy.

[0004] Inactivating mutations in PINK1 and Parkin can impair mitophagy and result in accumulation of damaged mitochondria and neuronal toxicity, which has been implicated in Parkinson's Disease. USP30 opposes the ligase activity of Parkin and is a negative regulator of mitophagy. USP30 inhibition is expected to promote mitophagy and restore mitochondrial health.

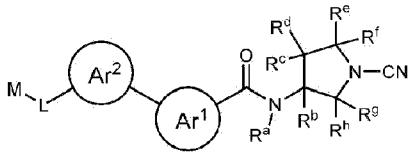
WO 2016/156816 describes compounds and methods for the manufacture of inhibitors of deubiquitylating enzymes (DUBs).

WO 2018/060742 describes a class of substituted-cyanopyrrolidines with activity as inhibitors

of deubiquitilating enzymes.
WO 2017/163078 describes compounds and methods for the manufacture of inhibitors of deubiquitylating enzymes (DUBs).
WO 2017/103614 describes compounds and methods for the manufacture of inhibitors of deubiquitylating enzymes (DUBs).
WO 2017/141036 describes compounds and methods for the manufacture of inhibitors of deubiquitylating enzymes (DUBs).

SUMMARY

[0005] The disclosure provides compounds useful for inhibiting USP30, including USP30 Inhibitor Compounds as defined herein. In some embodiments, the disclosure provides a compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

1. (i) R^a and R^b form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^c, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
2. (ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
3. (iii) R^a and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
4. (iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected

from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

5. (v) R^b and R^e form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
6. (vi) R^b and R^g form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^c, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
7. (vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
8. (viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
9. (ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
10. (x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
11. (xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
12. (xii) R^e and R^f together form =O; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently

hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

13. (xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
14. (xiv) R^g and R^h together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
15. (xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; and

Ar^1 is phenylene or 5-6 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *m* R^1 groups; and

Ar^2 is phenylene or 5-10 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *n* R^2 groups;

L is -O-, -S-, -NR^3-, -$C(R^4)_2$-, -$S(O)_2$-, or -S(O)-;

M is 3-6 membered cycloalkyl, phenyl, or 5-6 membered heteroaryl, wherein said cycloalkyl, phenyl, or heteroaryl is substituted with *p* R^5 groups;

each occurrence of R^1, R^2, and R^5 is independently halo, cyano, NO_2, oxo, hydroxyl, -R^6, -OR^6, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C_1-C_6 alkylene-R^6, C_1-C_6 alkoxy, Ci-C_6 haloalkoxy, -C_0-C_3 alkylene-NR^6R^7, -C_0-C_3 alkylene-NR^7R^8, -C_0-C_3 alkylene-$C(O)NR^6R^7$, -C_0-C_3 alkylene-$C(O)NR^7R^8$, -C_0-C_3 alkylene-$NR^7C(O)R^6$, -C_0-C_3 alkylene-$NR^7C(O)R^8$, -C_0-C_3 alkylene-$NR^7S(O)_2R^6$, -C_0-C_3 alkylene-$C(O)R^6$, -C_0-C_3 alkylene-$C(O)R^7$, -C_0-C_3 alkylene-SR^6, -C_0-C_3 alkylene-$S(O)R^6$, -C_0-C_3 alkylene-$S(O)_2R^6$, -C_0-C_3 alkylene-$S(O)_2R^7$, -C_0-C_3 alkyleneS$(O)_2NR^6R^7$, -C_0-C_3 alkylene-$S(O)_2NR^7R^8$, -C_0-C_3 alkylene-$NR^7C(O)NR^8R^9$, -C_0-C_3 alkylene-$NR^7S(O)_2NR^8R^9$, -C_0-C_3 alkylene-$C(O)OR^7$, -C_0-C_3 alkylene-$C(O)OR^6$, -C_0-C_3 alkylene-$OC(O)R^7$, -C_0-C_3 alkylene-$OC(O)R^6$, -C_0-C_3 alkylene-$NR^7C(O)OR^8$, or -C_0-C_3 alkylene-$NR^7S(O)_2R^8$;

R^3 is H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^4 is independently H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, or two R^4 groups together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl or heterocycloalkyl;

each R^6 is independently 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl, wherein said heteroaryl, heterocycloalkyl, aryl, or cycloalkyl is optionally substituted with 1-5 substituents independently selected from the group consisting of halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, 3-8 membered cycloalkyl, $-NR^{10}C(O)NR^{11}R^{12}$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)OR^{11}$, $-S(O)_2R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(O)OR^{10}$, $-S(O)_2NR^{10}R^{11}$, $-NR^{10}S(O)_2R^{11}$, $-OR^{10}$, $-OC(O)R^{10}$, $-OS(O)_2R^{10}$, $-OC(O)NR^{10}R^{11}$, $-OC(O)OR^{10}$, $-OS(O)_2NR^{10}R^{11}$, $-C(O)NR^{10}C(O)NR^{11}R^{12}$, $-C(O)C(O)R^{10}$, $-C(O)NR^{10}C(O)R^{11}$, $-C(O)NR^{10}C(O)OR^{11}$, $-C(O)S(O)_2R^{10}$, $-C(O)C(O)NR^{10}R^{11}$, $-C(O)C(O)OR^{10}$, $-C(O)S(O)_2NR^{10}R^{11}$, $-C(O)NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkylene-R^{10}, $-C_1$-C_6 alkylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)R^{10}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)OR^{10}$, $-C_1$-C_6 alkylene-$S(O)_2NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkenylene-R^{10}, $-C_1$-C_6 alkenylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkenylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)R^{10}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkenylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkenylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)OR^{10}$, $-C_1$-C_6 alkenylene-$S(O)_2NR^{10}R^{11}$, and $-C_1$-C_6 alkenylene-$NR^{10}S(O)_2R^{11}$;

each R^7, R^8, and R^9 is independently hydrogen or C_1-C_6 alkyl;

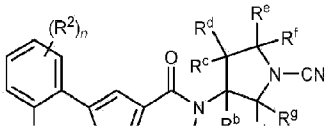
each R^{10}, R^{11}, and R^{12} is independently hydrogen, C_1-C_6 alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl;

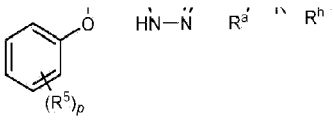
m is 0-4;

n is 0-4; and

p is 0-4.

[0006] In some embodiments, the disclosure provides a compound of formula (I-C):



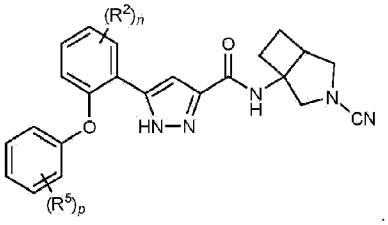


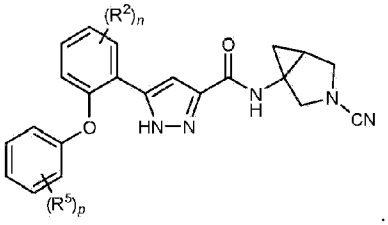
(I-C)

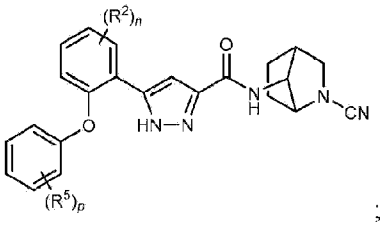
or a pharmaceutically acceptable salt thereof, wherein R^2, R^5, *n, p,* R^a, R^b, R^c, R^d, R^e, R^f, R^g, and

R^h are all as defined for formula (I) above.

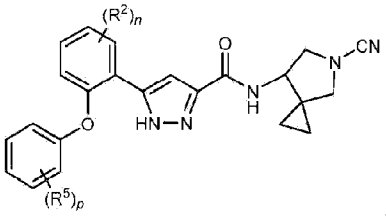
[0007] In some embodiments, a USP30 Inhibitor Compound is a compound selected from the group consisting of:





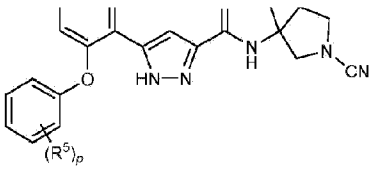


and



wherein R^2, R^5, *n,* and *p* are as defined with respect to formula (I) herein, or a pharmaceutically acceptable salt thereof, having an IC_{50} value of about ≤ 1 μM (and preferably ≤ 0.5 μM or ≤ 0.1 μM) and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1. In some embodiments, compounds of formula (I-C) are provided where R^2 and R^5 are both hydrogen.

[0008] In some embodiments, a USP30 Inhibitor Compound is a compound of the chemical formula:



wherein R^2, R^5, *n,* and *p* are as defined with respect to formula (I) herein, or a pharmaceutically acceptable salt thereof, having an IC_{50} value of about ≤ 1 μM (and preferably ≤ 0.5 μM or ≤ 0.1 μM) and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1.

[0009] In some embodiments, a compound is any compound selected from the compounds listed in Table 1 herein.

DETAILED DESCRIPTION

[0010] The present disclosure relates to compounds of formula (I), as defined herein, pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising same, and medical uses involving same. In some embodiments, the compounds of formula (I) are USP30 Inhibitor Compounds. In other embodiments, the compounds of formula (I) are useful, for example, as analytical tools and/or control compounds in biological assays (e.g., compounds of any of the following aspects and embodiments that are not USP30 Inhibitor Compounds).

[0011] USP30 Inhibitor Compounds are useful in the development of new therapies for Parkinson's disease (PD), and in methods of treating diseases or conditions by inhibiting USP30 (such as PD). Parkin (E3 ubiquitin ligase) and PINK1 (kinase) are key regulators of mitophagy. In healthy mitochondria, PINK1 localization to the mitochondrial outer membrane (MOM) and exposure to the cytosol is limited by rapid import to the mitochondrial inner membrane (MIM). Once localized to the MIM, PINK1 is processed by several proteases, such as presenilin associated rhomboid-like protease (PARL), to yield a truncated version of PINK1 which is subsequently degraded by the proteasome (Meissner et al., Autophagy. 2015, 11(9), 1484-1498). Upon mitochondrial depolarization or dysfunction, PINK1 accumulates in the MOM, recruiting and activating Parkin via PINK1-dependent phosphorylation of both ubiquitin and Parkin. Consequently, activated Parkin ubiquitinates MOM proteins like TOMM20 to trigger mitophagy (Pickrell et al., Neuron. 2015, 85(2), 257-273). USP30 is embedded in the MOM with its catalytic DUB domain oriented towards the cytosol and has been shown to antagonize Parkin-mediated ubiquitination of common substrates, consequently opposing Parkin-mediated mitophagy. Genetic silencing of USP30 results in increased ubiquitination of several Parkin substrates followed by increased mitophagy. In model organisms, USP30 depletion is able to rescue mitophagy defects caused by pathogenic Parkin mutations, as well as restore mitochondria morphology and function, and dopamine levels. (Nakamura, et al., Mol Biol Cell. 2008, 19(5), 1903-1911; Bingol, et al., Nature 2014, 510(7505):370-5). Therefore, inhibition of USP30 with a compound disclosed herein could present a novel treatment paradigm for PD by promoting mitochondrial turnover.

Definitions

[0012] As used herein, the term "alkyl" means a substituted or unsubstituted hydrocarbon chain that is completely saturated, including straight-chain alkyl groups and branched-chain alkyl groups, and that has a single point of attachment to the rest of the molecule. In some embodiments, a straight chain or branched chain alkyl has about 1-20 carbon atoms in its backbone (e.g., C_1-C_{20} for straight chain, C_2-C_{20} for branched chain), and alternatively, about 1-10. In some embodiments, an alkyl has about 1-8 carbon atoms. In some embodiments, an alkyl has about 1-6 carbon atoms. In some embodiments, an alkyl has about 1-5 carbon atoms. In some embodiments, an alkyl has about 1-4 carbon atoms. In some embodiments, an alkyl has about 1-3 carbon atoms. In some embodiments, an alkyl has about 1-2 carbon atoms.

[0013] As used herein, the term "alkylene" refers to a bivalent alkyl group. Exemplary alkylenes include $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_3)-$, etc. In some embodiments, an "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent.

[0014] As used herein, the term "alkenyl" refers to an alkyl group, as defined herein, having one or more double bonds.

[0015] As used herein, the term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent.

[0016] As used herein, the term "alkynyl" refers to an alkyl group, as defined herein, having one or more triple bonds.

[0017] The term "aryl" refers to ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system and exemplary groups include phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0018] The term "arylene" refers to a bivalent aryl group (e.g., phenylene).

[0019] As used herein, the term "cycloalkyl" refers to a cyclic alkyl group (e.g., a monocyclic

alkyl group or a bicyclic alkyl group). In some embodiments, "cycloalkyl" refers to a monocyclic C_3-C_8 cycloalkyl group. In some embodiments, "cycloalkyl" refers to a monocyclic C_3-C_6 cycloalkyl group.

[0020] The terms "halogen" or "halo" mean F, Cl, Br, or I.

[0021] The term "heteroaryl" refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms wherein the term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Exemplary heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The term "heteroaryl", as used herein, also includes groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Examplary groups include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted.

[0022] The term "heteroarylene" refers to a bivalent heteroaryl group.

[0023] As used herein, the term "heterocycloalkyl" refers to a stable 3- to 7-membered monocyclic or 7- to 10-membered bicyclic cyclic moiety that is saturated and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms independently selected from nitrogen, oxygen, and sulfur, including any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. As an example, in a saturated ring having 1-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or $^+$NR (as in *N*-substituted pyrrolidinyl). A heterocycloalkyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such heterocycloalkyl radicals include tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The term "heterocycloalkyl" also includes groups in which a heterocycloalkyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocycloalkyl ring.

[0024] As used herein, a "USP30 Inhibitor Compound" refers to a compound having an IC_{50} of

about 1 micromolar or less (i.e., an IC_{50} value of ≤ 1 μM and > 0.001 μM) in the Ubiquitin-Rhodamine 110 Assay for USP30 as described in Example 1 herein. For example, a USP30 Inhibitor can be a compound of formula (I) having an IC_{50} value of ≤ 0.5 μM and > 0.001 μM when tested in the Biochemical Assay of Example 1. In some embodiments, a USP30 Inhibitor is a compound of formula (I) having an IC_{50} value of ≤ 0.1 μM and > 0.001 μM when tested in the Biochemical Assay of Example 1.

[0025] As used herein, the term "pharmaceutically acceptable salt" refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, *i.e.,* salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977).

[0026] Unless otherwise stated, all chemical structures and chemical names depicted herein without stereochemical descriptors shall be understood to include all stereoisomeric (e.g., enantiomeric or diastereomeric) forms of the compound depicted by the structure or name, as well as all geometric and conformational isomeric forms of the compound; for example, the R and S configurations for each stereocenter. Unless otherwise stated, such structures and names shall be understood to include a stereochemically pure form of the compound and any mixture of enantiomers, diastereomers, or geometric (or conformational) isomers. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0027] Unless otherwise stated, all chemical structures and chemical names depicted herein with stereochemical descriptors (i.e., hash and wedge bonds in the chemical structures; (R)- and (S)- designators in the chemical names) shall be understood to refer to a compound having the relative stereochemistry (but not necessarily the absolute stereochemistry) indicated by the stereochemical descriptors. Unless otherwise stated, such structures and names shall be understood to include an enantiomerically pure form of the compound having the relative stereochemistry indicated by the stereochemical descriptors or any mixture of enantiomers. In some embodiments, the enantiomers are present in a racemic mixture. In other embodiments, the enantiomer having the absolute stereochemistry suggested by the stereochemical descriptors is present in substantially enantiomerically pure form. In other embodiments, the enantiomer having the absolute stereochemistry opposite to that suggested by the stereochemical descriptors is present in substantially enantiomerically pure form.

[0028] Unless otherwise stated, all chemical structures and chemical names depicted herein with stereochemical descriptors (i.e., hash and wedge bonds in the chemical structures; (R)- and (S)- designators in the chemical names) and an "absolute" descriptor ("abs") shall be understood to refer to a compound having the absolute stereochemistry indicated by the stereochemical descriptors. Unless otherwise stated, such structures and names shall be

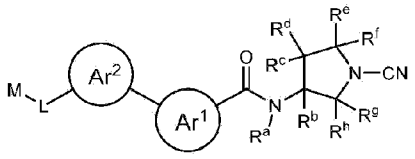
understood to include the compound in enantiomerically pure form or in a mixture with its enantiomer. In some embodiments, the enantiomers are present in a racemic mixture. In other embodiments, the enantiomer having the absolute stereochemistry indicated by the stereochemical descriptors is present in substantially enantiomerically pure form.

[0029] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[0030] It will be appreciated that throughout the present disclosure, unless otherwise indicated, reference to a compound of formula (I) is intended to also include formulas (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (LC-2), (LC-3), (I-C-4), (I-C-a), (I-C-b), (I-C-c), (I-C-d), (I-C-e), (LC-f), (I-D), (I-E), (I-E-1), (I-E-2), (I-E-3), (I-E-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), and (I-M-4), and compound species of such formulas disclosed herein.

Compounds of the Disclosure

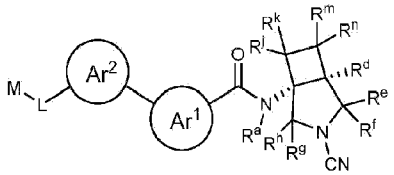
[0031] In one aspect, the disclosure relates to a compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein Ar^1, Ar^2, M, L, R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) above.

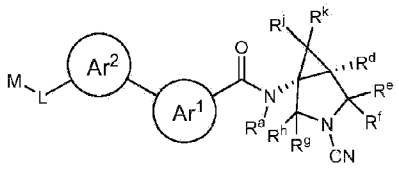
[0032] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-1):



(I-1)

wherein Ar^1, Ar^2, M, L, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) above, and wherein R^j, R^k, R^m, and R^n are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

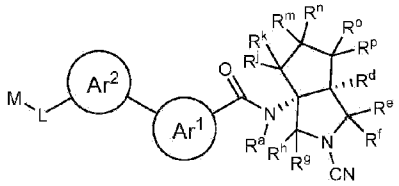
[0033] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-2):



(I-2)

wherein Ar^1, Ar^2, M, L, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) above, and wherein R^1 and R^k are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

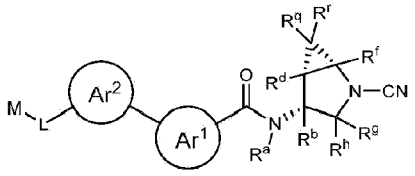
[0034] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-3):



(I-3)

wherein Ar^1, Ar^2, M, L, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) above, and wherein R^j R^k, R^m, R^n, R^o, and R^p are each independently hydrogen, halogen, C_1-C_3 alkyl, or Ci-C_3 haloalkyl.

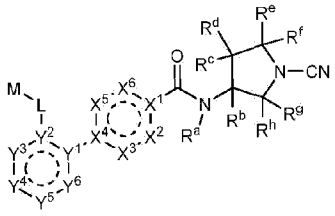
[0035] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-4):



(I-4)

wherein Ar^1, Ar^2, M, L, R^a, R^b, R^d, R^f, R^g, and R^h are all as defined for formula (I) above, and wherein R^q and R^r are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0036] In another aspect, the disclosure relates to a compound of formula (I-A):



(I-A);

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C or N;

X^2 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits;

X^3 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits;

X^4 is C or N;

X^5 is a bond, CH, CR^1, O, S, N, NH, or NR^1, as valency permits;

X^6 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits;

Y^1 is C or N;

Y^2 is C or N;

Y^3 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits;

Y^4 is a bond, CH, CR^2, O, S, N, NH, or NR^2, as valency permits;

Y^5 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits;

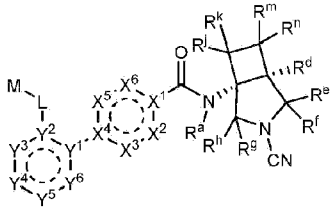
Y^6 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits,

provided that the ring comprising X^1, X^2, X^3, X^4, X^5, and X^6 is aromatic, and

that the ring comprising Y^1, Y^2, Y^3, Y^4, Y^5, and Y^6 is aromatic;

and wherein L, M, R^1, R^2, R^5, R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are are all as defined for formula (I) above.

[0037] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-A-1):



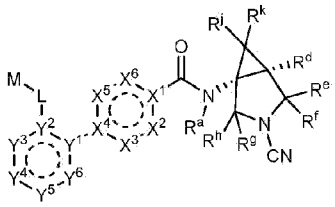
(I-A-1)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-A) above, and

wherein R^j, R^k, R^m, and R^n are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3

haloalkyl.

[0038] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-A-2):

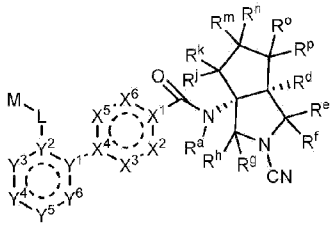


(I-A-2)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-A) above, and

wherein R^j and R^k are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0039] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-A-3):

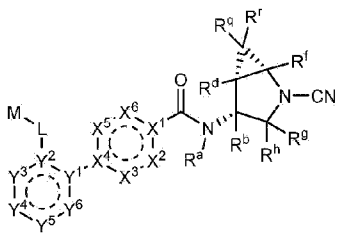


(I-A-3)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-A) above, and

wherein R^j, R^k, R^m, R^n, R^o, and R^p are each independently hydrogen, halogen, C_1-C_3 alkyl, or Ci-C_3 haloalkyl.

[0040] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-A-4):

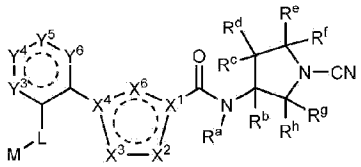


(I-A-4)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, R^a, R^b, R^d, R^f, R^g, and R^h are all as defined for formula (I-A) above, and

wherein R^q and R^r are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0041] In another aspect, the disclosure relates to a compound of formula (I-B):



(I-B);

or a pharmaceutically acceptable salt thereof, wherein:

Y^3 is CH, CR^2, or N;

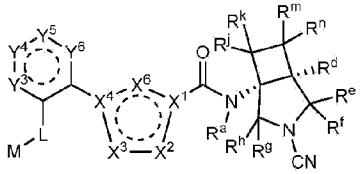
Y^4 is CH, CR^2, or N;

Y^5 is CH, CR^2, or N;

Y^6 is CH, CR^2, or N; and

wherein X^1, X^2, X^3, X^4, X^6, L, M, R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) above.

[0042] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-B-1):

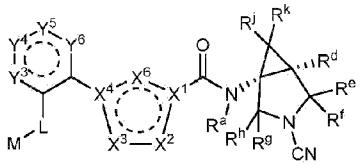


(I-B-1)

wherein M, L, X^1, X^2, X^3, X^4, X^6, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-B) above, and

wherein R^j, R^k, R^m, and R^n are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0043] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-B-2):

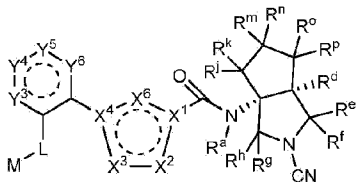


(I-B-2)

wherein M, L, X^1, X^2, X^3, X^4, X^6, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-B) above, and

wherein R^j and R^k are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0044] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-B-3):

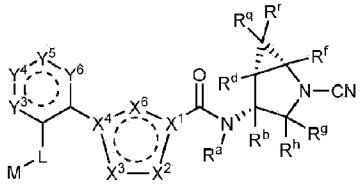


(I-B-3)

wherein M, L, X^1, X^2, X^3, X^4, X^6, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-B) above, and

wherein R^j, R^k, R^m, R^n, R^o, and R^p are each independently hydrogen, halogen, C_1-C_3 alkyl, or Ci-C_3 haloalkyl.

[0045] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-B-4):

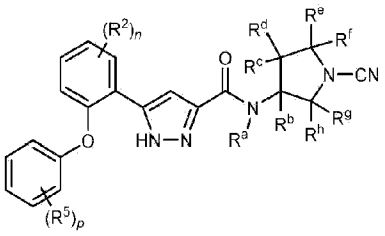


(I-B-4)

wherein M, L, X^1, X^2, X^3, X^4, X^6, Y^3, Y^4, Y^5, Y^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-B) above, and

wherein R^q and R^r are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

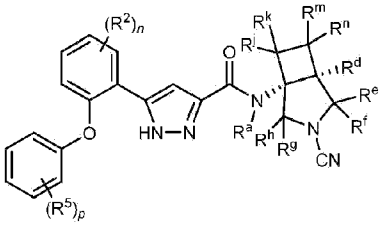
[0046] In another aspect, the disclosure relates to a compound of formula (I-C):



(I-C)

or a pharmaceutically acceptable salt thereof, wherein R^2, R^5, *n, p,* R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are are all as defined for formula (I) above.

[0047] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-C-1):

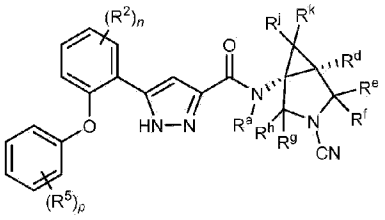


(I-C-1)

wherein R^2, R^5, *n, p,* R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-C) above, and

wherein R^j, R^k, R^m, and R^n are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0048] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-C-2):

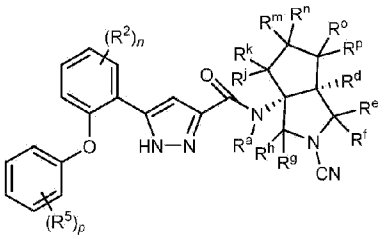


(I-C-2)

wherein R^2, R^5, *n, p,* R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-C) above, and

wherein R^j and R^k are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0049] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-C-3):

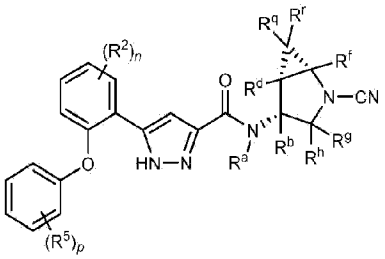


(I-C-3)

wherein R^2, R^5, *n, p,* R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-C) above, and

wherein R^j, R^k, R^m, R^n, R^o, and R^p are each independently hydrogen, halogen, C_1-C_3 alkyl, or Ci-C_3 haloalkyl.

[0050] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-C-4):

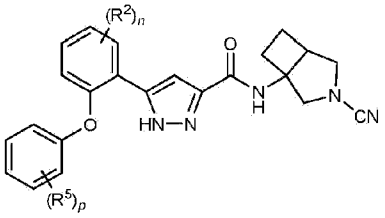


(I-C-4)

wherein R^2, R^5, *n, p,* R^a, R^b, R^d, R^f, R^g, and R^h are all as defined for formula (I-C) above, and

wherein R^q and R^r are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0051] In some embodiments, the disclosure relates to a compound of formula (I-C), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-a):

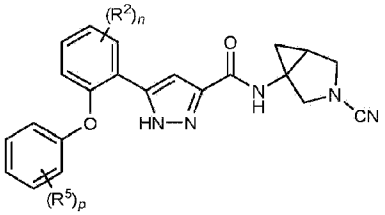


(I-C-a)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

[0052] In some embodiments, the disclosure relates to a compound of formula (I-C), or a

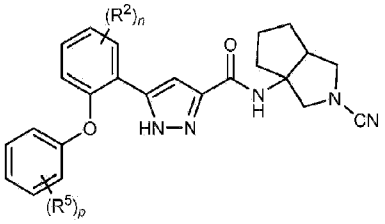
pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-b):



(I-C-b)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

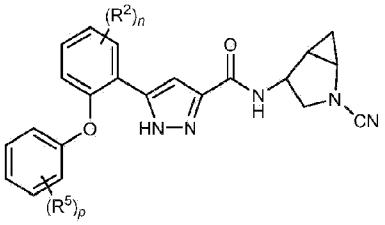
[0053] In some embodiments, the disclosure relates to a compound of formula (I-C), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-c):



(I-C-c)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

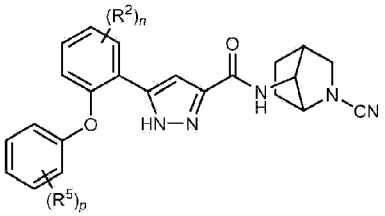
[0054] In some embodiments, the disclosure relates to a compound of formula (I-C), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-d):



(I-C-d)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

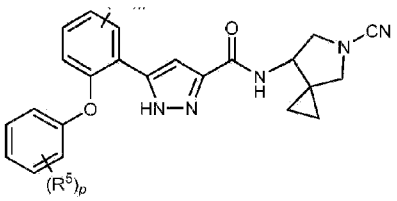
[0055] In some embodiments, the disclosure relates to a compound of formula (I-C), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-e):



(I-C-e)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

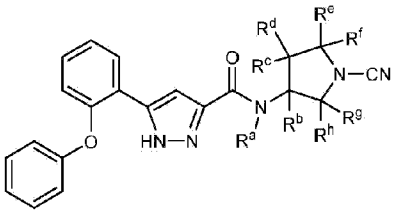
[0056] In some embodiments, the disclosure relates to a compound of formula (I-C), or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-C-f):



(I-C-f)

wherein R^2, R^5, *n,* and *p* are all as defined for formula (I-C) above.

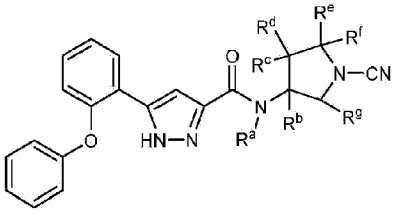
[0057] In another aspect, the disclosure relates to a compound of formula (I-D):



(I-D)

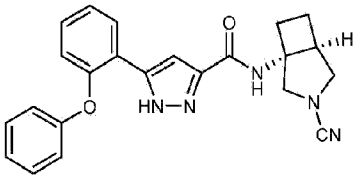
or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are all as defined for formula (I) above.

[0058] In another aspect, the disclosure relates to a compound of formula (I-E):



(I-E)

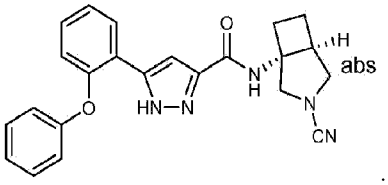
or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, and R^g are all as defined for formula (I) above. In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-E-1):



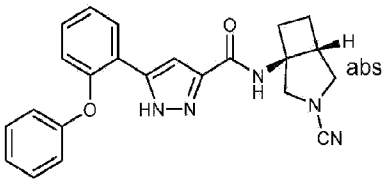
(I-E-1).

[0059] In some embodiments, the compound of formula (I-E-1) has the absolute stereochemistry of the first eluting isomer when a racemic mixture of the compound of formula (I-E-1) is separated by the procedure described in Example 3, Step 6. In some embodiments, the compound of formula (I-E-1) has the absolute stereochemistry of the second eluting isomer when a racemic mixture of the compound of formula (I-E-1) is separated by the procedure described in Example 3, Step 6.

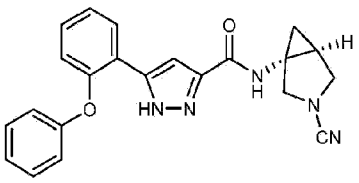
[0060] In some embodiments, the compound of formula (I-E-1) is:



[0061] In some embodiments, the compound of formula (I-E-1) is:



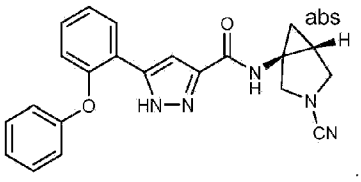
[0062] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-E-2):



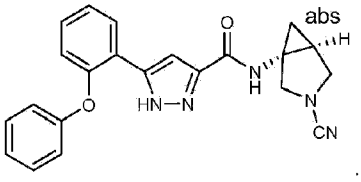
(I-E-2).

[0063] In some embodiments, the compound of formula (I-E-2) has the absolute stereochemistry of the first eluting isomer when a racemic mixture of the compound of formula (I-E-2) is separated by the procedure described in Example 4, Step 6. In some embodiments, the compound of formula (I-E-2) has the absolute stereochemistry of the second eluting isomer when a racemic mixture of the compound of formula (I-E-2) is separated by the procedure described in Example 4, Step 6.

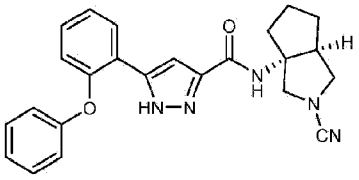
[0064] In some embodiments, the compound of formula (I-E-2) is:



[0065] In some embodiments, the compound of formula (I-E-2) is:



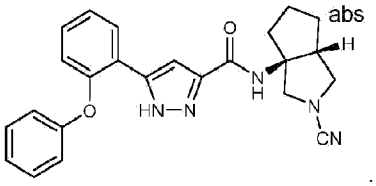
[0066] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-E-3):



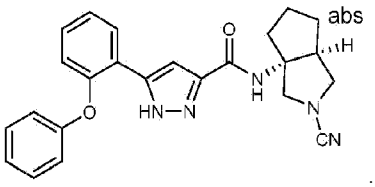
(I-E-3).

[0067] In some embodiments, the compound of formula (I-E-3) has the absolute stereochemistry of the first eluting isomer when a racemic mixture of the compound of formula (I-E-3) is separated by the procedure described in Example 2, Step 7. In some embodiments, the compound of formula (I-E-3) has the absolute stereochemistry of the second eluting isomer when a racemic mixture of the compound of formula (I-E-3) is separated by the procedure described in Example 2, Step 7.

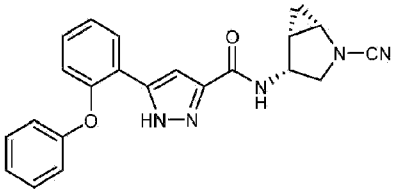
[0068] In some embodiments, the compound of formula (I-E-3) is:



[0069] In some embodiments, the compound of formula (I-E-3) is:



[0070] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-E-4):

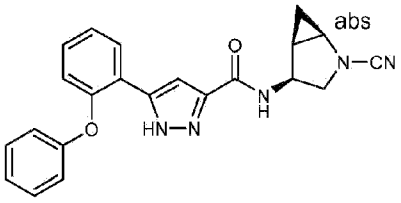


(I-E-4).

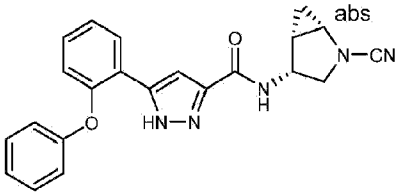
[0071] In some embodiments, the compound of formula (I-E-4) has the absolute stereochemistry of the first eluting isomer when a racemic mixture of the compound of formula (I-E-4) is separated by the procedure described in Example 2, Step 7. In some embodiments,

the compound of formula (I-E-4) has the absolute stereochemistry of the second eluting isomer when a racemic mixture of the compound of formula (I-E-4) is separated by the procedure described in Example 2, Step 7.

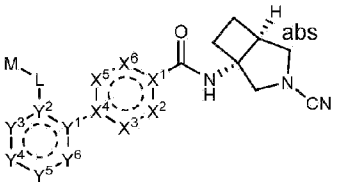
[0072] In some embodiments, the compound of formula (I-E-4) is:



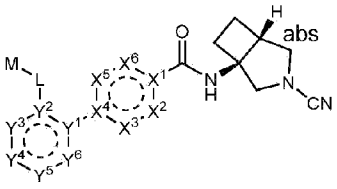
[0073] In some embodiments, the compound of formula (I-E-4) is:



[0074] In another aspect, the disclosure relates to a compound of formula (I-F-1) or (I-F-2):



(I-F-1)

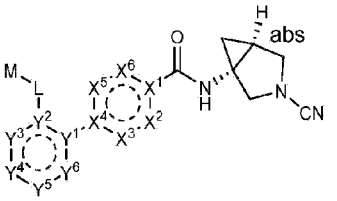


(I-F-2)

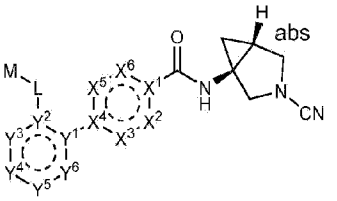
or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, L, and M are all as defined for formula (I-A) above.

[0075] In some embodiments, the compounds of formula (I-F-1) and (I-F-2) are present in a racemic mixure. In other embodiments, the compound of formula (I-F-1) or (I-F-2) is present in substantially enantiomerically pure form. The compounds of formula (I-F-1) and (I-F-2) can be separated from one another by chiral HPLC, such as by the procedure described in Example 2, Step 7 or Example 3, Step 6.

[0076] In another aspect, the disclosure relates to a compound of formula (I-G-1) or (I-G-2):



(I-G-1)



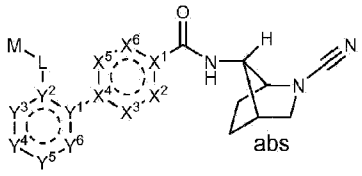
(I-G-2)

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5,

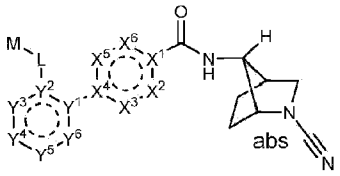
Y^6, L, and M are all as defined for formula (I-A) above.

[0077] In some embodiments, the compounds of formula (I-G-1) and (I-G-2) are present in a racemic mixure. In other embodiments, the compound of formula (I-G-1) or (I-G-2) is present in substantially enantiomerically pure form. The compounds of formula (I-G-1) and (I-G-2) can be separated from one another by chiral HPLC, such as by the procedure described in Example 2, Step 7, or Example 4, Step 6.

[0078] In another aspect, the disclosure relates to a compound of formula (I-H-1) or (I-H-2):



(I-H-1)

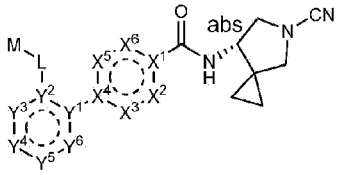


(I-H-2)

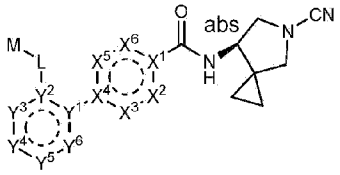
or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, L, and M are all as defined for formula (I-A) above.

[0079] In some embodiments, the compounds of formula (I-H-1) and (I-H-2) are present in a racemic mixure. In other embodiments, the compound of formula (I-H-1) or (I-H-2) is present in substantially enantiomerically pure form. The compounds of formula (I-H-1) and (I-H-2) can be separated from one another by chiral HPLC, such as by the procedure described in Example 2, Step 7.

[0080] In another aspect, the disclosure relates to a compound of formula (I-J-1) or (I-J-2):



(I-J-1)

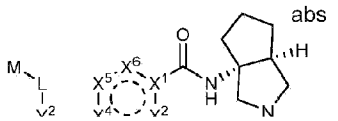


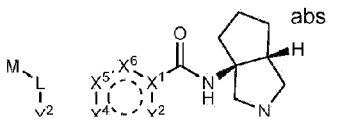
(I-J-2)

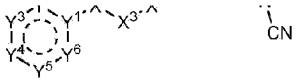
or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, L, and M are all as defined for formula (I-A) above.

[0081] In some embodiments, the compounds of formula (I-J-1) and (I-J-2) are present in a racemic mixure. In other embodiments, the compound of formula (I-J-1) or (I-J-2) is present in substantially enantiomerically pure form. The compounds of formula (I-J-1) and (I-J-2) can be separated from one another by chiral HPLC, such as by the procedure described in Example 2, Step 7.

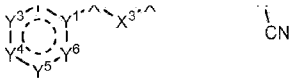
[0082] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-K-1) or (I-K-2):







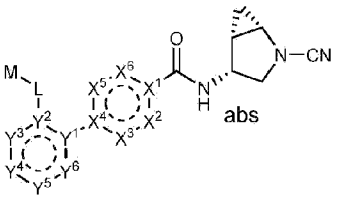
(I-K-1)



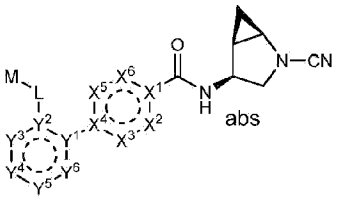
(I-K-2)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, and Y^6 are all as defined for formula (I-A) above.

[0083] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-L-1) or (I-L-2):



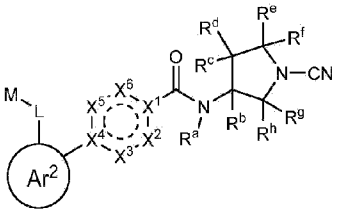
(I-L-1)



(I-L-2)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, Y^1, Y^2, Y^3, Y^4, Y^5, and Y^6 are all as defined for formula (I-A) above.

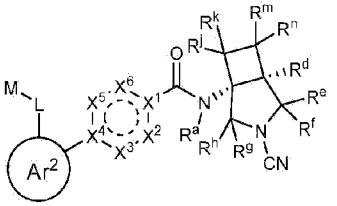
[0084] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-M):



(I-M)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I) and (I-A) above.

[0085] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-M-1):

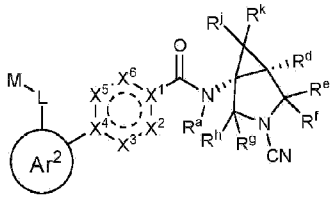


(I-M-1)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-M) above, and

wherein R^j, R^k, R^m, and R^n are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0086] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-M-2):

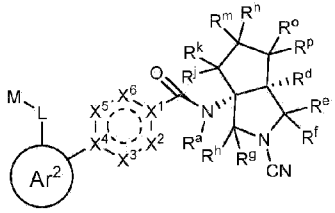


(I-M-2)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-M) above, and

wherein R^j and R^k are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0087] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-M-3):

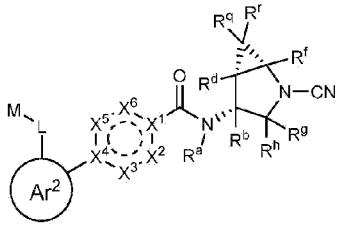


(I-M-3)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, R^a, R^d, R^e, R^f, R^g, and R^h are all as defined for formula (I-M) above, and

wherein R^j, R^k, R^m, R^n, R^o, and R^p are each independently hydrogen, halogen, C_1-C_3 alkyl, or Ci-C_3 haloalkyl.

[0088] In some embodiments, the present disclosure provides compounds, or pharmaceutically acceptable salts thereof, of formula (I-M-4):



(I-M-4)

wherein M, L, X^1, X^2, X^3, X^4, X^5, X^6, R^a, R^b, R^d, R^f, R^g, and R^h are all as defined for formula (I-

M) above, and

wherein R^q and R^r are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0089] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), or (I-4), or a pharmaceutically acceptable salt thereof, wherein Ar^1 is independently phenylene or 5-6 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *m* R^1 groups. In some embodiments, Ar^1 is phenylene substituted with *m* R^1 groups. In some embodiments, Ar^1 is phenylene substituted with 1-2 R^1 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, Ar^1 is phenylene. In some embodiments, Ar^1 is 5-6 membered heteroarylene substituted with *m* R^1 groups. In some embodiments, Ar^1 is 5-6 membered heteroarylene substituted with 1-2 R^1 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, Ar^1 is 5-membered heteroarylene substituted with *m* R^1 groups. In some embodiments, Ar^1 is pyrazole. In some embodiments, Ar^1 is thiazole. In some embodiments, Ar^1 is 6-membered heteroarylene substituted with *m* R^1 groups.

[0090] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein Ar^2 is independently phenylene or 5-10 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *n* R^2 groups. In some embodiments, Ar^2 is phenylene or 5-6 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *n* R^2 groups. In some embodiments, Ar^2 is phenylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is phenylene substituted with 1-2 R^2 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, Ar^2 is phenylene. In some embodiments, Ar^2 is 5-10 membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is 5-6 membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is 5-6 membered heteroarylene substituted with 1-2 R^2 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, Ar^2 is 5-membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is 6-membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is pyridine. In some embodiments, Ar^2 is 7-membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is 8-membered heteroarylene substituted with *n* R^2 groups. In some embodiments, Ar^2 is 9-membered heteroarylene

substituted with *n* R^2 groups. In some embodiments, Ar^2 is 10-membered heteroarylene substituted with n R^2 groups.

[0091] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (IF-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein L is -O-, -S-, $-NR^3-$, $-C(R^4)_2-$, $-S(O)_2-$, or -S(O)-. In some embodiments, L is -O-, -S-, or -NH-. In some embodiments, L is -O-. In some embodiments, L is -S-. In some embodiments, L is $-NR^3-$. In some embodiments, L is -NH-. In some embodiments, L is $-C(R^4)_2-$. In some embodiments, L is $-CH_2-$. In some embodiments, L is $-S(O)_2-$. In some embodiments, L is -S(O)-.

[0092] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (IF-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein M is 3-6 membered cycloalkyl, phenyl, or 5-6 membered heteroaryl, wherein said cycloalkyl, phenyl, or heteroaryl is substituted with *p* R^5 groups. In some embodiments, M is 3-6 membered cycloalkyl substituted with *p* R^5 groups. In some embodiments, M is 3-6 membered cycloalkyl. In some embodiments, M is 3-6 membered cycloalkyl substituted with 1-2 R^5 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, M is phenyl substituted with *p* R^5 groups. In some embodiments, M is phenyl. In some embodiments, M is phenyl substituted with 1-2 R^5 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 hydroxyalkyl. In some embodiments, M is phenyl substituted with fluoro. In some embodiments, M is 5-6 membered heteroaryl substituted with *p* R^5 groups. In some embodiments, M is 5-6 membered heteroaryl. In some embodiments, M is 5-6 membered heteroaryl substituted with 1-2 R^5 groups selected from the group consisting of halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl.

[0093] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (LC-2), (LC-3), (I-C-4), (I-C-a), (I-C-b), (I-C-c), (I-C-d), (I-C-e), (LC-f), (LF-1), (IF-2), (I-G-1), (I-G-2), (LH-1), (LH-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein each occurrence of R^1, R^2, and R^5 is independently halo, cyano, NO_2, oxo, hydroxyl, $-R^6$, $-OR^6$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-C_1$-C_6 alkylene-R^6, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $-C_0$-C_3 alkylene-NR^6R^7, $-C_0$-C_3 alkylene-NR^7R^8, $-C_0$-C_3 alkylene-$C(O)NR^6R^7$, $-C_0$-C_3 alkylene-$C(O)NR^7R^8$, $-C_0$-C_3 alkylene-$NR^7C(O)R^6$, $-C_0$-C_3 alkylene-$NR^7C(O)R^8$, $-C_0$-C_3 alkylene-

$NR^7S(O)_2R^6$, -C_0-C_3 alkylene-$C(O)R^6$, -C_0-C_3 alkylene-$C(O)R^7$, -C_0-C_3 alkylene-SR^6, -C_0-C_3 alkylene-$S(O)R^6$, -C_0-C_3 alkylene-$S(O)_2R^6$, -C_0-C_3 alkylene-$S(O)_2R^7$, -C_0-C_3 alkylene$S(O)_2NR^6R^7$, -C_0-C_3 alkylene-$S(O)_2NR^7R^8$, -C_0-C_3 alkylene-$NR^7C(O)NR^8R^9$, -C_0-C_3 alkylene-$NR^7S(O)_2NR^8R^9$, -C_0-C_3 alkylene-$C(O)OR^7$, -C_0-C_3 alkylene-$C(O)OR^6$, -C_0-C_3 alkylene-$OC(O)R^7$, -C_0-C_3 alkylene-$OC(O)R^6$, -C_0-C_3 alkylene-$NR^7C(O)OR^8$, or -C_0-C_3 alkylene-$NR^7S(O)_2R^8$. In some embodiments, each occurrence of R^1 is independently halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, each occurrence of R^1 is independently halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, each occurrence of R^1 is fluoro. In some embodiments, each occurrence of R^1 is cyano. In some embodiments, each occurrence of R^1 is hydroxyl. In some embodiments, each occurrence of R^1 is C_1-C_6 alkyl. In some embodiments, each occurrence of R^1 is C_1-C_6 alkoxy. In some embodiments, each occurrence of R^1 is C_1-C_6 haloalkyl. In some embodiments, each occurrence of R^1 is C_1-C_6 hydroxyalkyl. In some embodiments, each occurrence of R^2 is independently halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, each occurrence of R^2 is independently halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, each occurrence of R^2 is fluoro. In some embodiments, each occurrence of R^2 is cyano. In some embodiments, each occurrence of R^2 is hydroxyl. In some embodiments, each occurrence of R^2 is C_1-C_6 alkyl. In some embodiments, each occurrence of R^2 is C_1-C_6 alkoxy. In some embodiments, each occurrence of R^2 is C_1-C_6 haloalkyl. In some embodiments, each occurrence of R^2 is C_1-C_6 hydroxyalkyl. In some embodiments, each occurrence of R^5 is independently halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl. In some embodiments, each occurrence of R^5 is independently halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, each occurrence of R^5 is fluoro. In some embodiments, each occurrence of R^5 is cyano. In some embodiments, each occurrence of R^5 is hydroxyl. In some embodiments, each occurrence of R^5 is C_1-C_6 alkyl. In some embodiments, each occurrence of R^5 is C_1-C_6 alkoxy. In some embodiments, each occurrence of R^5 is C_1-C_6 haloalkyl. In some embodiments, each occurrence of R^5 is C_1-C_6 hydroxyalkyl.

[0094] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (IF-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein R^3 is H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. In some embodiments, R^3 is H. In some embodiments, R^3 is

C_1-C_6 alkyl. In some embodiments, R^3 is C_1-C_6 haloalkyl.

[0095] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (IF-1), (I-F-2), (I-G-1), (I-G-2), (LH-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, or two R^4 groups together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl or heterocycloalkyl. In some embodiments, each R^4 is H. In some embodiments, two R^4 groups together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl. In some embodiments, two R^4 groups together with the carbon atom to which they are attached form a 3-6 membered heterocycloalkyl.

[0096] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (LC-2), (LC-3), (LC-4), (LC-a), (LC-b), (I-C-c), (I-C-d), (I-C-e), (I-C-f), (LF-1), (IF-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (LL-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein each R^6 is 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl, wherein said heteroaryl, heterocycloalkyl, aryl, or cycloalkyl is optionally substituted with 1-5 substituents independently selected from the group consisting of halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, 3-8 membered cycloalkyl, $-NR^{10}C(O)NR^{11}R^{12}$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)OR^{11}$, $-S(O)_2R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(O)OR^{10}$, $-S(O)_2NR^{10}R^{11}$, $-NR^{10}S(O)_2R^{11}$, $-OR^{10}$, $-OC(O)R^{10}$, $-OS(O)_2R^{10}$, $-OC(O)NR^{10}R^{11}$, $-OC(O)OR^{10}$, $-OS(O)_2NR^{10}R^{11}$, $-C(O)NR^{10}C(O)NR^{11}R^{12}$, $-C(O)C(O)R^{10}$, $-C(O)NR^{10}C(O)R^{11}$, $-C(O)NR^{10}C(O)OR^{11}$, $-C(O)S(O)_2R^{10}$, $-C(O)C(O)NR^{10}R^{11}$, $-C(O)C(O)OR^{10}$, $-C(O)S(O)_2NR^{10}R^{11}$, $-C(O)NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkylene-R^{10}, $-C_1$-C_6 alkylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)R^{10}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)OR^{10}$, $-C_1$-C_6 alkyleneS$(O)_2NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkenylene-R^{10}, $-C_1$-C_6 alkenylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkenylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)R^{10}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkenylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkenylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)OR^{10}$, $-C_1$-C_6 alkenylene-$S(O)_2NR^{10}R^{11}$, and $-C_1$-C_6 alkenylene-$NR^{10}S(O)_2R^{11}$. In some embodiments, each R^6 is independently optionally substituted 5-10 membered heteroaryl. In some embodiments, each R^6 is

independently optionally substituted 4-10 membered heterocycloalkyl. In some embodiments, each R^6 is independently optionally substituted 6-10 membered aryl. In some embodiments, each R^6 is independently optionally substituted 3-8 membered cycloalkyl.

[0097] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (I-C-2), (LC-3), (I-C-4), (I-C-a), (I-C-b), (I-C-c), (I-C-d), (I-C-e), (I-C-f), (LF-1), (IF-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein each R^7, R^8, and R^9 is independently hydrogen or C_1-C_6 alkyl. In some embodiments, each R^7, R^8, and R^9 is independently hydrogen.

[0098] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (I-C-2), (LC-3), (LC-4), (I-C-a), (LC-b), (I-C-c), (I-C-d), (I-C-e), (I-C-f), (LF-1), (IF-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (LL-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein each R^{10}, R^{11}, and R^{12} is independently hydrogen, C_1-C_6 alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl. In some embodiments, each R^{10}, R^{11}, and R^{12} is independently hydrogen.

[0099] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), or (I-4), or a pharmaceutically acceptable salt thereof, wherein *m* is 0-4 (i.e., *m* is 0, 1, 2, 3, or 4). In some embodiments, *m* is 0. In some embodiments, *m* is 1. In some embodiments, *m* is 2. In some embodiments, *m* is 3. In some embodiments, *m* is 4. In some embodiments, *m* is 0, 1, or 2. In some embodiments, *m* is 1 or 2.

[0100] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-C), (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-C-a), (I-C-b), (I-C-c), (I-C-d), (I-C-e), (I-C-f), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein *n* is 0-4 (i.e., *n* is 0, 1, 2, 3, or 4). In some embodiments, *n* is 0. In some embodiments, *n* is 1. In some embodiments, *n* is 2. In some embodiments, *n* is 3. In some embodiments, *n* is 4. In some embodiments, *n* is 0, 1, or 2. In some embodiments, *n* is 1 or 2.

[0101] In some embodiments, the disclosure relates to a compound of formula (I), (I-1), (I-2), (I-3), (I-4), (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C), (I-C-1), (I-C-2), (I-C-3), (LC-4), (I-C-a), (I-C-b), (I-C-c), (I-C-d), (I-C-e), (I-C-f), (LF-1), (IF-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (LL-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein *p* is 0-4 (i.e., *p* is 0, 1, 2, 3, or 4). In some embodiments, *p* is 0. In some embodiments, *p* is 1. In some embodiments, *p* is 2. In some embodiments, *p* is 3. In some embodiments, *p* is 4. In some embodiments, *p* is 0, 1, or 2. In some embodiments, *p* is 1 or 2. In some embodiments, *n* and

p are both 0. In some embodiments, *m* and *n* are both 0. In some embodiments, *m* and *n* are both 0. In some embodiments, *m, n,* and *p* are 0. In some embodiments, *m* and *n* are 0, and *p* is 1.

[0102] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a and R^b form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^a and R^b form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^c, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^b form a C_1 alkylene group between the atoms to which they are attached; and R^c, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^b form a C_2 alkylene group between the atoms to which they are attached; and R^c, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^b form a C_3 alkylene group between the atoms to which they are attached; and R^c, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^b form a C_4 alkylene group between the atoms to which they are attached; and R^c, R^d, R^e, R^f, R^g, and R^h are each hydrogen.

[0103] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^e form a C_1 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^a and R^e form a C_2 alkylene group between the atoms to which they are attached, and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen.

[0104] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^a and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^a and R^g form a C_1 alkylene group between the

atoms to which they are attached; and R^b, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^a and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^a and R^g form a C_3 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^e, R^f, and R^h are each hydrogen.

[0105] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^c form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^c form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^c form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^c form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^c form a C_4 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen.

[0106] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^b and R^e form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^b and R^e form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^e form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^e form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^b and R^e form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^f, R^g, and R^h are each hydrogen.

[0107] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B),

(I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^b and R^g form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^b and R^g form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^b and R^g form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^b and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^b and R^g form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^b and R^g form a C_4 alkylene group between the atoms to which they are attached; and R^a, R^c, R^d, R^e, R^f, and R^h are each hydrogen.

[0108] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3 membered cycloalkyl or a 4 membered heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3 membered cycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, $R^c$and R^d together with the atom to which they are attached, form a 4 membered cycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 5 membered cycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 6 membered cycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3-6 membered heterocycloalkyl ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3-6

membered heterocycloalkyl ring, wherein the 3-6 membered heterocycloalkyl ring contains O, S, or NH; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 3 membered heterocycloalkyl ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 4 membered heterocycloalkyl ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form an oxetane ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 5 membered heterocycloalkyl ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together with the atom to which they are attached, form a 6 membered heterocycloalkyl ring; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^d together form =O. In some embodiments, R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen.

[0109] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^e form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^e form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^e form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen. In some embodiments, R^c and R^e form a C_4 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen.

[0110] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^c and R^g form a C_1-C_2 alkylene group between

the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^c and R^g form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^c and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen. In some embodiments, R^c and R^g form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen.

[0111] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 4 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 5 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 6 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3-6 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3-6 membered heterocycloalkyl ring, wherein the 3-6 membered heterocycloalkyl ring contains O, S, or NH; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 3 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 4 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form an oxetane ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 5 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each

hydrogen. In some embodiments, R^e and R^f together with the atom to which they are attached, form a 6 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen. In some embodiments, R^e and R^f together form =O. In some embodiments, R^e and R^f together form =O; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen.

[0112] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each hydrogen. In some embodiments, R^e and R^g form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^b are each hydrogen. In some embodiments, R^e and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each hydrogen. In some embodiments, R^e and R^g form a C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each hydrogen.

[0113] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^g and R^h together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3-6 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 4 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 5 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 6 membered cycloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3-6

membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3-6 membered heterocycloalkyl ring, wherein the 3-6 membered heterocycloalkyl ring contains O, S, or NH; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 3 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 4 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form an oxetane ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 5 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together with the atom to which they are attached, form a 6 membered heterocycloalkyl ring; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen. In some embodiments, R^g and R^h together form =O. In some embodiments, R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen.

[0114] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

[0115] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen; or

(iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen; or

(x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen; or

(xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen; or

(xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen; or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen.

[0116] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen; or

(iv) R^b and R^c form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-membered cycloalkyl or a 4-membered heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(ix) R^c and R^e form a C_1 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen; or

(x) R^c and R^g form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen; or

(xi) R^e and R^f together with the atom to which they are attached, form a 4-membered heterocycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen; or

(xiii) R^e and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen; or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen.

[0117] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, and R^g are each hydrogen; or

(iv) R^b and R^c form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^e, R^d, R^f, and R^g are each hydrogen; or

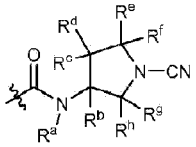
(vii) R^c and R^d together with the atom to which they are attached, form a 3 membered cycloalkyl; and R^a, R^b, R^e, R^f, and R^g are each hydrogen; or

(x) R^c and R^g form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, and R^f are each hydrogen; or

(xi) R^e and R^f together with the atom to which they are attached, form a 4 membered heterocycloalkyl; and R^a, R^b, R^c, R^d, and R^g are each hydrogen; or

(xiii) R^e and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, and R^f are each independently hydrogen.

[0118] In some embodiments, the disclosure relates to a compound of formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), or (I-M), or a pharmaceutically acceptable salt thereof, wherein



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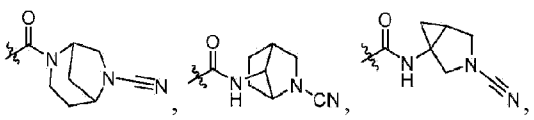

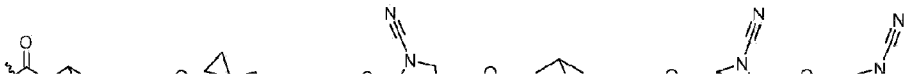

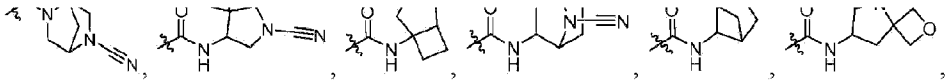

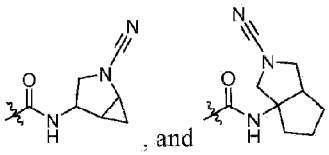

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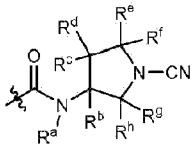

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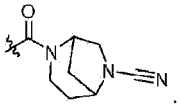

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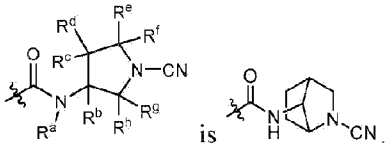

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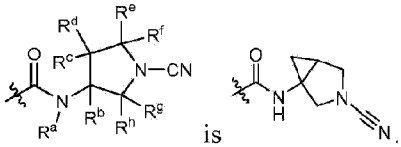

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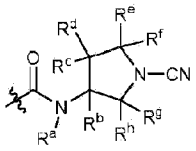

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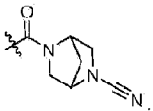

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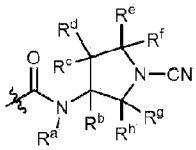

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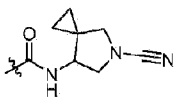

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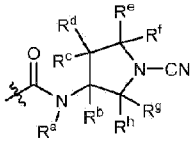

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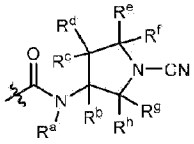
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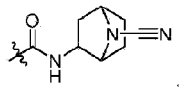

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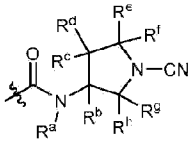
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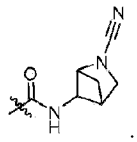

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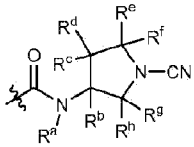

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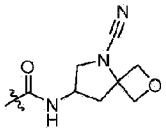

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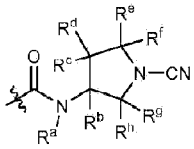

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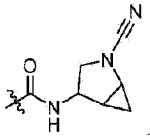

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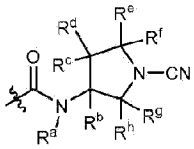

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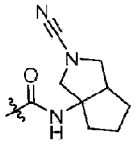


[0119] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (LH-1), (I-H-2), (LJ-1), (I-J-2), (LK-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C or N. In some embodiments, X^1 is C. In some embodiments, X^1 is N.

[0120] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-

1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^2 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits. In some embodiments, X^2 is CH. In some embodiments, X^2 is CR^1. In some embodiments, X^2 is O. In some embodiments, X^2 is S. In some embodiments, X^2 is N. In some embodiments, X^2 is NH. In some embodiments, X^2 is NR^1.

[0121] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (LH-1), (I-H-2), (LJ-1), (I-J-2), (LK-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^3 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits. In some embodiments, X^3 is CH. In some embodiments, X^3 is CR^1. In some embodiments, X^3 is O. In some embodiments, X^3 is S. In some embodiments, X^3 is N. In some embodiments, X^3 is NH. In some embodiments, X^3 is NR^1.

[0122] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (LH-1), (I-H-2), (LJ-1), (I-J-2), (I-K-1), (I-K-2), (LL-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^4 is C or N. In some embodiments, X^4 is C. In some embodiments, X^4 is N.

[0123] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^5 is a bond, CH, CR^1, O, S, N, NH, or NR^1, as valency permits. In some embodiments, X^5 is a bond. In some embodiments, X^5 is CH. In some embodiments, X^5 is CR^1. In some embodiments, X^5 is O. In some embodiments, X^5 is S. In some embodiments, X^5 is N. In some embodiments, X^5 is NH. In some embodiments, X^5 is NR^1.

[0124] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^6 is CH, CR^1, O, S, N, NH, or NR^1, as valency permits. In some embodiments, X^6 is CH. In some embodiments, X^6 is CR^1. In some embodiments, X^6 is O. In some embodiments, X^6 is S. In some embodiments, X^6 is N. In some embodiments, X^6 is NH. In some embodiments, X^6 is NR^1.

[0125] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-

K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; X^4 is C; X^5 is a bond; and X^6 is CH.

[0126] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is CH; X^4 is C; X^5 is a bond; and X^6 is S.

[0127] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), (I-L-2), (I-M), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is CH; X^3 is CH; X^4 is C; X^5 is CH; and X^6 is C.

[0128] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C or N. In some embodiments, Y^1 is C. In some embodiments, Y^1 is N.

[0129] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^2 is C or N. In some embodiments, Y^2 is C. In some embodiments, Y^2 is N.

[0130] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits. In some embodiments, Y^3 is CH. In some embodiments, Y^3 is CR^2. In some embodiments, Y^3 is O. In some embodiments, Y^3 is S. In some embodiments, Y^3 is N. In some embodiments, Y^3 is NH. In some embodiments, Y^3 is NR^2.

[0131] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^4 is a bond, CH, CR^2, O, S, N, NH, or NR^2, as valency permits. In some embodiments, Y^4 is a bond. In some embodiments, Y^4 is CH. In some embodiments, Y^4 is CR^2. In some embodiments, Y^4 is O. In some embodiments, Y^4 is S. In some embodiments, Y^4 is N. In some embodiments, Y^4 is NH. In some embodiments, Y^4 is NR^2.

[0132] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-

A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^5 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits. In some embodiments, Y^5 is CH. In some embodiments, Y^5 is CR^2. In some embodiments, Y^5 is O. In some embodiments, Y^5 is S. In some embodiments, Y^5 is N. In some embodiments, Y^5 is NH. In some embodiments, Y^5 is NR^2.

[0133] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-B), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^6 is CH, CR^2, O, S, N, NH, or NR^2, as valency permits. In some embodiments, Y^6 is CH. In some embodiments, Y^6 is CR^2. In some embodiments, Y^6 is O. In some embodiments, Y^6 is S. In some embodiments, Y^6 is N. In some embodiments, Y^6 is NH. In some embodiments, Y^6 is NR^2.

[0134] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0135] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CR^2; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0136] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CR^2; Y^5 is CH; and Y^6 is CH.

[0137] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is CR^2; and Y^6 is CH.

[0138] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is N; Y^4 is CH; Y^5 is CH; and Y^6 is CR^2. In some embodiments, the disclosure relates to a compound of formula (I-A), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is

C; Y^3 is N; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0139] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C, Y^2 is C; Y^3 is CH; Y^4 is N; Y^5 is CH; and Y^6 is CH.

[0140] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (I-L-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is N; and Y^6 is CH.

[0141] In some embodiments, the disclosure relates to a compound of formula (I-A), (I-A-1), (I-A-2), (I-A-3), (I-A-4), (I-F-1), (I-F-2), (I-G-1), (I-G-2), (I-H-1), (I-H-2), (I-J-1), (I-J-2), (I-K-1), (I-K-2), (LL-1), or (I-L-2), or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is N.

[0142] In some embodiments, the disclosure relates to a compound of formula (LA-1), (I-A-2), (I-A-3), (I-A-4), (I-B-1), (I-B-2), (I-B-3), (I-B-4), (I-C-1), (I-C-2), (I-C-3), (I-C-4), (I-M-1), (I-M-2), (I-M-3), or (I-M-4), or a pharmaceutically acceptable salt thereof, wherein R^j, R^k, R^m, R^n, R^o, R^p, R^q, and R^r, when present, are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl. In some embodiments, R^j, R^k, R^m, R^n, R^o, R^p, R^q, and R^r, when present, are each hydrogen.

[0143] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; X^4 is C; and X^6 is CH.

[0144] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is CH; X^4 is C; and X^6 is S.

[0145] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0146] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^2; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0147] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CR^2; Y^5 is CH; and Y^6 is CH.

[0148] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CH; Y^5 is CR^2; and Y^6 is CH.

[0149] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is CR^2.

[0150] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is N; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

[0151] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is N; Y^5 is CH; and Y^6 is CH.

[0152] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CH; Y^5 is N; and Y^6 is CH.

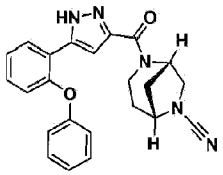
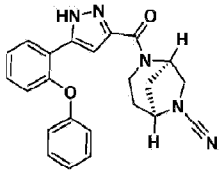
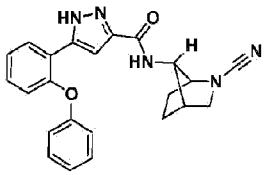
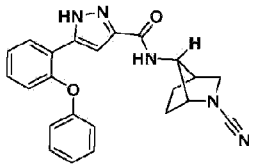
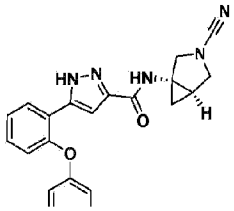
[0153] In some embodiments, the disclosure relates to a compound of formula (I-B), (I-B-1), (I-B-2), (I-B-3), or (I-B-4), or a pharmaceutically acceptable salt thereof, wherein Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is N.

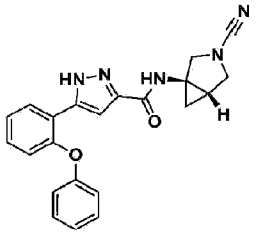
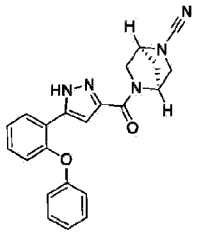
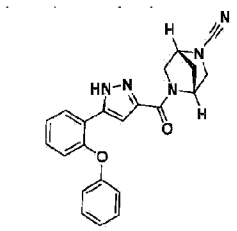
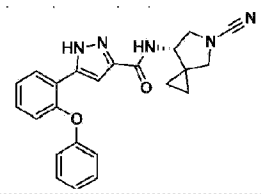
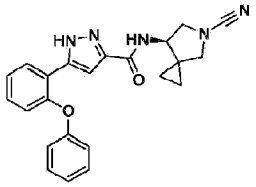
[0154] In some embodiments, the disclosure relates to a compound provided herein, or a pharmaceutically acceptable salt thereof, that is a USP30 Inhibitor Compound having an IC50 value of ≤ 1 μM and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1.

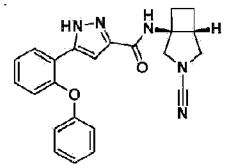
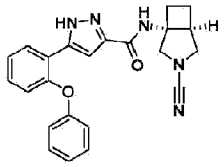
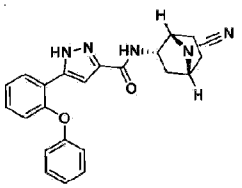
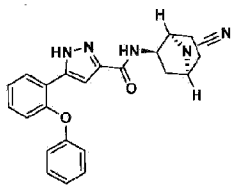
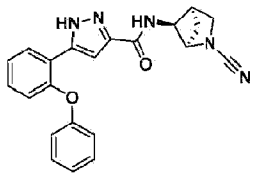
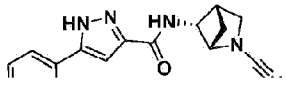
[0155] In another aspect, the disclosure relates to a compound selected from Table 1, or a pharmaceutically acceptable salt thereof. Each pair of compounds listed in Table 1 (i.e., compounds 1-a and 1-b, compounds 2-a and 2-b, etc.) was obtained as a racemic mixture, and were then separated by chiral HPLC according to the procedure described in Example 2, Step 7, or a similar method, to obtain the individual compounds in substantially enantiomerically pure form. For each pair of compounds, the first compound (i.e., compounds 1-a, 2-a, etc.) was the first eluting isomer, and the second compound (i.e., compounds 1-b, 2-

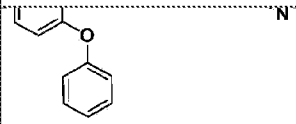
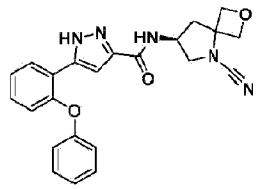
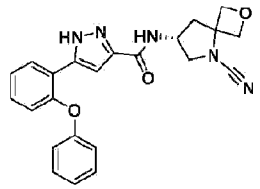
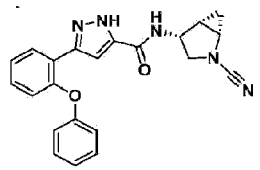
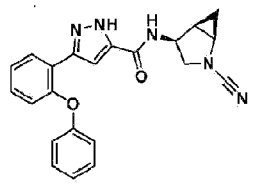
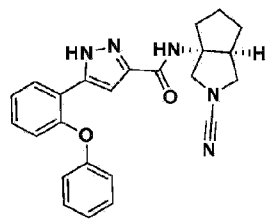
b, etc.) was the second eluting isomer. The stereochemical descriptors reflect the relative stereochemistry of each compound. The absolute stereochemistry of each compound was arbitrarily assigned. In some embodiments, the compound selected from Table 1, or a pharmaceutically acceptable salt thereof, is present in a racemic mixture. In some embodiments, the compound selected from Table 1, or a pharmaceutically acceptable salt thereof, is present in substantially enantiomerically pure form.

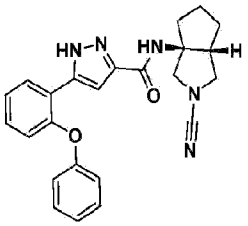
Table 1. Compounds of the Disclosure

Compound Number	Compound Structure and Chemical Name
1-a	
	(1S,5R)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile
1-b	
	(1R,5S)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile
2-a	
	N-((1S,4S,7S)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
2-b	
	N-((1R,4R,7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
3-a	

Compound Number	Compound Structure and Chemical Name
	
	N-((1S, 5R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
3-b	
	N-((1R, 5S)-3-cyano-3-azabicyclo[3.1.0]hexan-l-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
4-a	
	(1S,4S)-5-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,5 -diazabicyclo[2.2.1]heptane-2-carbonitrile
4-b	
	(1R,4R)-5-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carbonitrile
5-a	
	(S)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
5-b	

Compound Number	Compound Structure and Chemical Name
	(R)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
6-a	
	N-((1R,5S)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
6-b	
	N-((1S,5R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
7-a	
	N-((1S,2S,4R)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
7-b	
	N-((1R,2R,4S)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
8-a	
	N-[(1R,4R,5S)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl]-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
8-b	

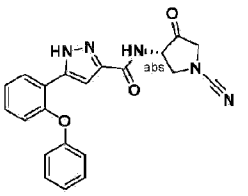
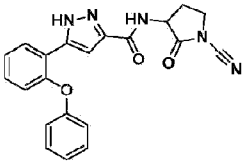
Compound Number	Compound Structure and Chemical Name
	
	N-((1S,4S,5R)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
9-a	
	(S)-N-(5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
9-b	
	(R)-N-(5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
13-a	
	N-((1S,4R,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
13-b	
	N-((1R,4S,SR)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
20-a	

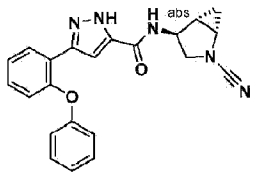
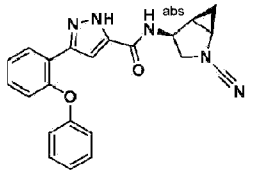
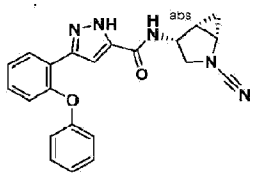
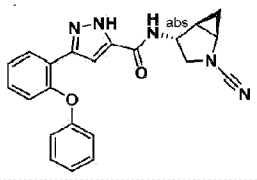
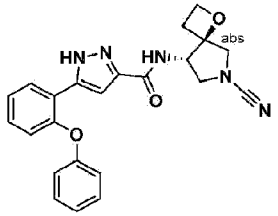
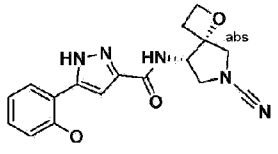
Compound Number	Compound Structure and Chemical Name
	N-((3aR,6aS)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
20-b	
	N-((3aS,6aR)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide

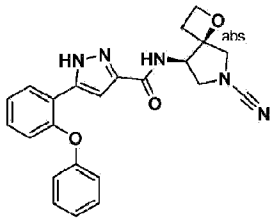
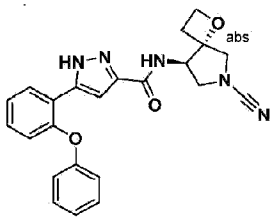
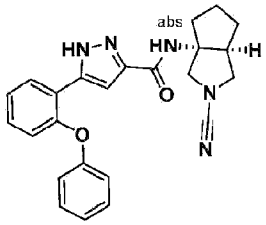
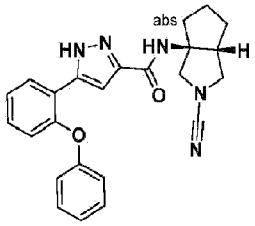
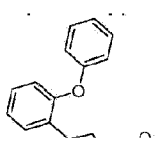
[0156] In another aspect, the disclosure relates to a compound selected from Table 2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, is present in a racemic mixture with its enantiomer. In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, is present in substantially enantiomerically pure form.

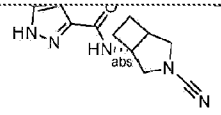
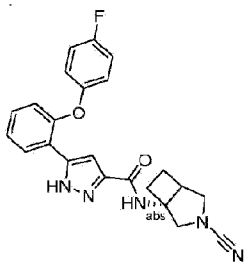
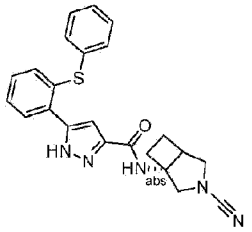
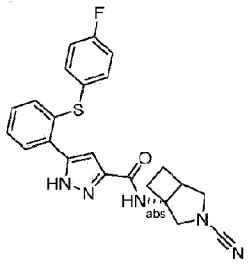
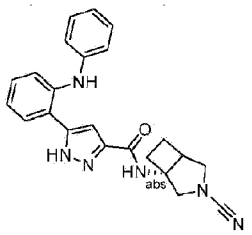
[0157] In another aspect, the disclosure relates to the enantiomer of a compound selected from Table 2, or a pharmaceutically acceptable salt thereof. In some embodiments, the enantiomer, or a pharmaceutically acceptable salt thereof, is present in a racemic mixture. In some embodiments, the enantiomer, or a pharmaceutically acceptable salt thereof, is present in substantially enantiomerically pure form.

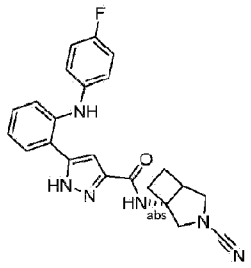
Table 2. Compounds of the Disclosure

Compound Number	Compound Structure and Chemical Name
10	
	(S)-N-(1-cyano-4-oxopyrrolidin-3-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
11	
	N-(1-cyano-2-oxopyrrolidin-3-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide

Compound Number	Compound Structure and Chemical Name
12	
	N-((1S,4S,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
13	
	N-((1R,4S,SR)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
14	
	N-((1S,4R,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
15	
	N-((1R,4R,5R)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide
16	
	N-((4S,8S)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
17	

Compound Number	Compound Structure and Chemical Name
	
	N-((4R,8S)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
18	
	N-((4S,8R)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3 -carboxamide
19	
	N-((4R,8R)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
20	
	N-((3aR,6aS)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
21	
	N-((3aS,6aR)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
22	

Compound Number	Compound Structure and Chemical Name
	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
23	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-(4-fluorophenoxy)phenyl)-1H-pyrazole-3-carboxamide
24	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-(phenylthio)phenyl)-1H-pyrazole-3-carboxamide
25	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-((4-fluorophenyl)thio)phenyl)-1H-pyrazole-3-carboxamide
26	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-(phenylamino)phenyl)-1H-pyrazole-3-carboxamide

Compound Number	Compound Structure and Chemical Name
27	
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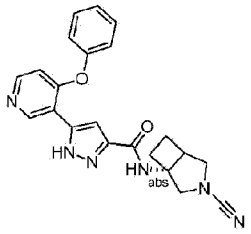
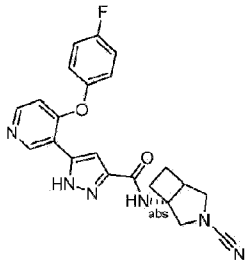
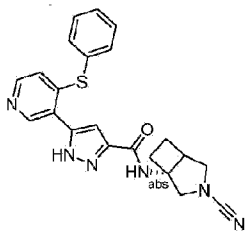
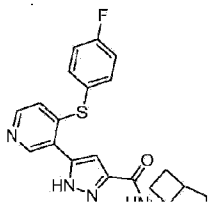
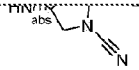
28	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(4-phenoxypyridin-3-yl)-1H-pyrazole-3-carboxamide
29	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(4-(4-fluorophenoxy)pyridin-3-yl)-1H-pyrazole-3-carboxamide
30	
	N-((1R)-3-cyano-3-azabicyclo[32.0]heptan-1-yl)-5-(4-(phenylthio)pyridin-3-yl)-1H-pyrazole-3-carboxamide
31	

Compound Number	Compound Structure and Chemical Name
	
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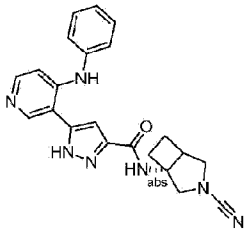
32	
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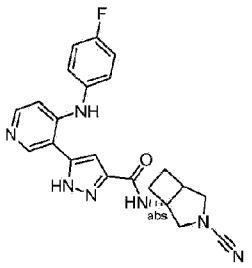
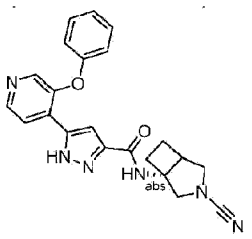
33	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(4-((4-fluorophenyl)amino)pyridin-3-yl)-1H-pyrazole-3-carboxamide
34	
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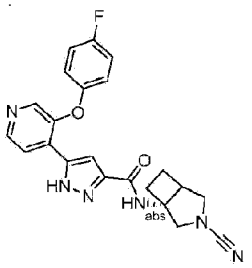
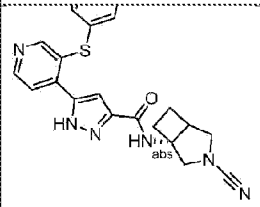
35	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-(4-fluorophenoxy)pyridin-4-yl)-1H-pyrazole-3-carboxamide
36	

Compound Number	Compound Structure and Chemical Name
	
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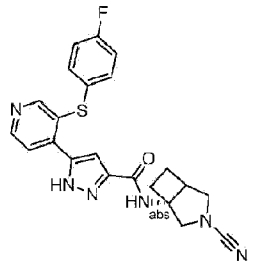
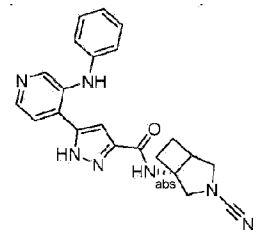
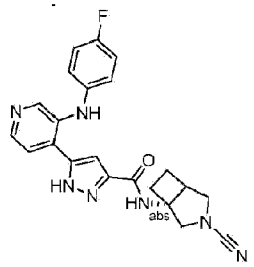
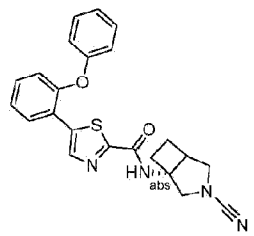
37	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-((4-fluorophenyl)thio)pyridin-4-yl)-1H-pyrazole-3-carboxamide
38	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-(phenylamino)pyridin-4-yl)-1H-pyrazole-3-carboxamide
39	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-((4-fluorophenyl)amino)pyridin-4-yl)-1H-pyrazole-3-carboxamide
40	

Compound Number	Compound Structure and Chemical Name
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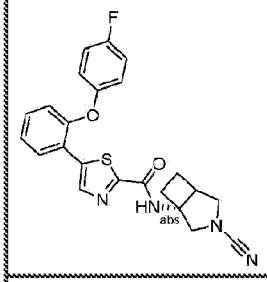
41	
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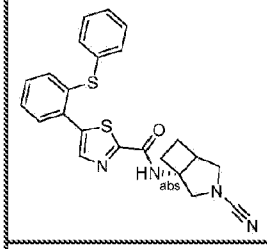
42	
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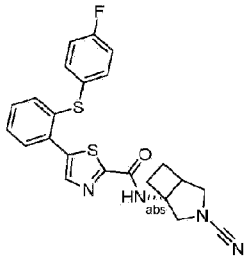
43	
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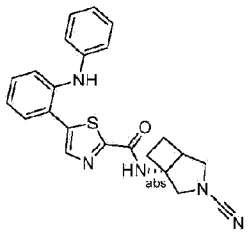
44	
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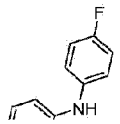
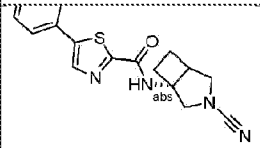
45	

Compound Number	Compound Structure and Chemical Name
	
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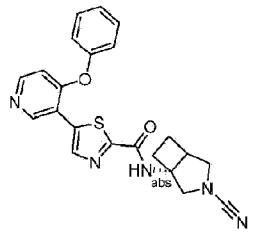
46	
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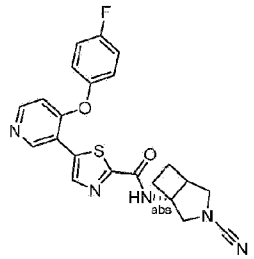
47	
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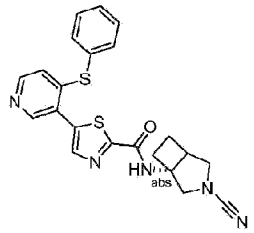
48	
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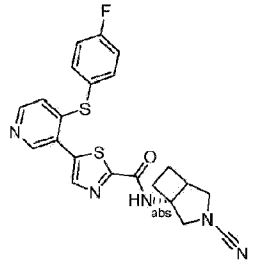
49	
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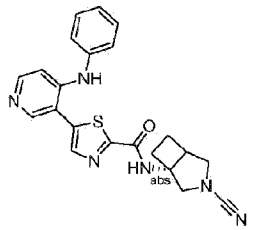
Compound Number	Compound Structure and Chemical Name
50	
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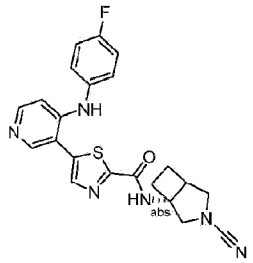
51	
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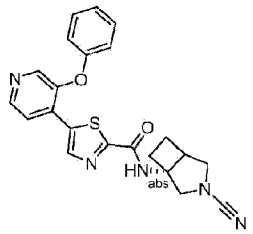
52	
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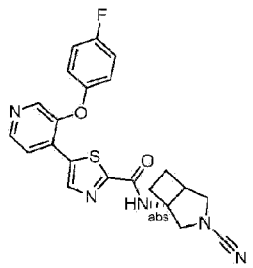
53	
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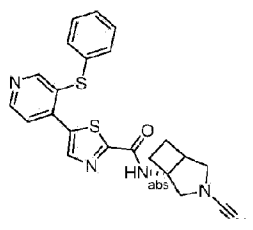
54	

Compound Number	Compound Structure and Chemical Name
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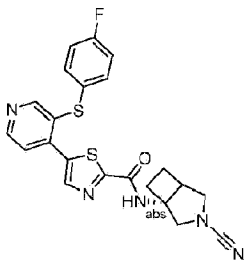
55	
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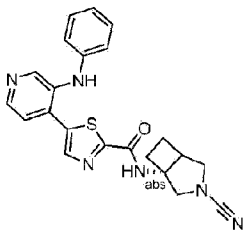
56	
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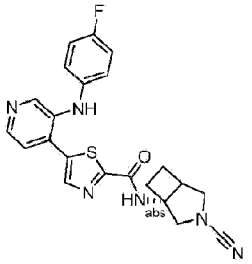
57	
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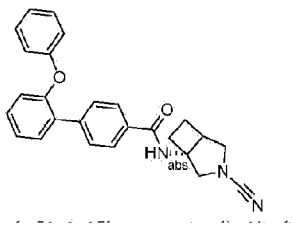
58	
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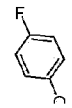
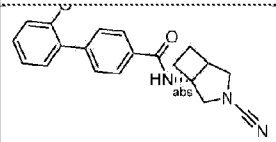
59	

Compound Number	Compound Structure and Chemical Name
	
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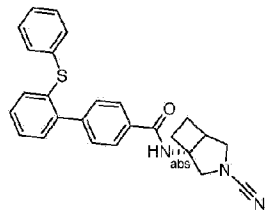
60	
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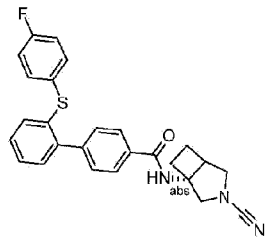
61	
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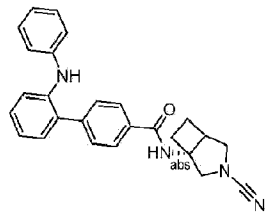
62	
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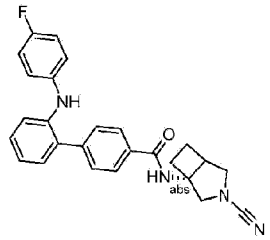
63	
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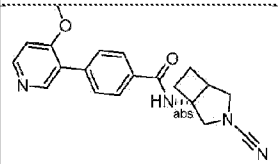
64	

Compound Number	Compound Structure and Chemical Name
	
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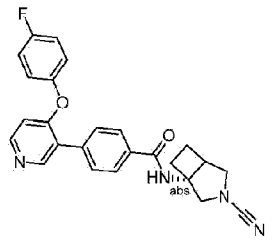
65	
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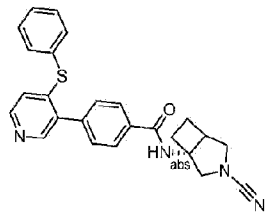
66	
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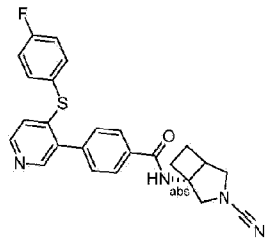
67	
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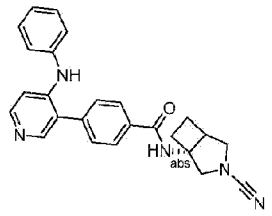
68	
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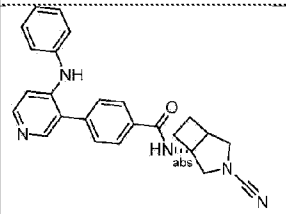
69	

Compound Number	Compound Structure and Chemical Name
	
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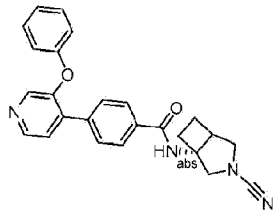
70	
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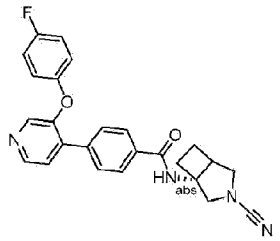
71	
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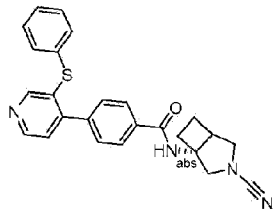
72	
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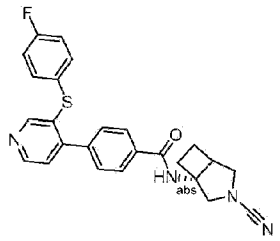
73	
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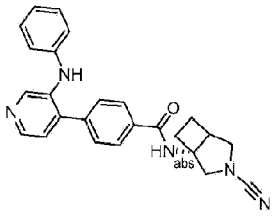
Compound Number	Compound Structure and Chemical Name
74	
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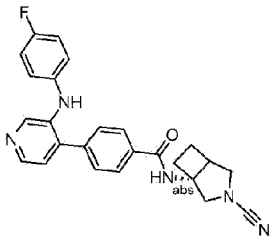
75	
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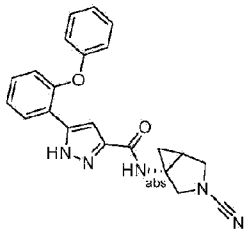
76	
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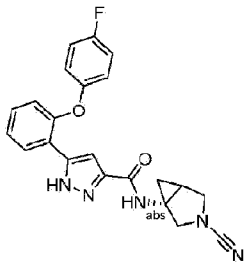
77	
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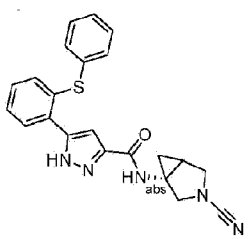
78	

Compound Number	Compound Structure and Chemical Name
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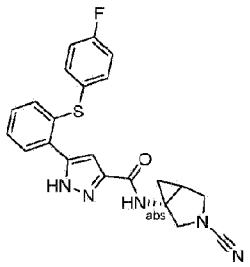
79	
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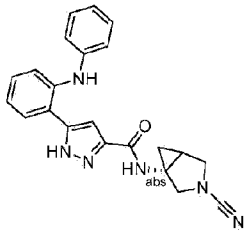
80	
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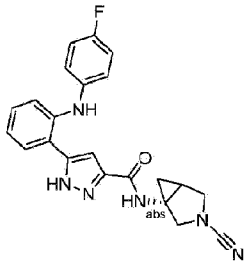
81	
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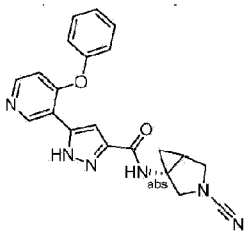
82	
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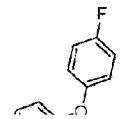
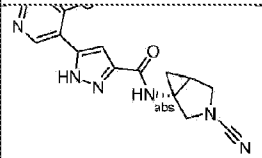
83	

Compound Number	Compound Structure and Chemical Name
	
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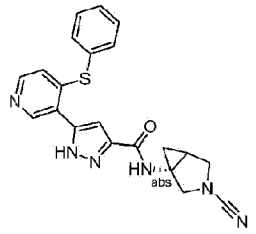
84	
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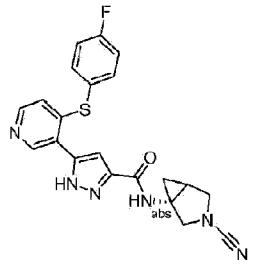
85	
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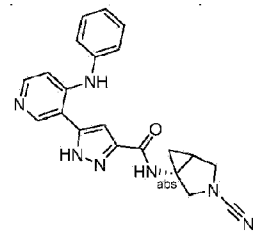
86	
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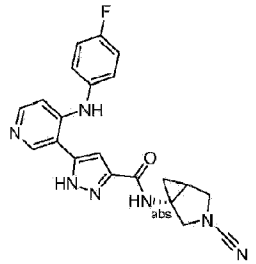
87	
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Compound Number	Compound Structure and Chemical Name
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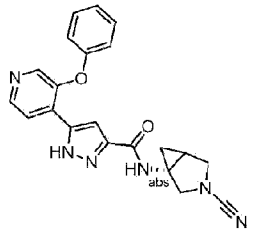
88	
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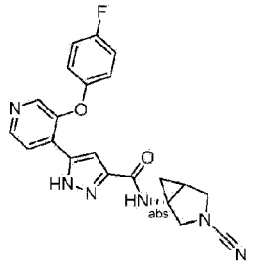
89	
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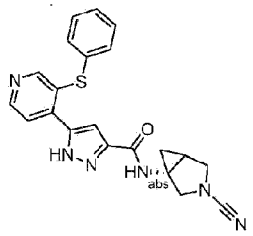
90	
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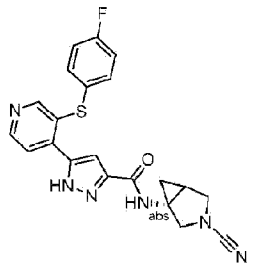
91	
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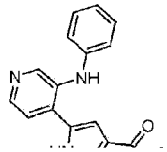
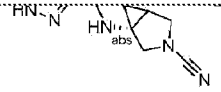
92	

Compound Number	Compound Structure and Chemical Name
	
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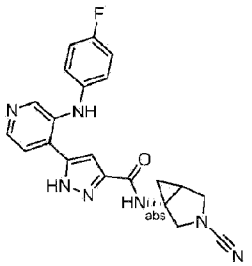
93	
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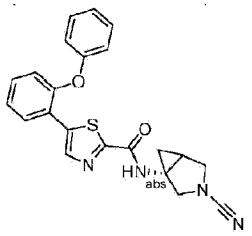
94	
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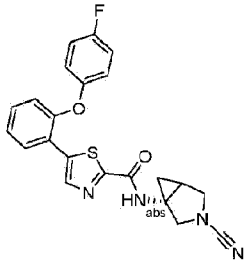
95	
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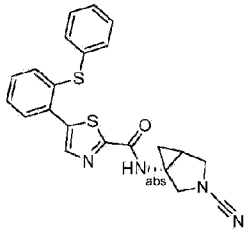
96	
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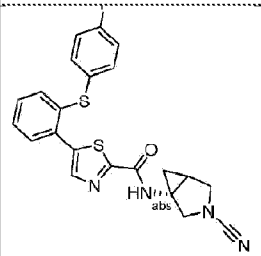
97	

Compound Number	Compound Structure and Chemical Name
	
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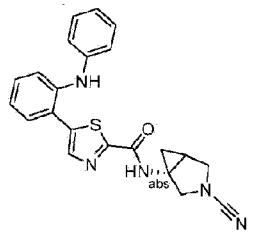
98	
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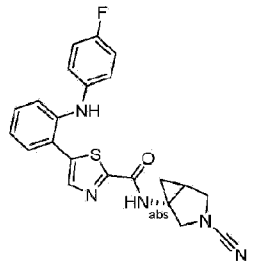
99	
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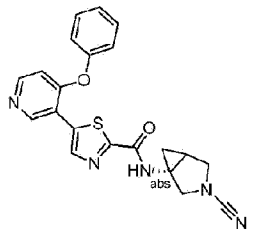
100	
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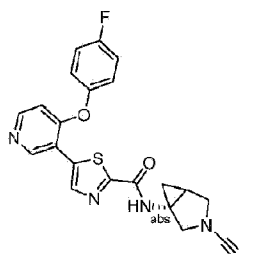
101	

Compound Number	Compound Structure and Chemical Name
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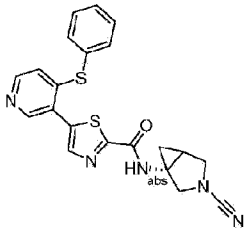
102	
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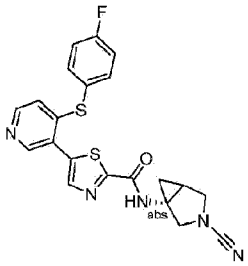
103	
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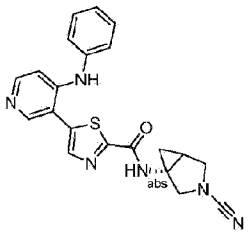
104	
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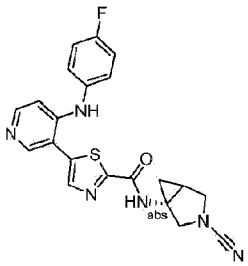
105	
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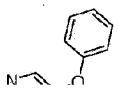
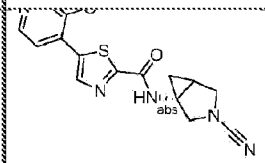
106	

Compound Number	Compound Structure and Chemical Name
	
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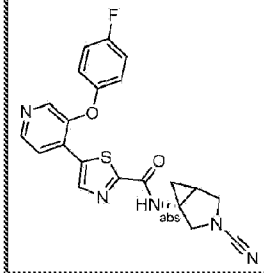
107	
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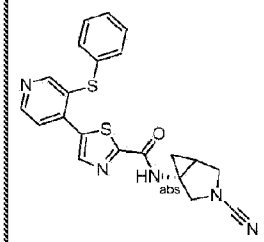
108	
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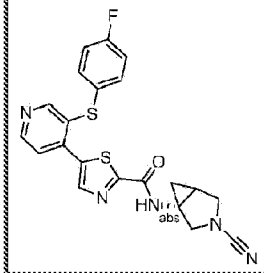
109	
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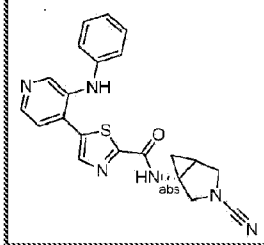
110	
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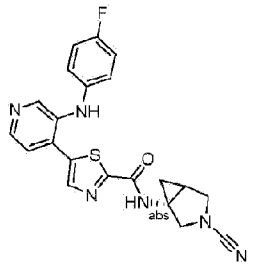
Compound Number	Compound Structure and Chemical Name
111	
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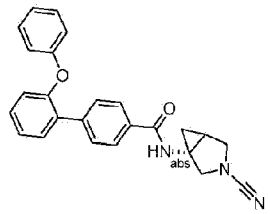
112	
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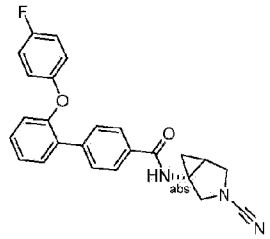
113	
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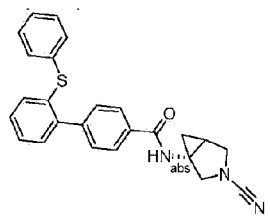
114	
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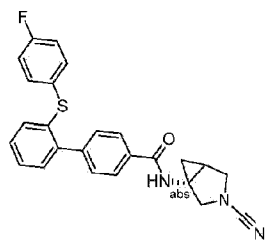
115	

Compound Number	Compound Structure and Chemical Name
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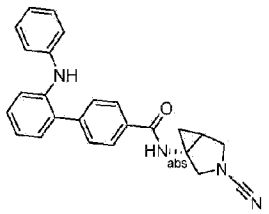
116	
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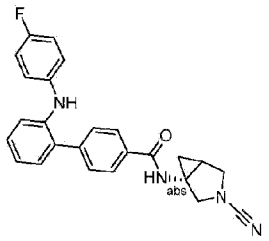
117	
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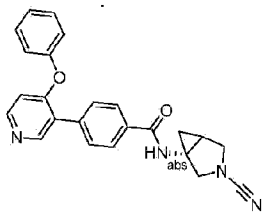
118	
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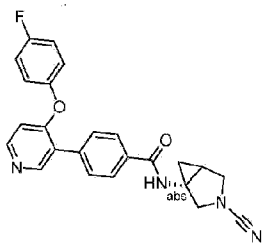
119	
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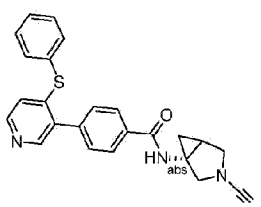
120	

Compound Number	Compound Structure and Chemical Name
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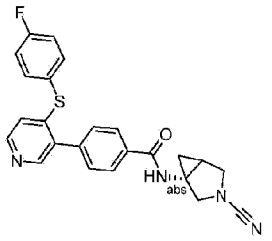
121	
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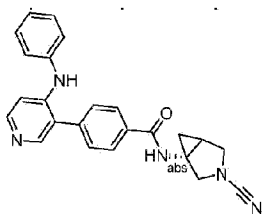
122	
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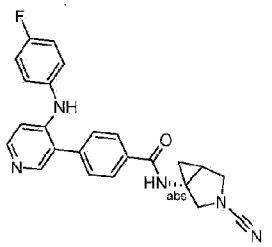
123	
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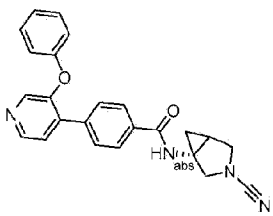
124	
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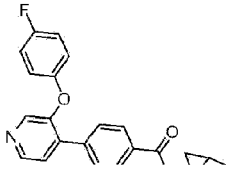
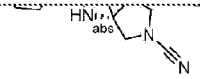
125	

Compound Number	Compound Structure and Chemical Name
	
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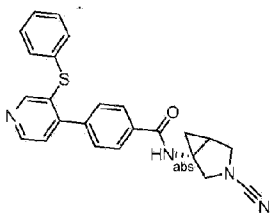
126	
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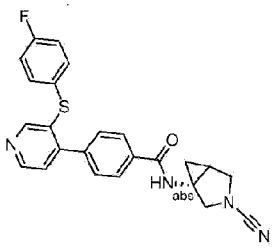
127	
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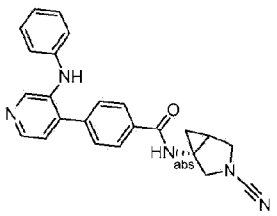
128	
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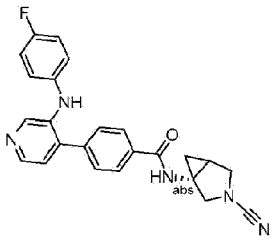
129	
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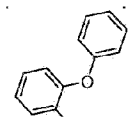
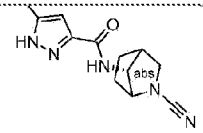
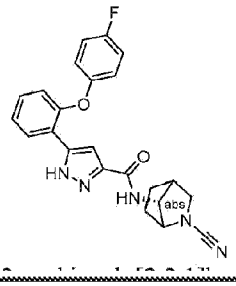
130	

Compound Number	Compound Structure and Chemical Name
	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide
131	
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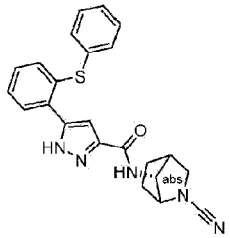
132	
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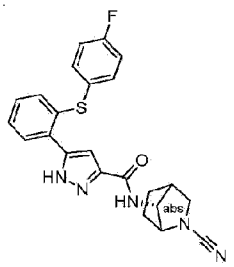
133	
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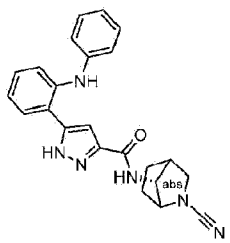
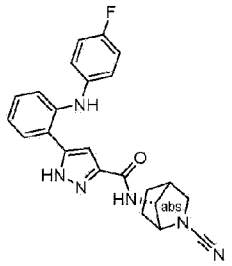
134	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(phenylamino)phenyl)-1H-pyrazole-3-carboxamide

Compound Number	Compound Structure and Chemical Name
135	
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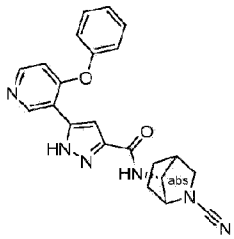
136	
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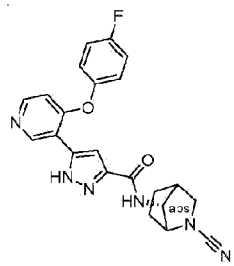
137	
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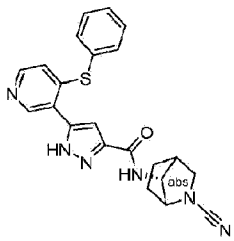
138	
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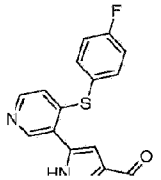
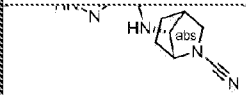
139	

Compound Number	Compound Structure and Chemical Name
	
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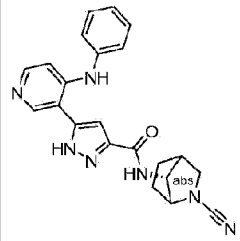
140	
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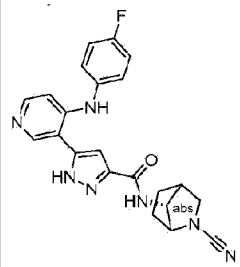
141	
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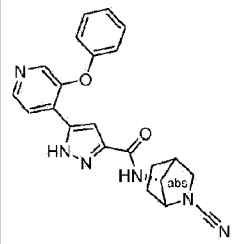
142	
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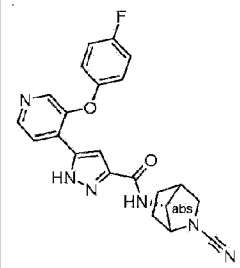
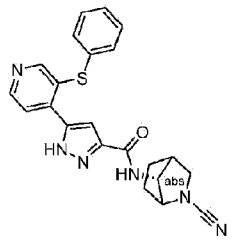
143	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(4-fluorophenoxy)pyridin-4-yl)-1H-pyrazole-3-carboxamide

Compound Number	Compound Structure and Chemical Name
144	
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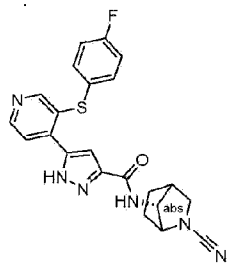
145	
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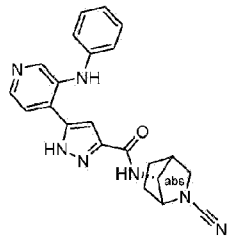
146	
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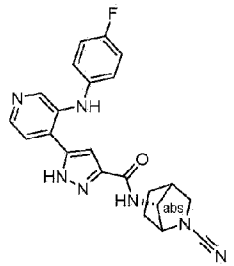
147	
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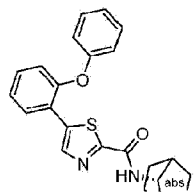
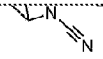
148	

Compound Number	Compound Structure and Chemical Name
	
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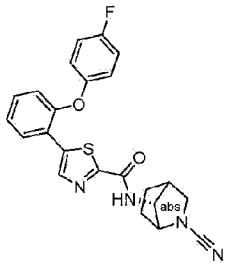
149	
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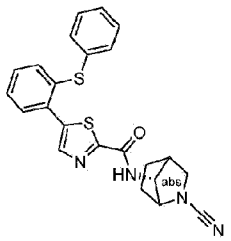
150	
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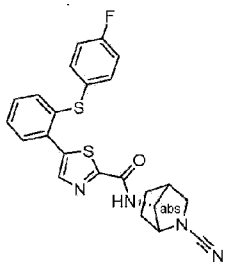
151	
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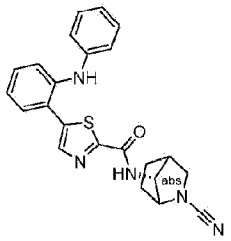
152	
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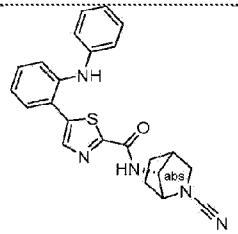
153	

Compound Number	Compound Structure and Chemical Name
	
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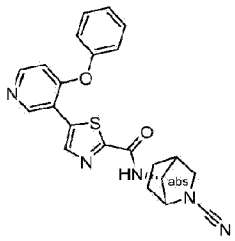
154	
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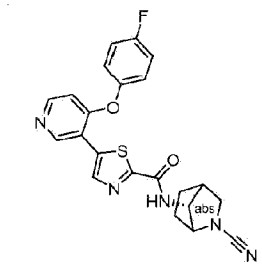
155	
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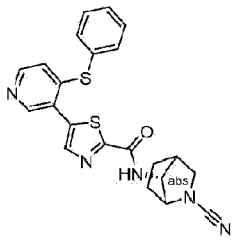
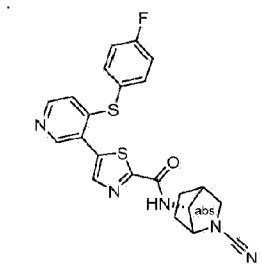
156	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(phenylthio)pyridin-3-yl)thiazole-2-carboxamide
157	

Compound Number	Compound Structure and Chemical Name
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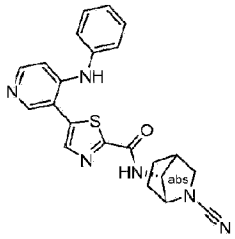
158	
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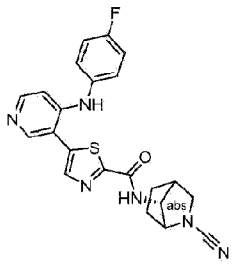
159	
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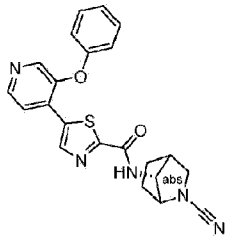
160	
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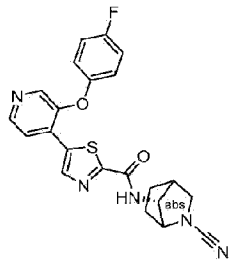
161	
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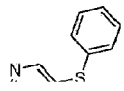
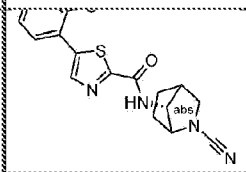
162	

Compound Number	Compound Structure and Chemical Name
	
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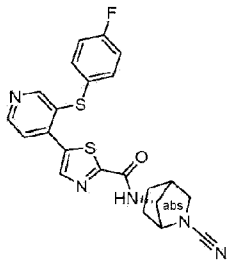
163	
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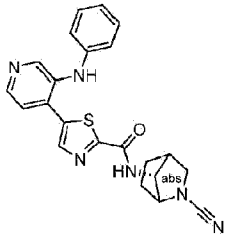
164	
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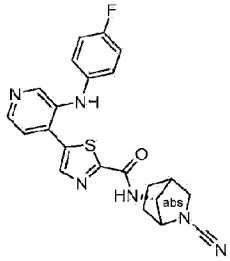
165	
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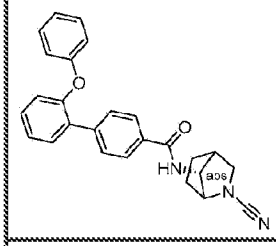
166	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-phenoxy-[1,1'-

Compound Number	Compound Structure and Chemical Name
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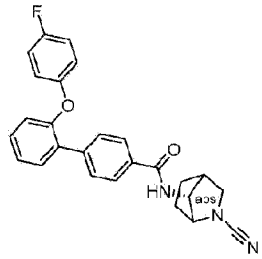
167	
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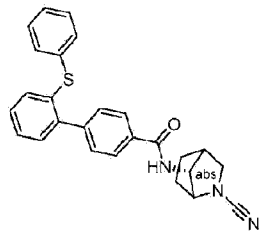
168	
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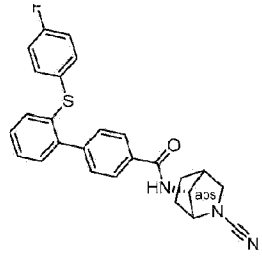
169	
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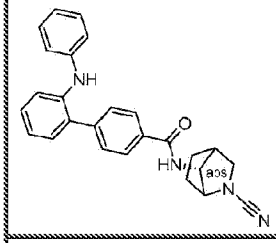
170	
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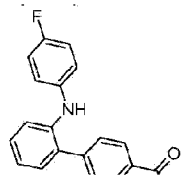
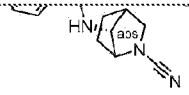
171	

Compound Number	Compound Structure and Chemical Name
	
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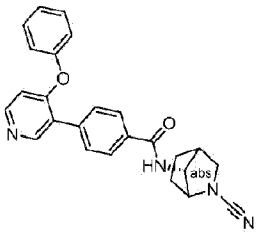
172	
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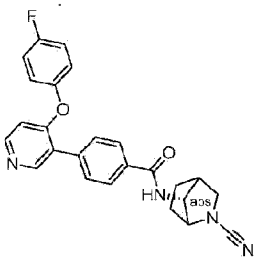
173	
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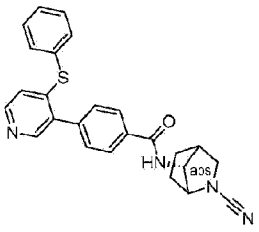
174	
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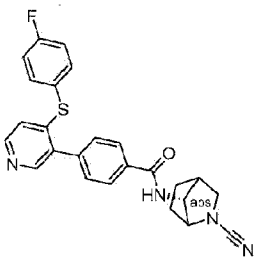
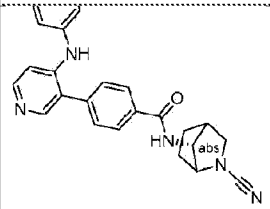
175	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-((4-fluorophenyl)thio)pyridin-3-yl)benzamide
176	

Compound Number	Compound Structure and Chemical Name
	
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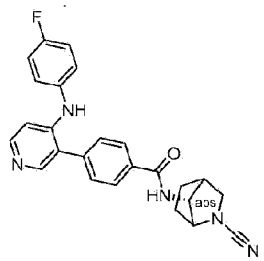
177	
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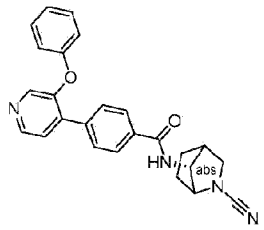
178	
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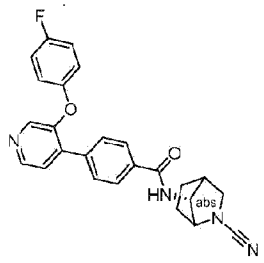
179	
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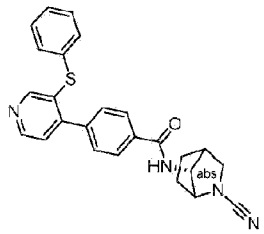
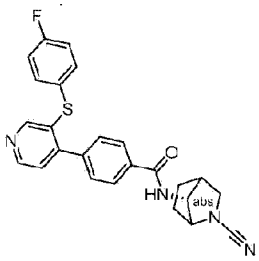
180	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-

Compound Number	Compound Structure and Chemical Name
	(phenylthio)pyridin-4-yl)benzamide
181	
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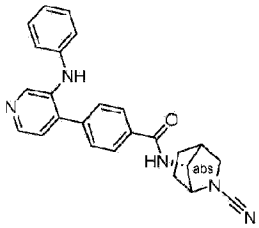
182	
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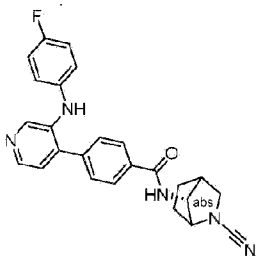
183	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-((4-fluorophenyl)amino)pyridin-4-yl)benzamide

[0158] In some embodiments, a compound described herein is provided in non-salt form. In some embodiments, a compound described herein is provided as a pharmaceutically acceptable salt.

[0159] In another aspect, the disclosure relates to a compound, or a pharmaceutically acceptable salt thereof, prepared by a method comprising: preparing a compound of the present disclosure as a mixture of stereoisomers; separating the stereoisomers by chiral HPLC according to the procedure described in Example 2, Step 7; isolating one or more stereoisomers that are USP30 Inhibitor Compounds having an IC_{50} value of ≤ 1 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1; and optionally treating the isolated stereoisomer with an acid or base to afford a pharmaceutically acceptable

salt thereof.

[0160] In some embodiments, the compound is the 1st eluting isomer. In some embodiments, the compound is the 2nd eluting isomer. In some embodiments, the compound is the 3rd eluting isomer. In some embodiments, the compound is the 4th eluting isomer. In some embodiments, the compound is the 5th, 6th, 7th, or 8th eluting isomer.

[0161] In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is a USP30 Inhibitor Compound having an IC_{50} value of ≤ 1 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1. In some embodiments, the IC_{50} value is ≤ 0.1 μM.

Pharmaceutical Compositions and Routes of Administration

[0162] The disclosure also relates to a pharmaceutical composition comprising one or more compounds provided herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embdiments, the pharmaceutical composition comprises a therapeutically effective amount of the one or more compounds, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is for use in a method of treating a neurodegenerative disorder, such as Parkinson's Disease.

[0163] The compounds and pharmaceutically acceptable salts disclosed herein may be administered via any mode of administration for therapeutic agents, consistent with conventional pharmaceutical practices. In some embodiments, the pharmaceutical compositions reported herein can be provided in a unit dosage form. In some embodiments, the pharmaceutical compositions reported herein can be provided in an oral dosage form. In some embodiments, the pharmaceutical compositions described herein can be provided in a solid oral dosage form, such as a tablet, capsule, powder, or cachet.

[0164] The pharmaceutical compositions described herein can be prepared according to conventional mixing, granulating or coating methods. For example, oral dosage forms (e.g., tablets) may be prepared by dry blending or dry granulation. The pharmaceutical compositions described herein can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the compound or pharmaceutically acceptable salt by weight or volume. The pharmaceutically acceptable carriers employed in the pharmaceutical compositions described herein may include one or more pharmaceutical excipients, such as fillers, disintegrants, lubricants, glidants, anti-adherents, anti-statics, surfactants, or stabilizing additives. Suitable solid carriers are known in the art, *e.g.,* magnesium carbonate, magnesium stearate, talc, sugar or lactose. With some drugs, the presence of such additives promotes the stability and dispersibility of the agent in solution. Suitable, but non-limiting, examples of

stabilizing additives include gum acacia, gelatin, methyl cellulose, polyethylene glycol, carboxylic acids and salts thereof, and polylysine. In some embodiments, the stabilizing additives are gum acacia, gelatin and methyl cellulose. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pa.

[0165] The pharmaceutical compositions described herein may contain the compound or pharmaceutically acceptable salt in substantially pure form, such as at least 60% pure, more suitably at least 75% pure, preferably at least 85% pure and most preferably at least 98% pure (w/w).

[0166] The compounds and pharmaceutically acceptable salts described herein are preferably administered in a therapeutically effective amount (e.g., an amount having a suitable favorable therapeutic index). The amount and frequency of administration will be regulated according to the judgment of the attending clinician considering such factors as the age, gender, condition and size of the patient, as well as severity of the medical condition being treated; the route of administration; the renal or hepatic function of the patient; and the particular compound or pharmaceutically acceptable salt employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

Uses of Compounds Disclosed Herein

[0167] The present disclosure also provides uses of compounds of formula (I). Compounds of formula (I) are useful in medicine. For examples, compounds and compositions described herein are inhibitors of USP30. Without wishing to be bound by any particular theory, such inhibition of USP30 can provide treatment of the symptoms and/or underlying causes of diseases or conditions associated with USP30 activity. In some embodiments, inhibitors of USP30 can be used to treat neurodegenerative and neurologic diseases or conditions, such as Parkinson's disease.

[0168] Provided herein are compounds and compositions for use in methods of treating a disease or disorder associated with a ubiquitin-specific protease (e.g., USP30), comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition provided herein. In some embodiments, the disease or disorder associated with a ubiquitin-specific protease (e.g., USP30) is a neurodegenerative disease or disorder (e.g., Parkinson's disease).

[0169] The present disclosure also provides compounds and compositions for use in methods of inhibiting a ubiquitin-specific protease (e.g., USP30) in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound or composition

provided herein.

[0170] The present disclosure also provides compounds and compositions for use in methods of treating a neurodegenerative disease or disorder (e.g., Parkinson's disease) in a patient in need thereof, comprising administering to the patient a therapeutically effecetive amount of a compound or composition provided herein.

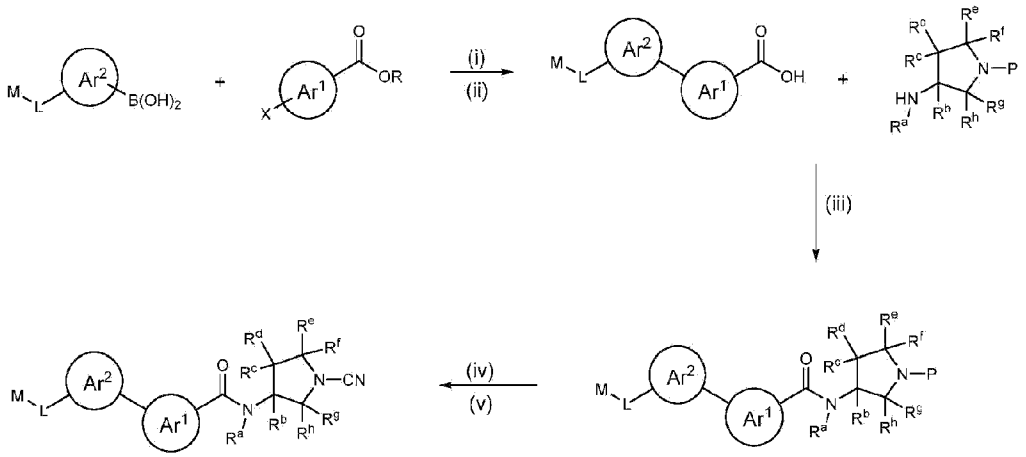
[0171] The present disclosure also provides compounds for use in method of inhibiting a ubiquitin-specific protease (e.g., USP30) in a patient in need thereof. In some embodiments, the present disclosure provides compounds for use in a method of treating a neurodegenerative disease or disorder (e.g., Parkinson's disease) in a patient in need thereof.

Synthesis of Compounds Disclosed Herein

[0172] The compounds and pharmaceutically acceptable salts disclosed herein may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

[0173] In general, the compounds of formula (I) can be synthesized by the methods outlined in Scheme 1, by the specific procedures discussed in Examples 2-4, and/or by methods otherwise known to one skilled in the art. The starting materials for the synthesis described in Scheme 1 are commercially available or can be prepared by methods known to one skilled in the art.

Scheme 1. Synthesis of Compounds of Formula I



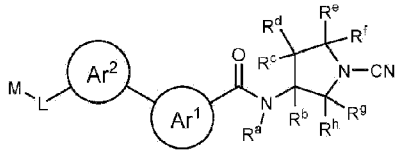
(i) cross coupling catalyst (e.g., XPhos-Pd), base (e.g., K_3PO_4), solvent (e.g., dioxane, H_2O) (X is a leaving group, e.g., Br; R is an alkyl group, e.g., Me); (ii) Base (e.g., LiOH), solvent (e.g.,

THF, H_2O); (iii) amide coupling agent (e.g., HATU), base (e.g., DIEA), solvent (e.g., DMF) (P is a protecting group, e.g., Boc); (iv) deprotection conditions (e.g., acid, e.g., CF_3COOH), solvent (e.g., CH_2Cl_2); (v) cyanation agent (e.g., BrCN), base (e.g., $NaHCO_3$).

Exemplary Embodiments

[0174] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the disclosure:

1. 1. A compound of formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is phenylene or 5-6 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *m* R^1 groups;

Ar^2 is phenylene or 5-6 membered heteroarylene, wherein said phenylene or heteroarylene is substituted with *n* R^2 groups;

L is -O-, -S-, $-NR^3-$, $-C(R^4)_2-$, $-S(O)_2-$, or -S(O)-;

M is 3-6 membered cycloalkyl, phenyl, or 5-6 membered heteroaryl, wherein said cycloalkyl, phenyl, or heteroaryl is substituted with *p* R^5 groups;

each occurrence of R^1, R^2, and R^5 is independently halo, cyano, NO_2, oxo, hydroxyl, $-R^6$, $-OR^6$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-C_1$-C_6 alkylene-R^6, C_1-C_6 alkoxy, Ci-C_6 haloalkoxy, $-C_0$-C_3 alkylene-NR^6R^7, $-C_0$-C_3 alkylene-NR^7R^8, $-C_0$-C_3 alkylene-$C(O)NR^6R^7$, - C_0-C_3 alkylene-$C(O)NR^7R^8$, $-C_0$-C_3 alkylene-$NR^7C(O)R^6$, $-C_0$-C_3 alkylene-$NR^7C(O)R^8$, $-C_0$-C_3 alkylene-$NR^7S(O)_2R^6$, $-C_0$-C_3 alkylene-$C(O)R^6$, $-C_0$-C_3 alkylene-$C(O)R^7$, $-C_0$-C_3 alkylene-SR^6, - C_0-C_3 alkylene-$S(O)R^6$, $-C_0$-C_3 alkylene-$S(O)_2R^6$, $-C_0$-C_3 alkylene-$S(O)_2R^7$, $-C_0$-C_3 alkylene$S(O)_2NR^6R^7$, $-C_0$-C_3 alkylene-$S(O)_2NR^7R^8$, $-C_0$-C_3 alkylene-$NR^7C(O)NR^8R^9$, $-C_0$-C_3 alkylene-$NR^7S(O)_2NR^8R^9$, $-C_0$-C_3 alkylene-$C(O)OR^7$, $-C_0$-C_3 alkylene-$C(O)OR^6$, $-C_0$-C_3 alkylene-$OC(O)R^7$, $-C_0$-C_3 alkylene-$OC(O)R^6$, $-C_0$-C_3 alkylene-$NR^7C(O)OR^8$, or $-C_0$-C_3 alkylene-$NR^7S(O)_2R^8$;

R^3 is H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or two R^4 groups together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl or heterocycloalkyl;

each R^6 is independently 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl, wherein said heteroaryl, heterocycloalkyl, aryl, or cycloalkyl is optionally substituted with 1-5 substituents independently selected from the group consisting of halo, oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, 3-8 membered cycloalkyl, $-NR^{10}C(O)NR^{11}R^{12}$, $-NR^{10}R^{11}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)OR^{11}$, $-S(O)_2R^{10}$, $-C(O)NR^{10}R^{11}$, $-C(O)OR^{10}$, $-S(O)_2NR^{10}R^{11}$, $-NR^{10}S(O)_2R^{11}$, $-OR^{10}$, $-OC(O)R^{10}$, $-OS(O)_2R^{10}$, $-OC(O)NR^{10}R^{11}$, $-OC(O)OR^{10}$, $-OS(O)_2NR^{10}R^{11}$, $-C(O)R^{10}$, $-C(O)NR^{10}C(O)NR^{11}R^{12}$, $-C(O)NR^{10}R^{11}$, $-C(O)C(O)R^{10}$, $-C(O)NR^{10}C(O)R^{11}$, $-C(O)NR^{10}C(O)OR^{11}$, $-C(O)S(O)_2R^{10}$, $-C(O)C(O)NR^{10}R^{11}$, $-C(O)C(O)OR^{10}$, $-C(O)S(O)_2NR^{10}R^{11}$, $-C(O)NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkylene-R^{10}, $-C_1$-C_6 alkylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)R^{10}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$C(O)OR^{10}$, $-C_1$-C_6 alkylene-$S(O)_2NR^{10}R^{11}$, $-C_1$-C_6 alkylene-$NR^{10}S(O)_2R^{11}$, $-C_1$-C_6 alkenylene-R^{10}, $-C_1$-C_6 alkenylene-$NR^{10}C(O)NR^{11}R^{12}$, $-C_1$-C_6 alkenylene-$NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)R^{10}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)R^{11}$, $-C_1$-C_6 alkenylene-$NR^{10}C(O)OR^{11}$, $-C_1$-C_6 alkenylene-$S(O)_2R^{10}$, $-C_1$-C_6 alkenylene-$C(O)NR^{10}R^{11}$, $-C_1$-C_6 alkenylene-$C(O)OR^{10}$, $-C_1$-C_6 alkenylene-$S(O)_2NR^{10}R^{11}$, and $-C_1$-C_6 alkenylene-$NR^{10}S(O)_2R^{11}$;

each R^7, R^8, and R^9 is independently hydrogen or C_1-C_6 alkyl;

each R^{10}, R^{11}, and R^{12} is independently hydrogen, C_1-C_6 alkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, 6-10 membered aryl, or 3-8 membered cycloalkyl;

m is 0-4;

n is 0-4;

p is 0-4;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

1. (i) R^a and R^b form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^c, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
2. (ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
3. (iii) R^a and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
4. (iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
5. (v) R^b and R^e form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
6. (vi) R^b and R^g form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^c, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
7. (vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and

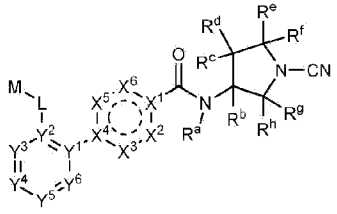
R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

8. (viii) R^c and R^d together form =0; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
9. (ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
10. (x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
11. (xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
12. (xii) R^e and R^f together form =O; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
13. (xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
14. (xiv) R^g and R^h together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or
15. (xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

2. 2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are

attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

3. 3. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
4. 4. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
5. 5. The compound of embodiment 1, wherein the compound has formula (I-A):



(I-A);

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C or N;

X^2 is CH, CR^1, O, S, N, NH, or NR^1;

X^3 is CH, CR^1, O, S, N, NH, or NR^1;

X^4 is C or N;

X^5 is a bond, CH, CR^1, O, S, N, NH, or NR^1;

X^6 is CH, CR^1, O, S, N, NH, or NR^1;

Y^1 is CorN;

Y^2 is C or N;

Y^3 is CH, CR^2, O, S, N, NH, or NR^2;

Y^4 is a bond, CH, CR^2, O, S, N, NH, or NR^2;

Y^5 is CH, CR^2, O, S, N, NH, or NR^2;

Y^6 is CH, CR^2, O, S, N, NH, or NR^2;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3

haloalkyl; or

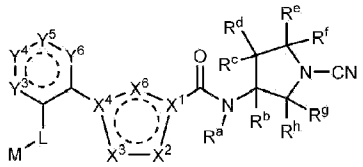
(xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

6. 6. The compound of embodiment 5, or a pharmaceutically acceptable salt thereof, wherein R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
7. 7. The compound of embodiment 5, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
8. 8. The compound of embodiment 5, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
9. 9. The compound of any one of embodiments 5-8, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; X^4 is C; X^5 is a bond; and X^6 is CH.
10. 10. The compound of any one of embodiments 5-9, or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is CH.

11. 11. The compound of any one of embodiments 5-10, or a pharmaceutically acceptable salt thereof, wherein L is O.
12. 12. The compound of any one of embodiments 5-11, or a pharmaceutically acceptable salt thereof, wherein M is phenyl substituted with *p* R^5 groups.
13. 13. The compound of embodiment 1, wherein the compound has formula (I-B):



(I-B);

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C or N;

X^2 is CH, CR^1, O, S, N, NH, or NR^1;

X^3 is CH, CR^1, O, S, N, NH, or NR^1;

X^4 is C or N;

X^6 is CH, CR^1, O, S, N, NH, or NR^1;

Y^3 is CH, CR^2, or N;

Y^4 is CH, CR^2, or N;

Y^5 is CH, CR^2, or N;

Y^6 is CH, CR^2, or N;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached, wherein said C_1-C_2 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^b, R^c, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

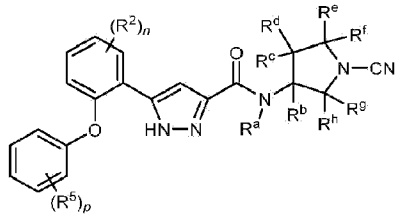
(xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl; or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

14. 14. The compound of embodiment 13, or a pharmaceutically acceptable salt thereof, wherein R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached, wherein said C_1-C_3 alkylene group is substituted with 0-4 substituents selected

from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^d, R^e, R^f, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.

15. 15. The compound of embodiment 13, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached, wherein said C_1-C_4 alkylene group is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^d, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
16. 16. The compound of embodiment 13, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl, wherein said 3-6 membered cycloalkyl or heterocycloalkyl is substituted with 0-4 substituents selected from the group consisting of halogen, C_1-C_3 alkyl, and C_1-C_3 haloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each independently hydrogen, halogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl.
17. 17. The compound of any one of embodiments 13-16, or a pharmaceutically acceptable salt thereof, wherein X^1 is C; X^2 is N; X^3 is NH; X^4 is C; and X^6 is CH.
18. 18. The compound of any one of embodiments 13-17, or a pharmaceutically acceptable salt thereof, wherein Y^1 is C; Y^2 is C; Y^3 is CH; Y^4 is CH; Y^5 is CH; and Y^6 is CH.
19. 19. The compound of any one of embodiments 13-18, or a pharmaceutically acceptable salt thereof, wherein L is O.
20. 20. The compound of any one of embodiments 13-19, or a pharmaceutically acceptable salt thereof, wherein M is phenyl substituted with *p* R^5 groups.
21. 21. The compound of embodiment 1, wherein the compound has formula (I-C):



(I-C);

or a pharmaceutically acceptable salt thereof, wherein:

R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen; or

(iv) R^b and R^c form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(ix) R^c and R^e form a C_1-C_4 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen; or

(x) R^c and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen; or

(xi) R^e and R^f together with the atom to which they are attached, form a 3-6 membered cycloalkyl or heterocycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen; or (xiii) R^e and R^g form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen.

22. 22. The compound of embodiment 21, or a pharmaceutically acceptable salt thereof, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, and R^h are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, R^g, and R^h are each hydrogen; or

(iv) R^b and R^c form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen; or

(vii) R^c and R^d together with the atom to which they are attached, form a 3-membered cycloalkyl or a 4-membered heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(viii) R^c and R^d together form =O; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen; or

(ix) R^c and R^e form a Ci alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^f, R^g, and R^h are each hydrogen; or

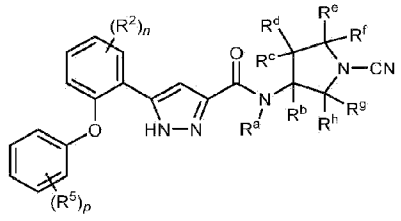
(x) R^c and R^g form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen; or

(xi) R^e and R^f together with the atom to which they are attached, form a 4-membered heterocycloalkyl; and R^a, R^b, R^c, R^d, R^g, and R^h are each hydrogen; or

(xiii) R^e and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, R^f, and R^h are each independently hydrogen or

(xv) R^g and R^h together form =O; and R^a, R^b, R^c, R^d, R^e, and R^f are each hydrogen.

23. 23. The compound of embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R^c and R^g form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, R^f, and R^h are each hydrogen.
24. 24. The compound of embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c form a C_1-C_3 alkylene group between the atoms to which they are attached; and R^a, R^d, R^e, R^f, R^g, and R^h are each hydrogen.
25. 25. The compound of embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R^c and R^d together with the atom to which they are attached, form a 3-membered cycloalkyl or a 4-membered heterocycloalkyl; and R^a, R^b, R^e, R^f, R^g, and R^h are each hydrogen.
26. 26. The compound of any one of embodiments 21-25, or a pharmaceutically acceptable salt thereof, wherein *n* and *p* are 0.
27. 27. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1.
28. 28. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 2.
29. 29. The compound of any one of embodiments 1-28, or a pharmaceutically acceptable salt thereof, that is a USP30 Inhibitor Compound having an IC50 value of ≤ 1 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1.
30. 30. The compound of embodiment 29, or a pharmaceutically acceptable salt thereof, wherein the IC50 value is ≤ 0.1 μM.
31. 31. A compound of formula (I-C)



(I-C),

or a pharmaceutically acceptable salt thereof, that is a USP30 Inhibitor Compound having an IC_{50} value of ≤ 1 μM and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1, wherein:

each occurrence of R^2 and R^5 is independently halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl;

n is 0-4;

p is 0-4;

R^h is hydrogen;

R^a, R^b, R^c, R^d, R^e, R^f, and R^g are defined as follows:

(ii) R^a and R^e form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^b, R^c, R^d, R^f, and R^g are each hydrogen; or

(iv) R^b and R^c form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^e, R^d, R^f, and R^g are each hydrogen; or

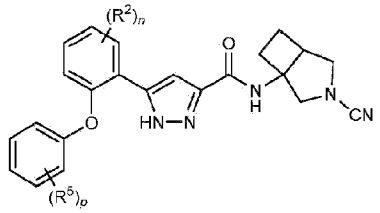
(vii) R^c and R^d together with the atom to which they are attached, form a 3 membered cycloalkyl; and R^a, R^b, R^e, R^f, and R^g are each hydrogen; or

(x) R^c and R^g form a C_1-C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^d, R^e, and R^f are each hydrogen; or

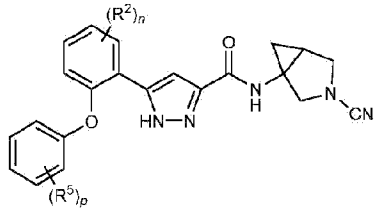
(xi) R^e and R^f together with the atom to which they are attached, form a 4 membered heterocycloalkyl; and R^a, R^b, R^c, R^d, and R^g are each hydrogen; or

(xiii) R^e and R^g form a C_2 alkylene group between the atoms to which they are attached; and R^a, R^b, R^c, R^d, and R^f are each independently hydrogen.

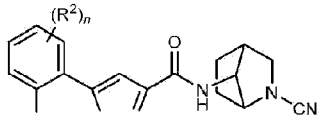
32. 32. The compound of embodiment 31, or a pharmaceutically acceptable salt thereof, wherein the compound has the following formula

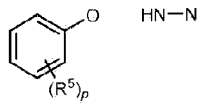


33. 33. The compound of embodiment 31, or a pharmaceutically acceptable salt thereof, wherein the compound has the following formula

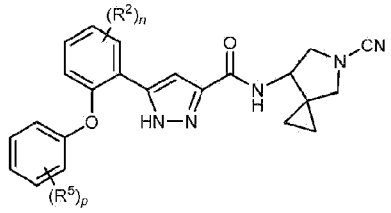


34. 34. The compound of embodiment 31, or a pharmaceutically acceptable salt thereof, wherein the compound has the following formula

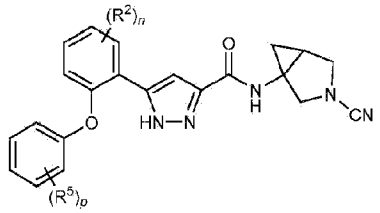




35. 35. The compound of embodiment 31, or a pharmaceutically acceptable salt thereof, wherein the compound has the following formula



36. 36. The compound of any one of embodiments 31-35, or a pharmaceutically acceptable salt thereof, wherein *n* and *p* are 0.
37. 37. A pharmaceutical composition comprising the compound of any one of embodiments 1-36, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
38. 38. A method of inhibiting a ubiquitin-specific protease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of embodiments 1-36, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 37.
39. 39. The method of embodiment 38, wherein the ubiquitin-specific protease is USP30.
40. 40. A method of treating a neurodegenerative disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of embodiments 1-36, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 37.
41. 41. The method of embodiment 40, wherein the neurodegenerative disorder is Parkinson's Disease.
42. 42. A compound of any one of embodiments 1-36, or a pharmaceutically acceptable salt thereof, for use in a method of inhibiting a ubiquitin-specific protease in a patient in need thereof.
43. 43. The compound or pharmaceutically acceptable salt for use of embodiment 42, wherein the ubiquitin-specific protease is USP30.
44. 44. A compound of any one of embodiments 1-36, or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurodegenerative disorder in a patient in need thereof.
45. 45. The compound or pharmaceutically acceptable salt for use of embodiment 44, wherein the neurodegenerative disorder is Parkinson's Disease.
46. 46. A USP30 Inhibitor Compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

each occurrence of R^2 and R^5 is independently halo, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_1-C_6 haloalkyl, or C_1-C_6 hydroxyalkyl;

n is 0-4;

p is 0-4.

47. 47. The compound of any one of embodiments 1-36 or 44-46, having an IC_{50} value of ≤ 0.5 μM and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1
48. 48. The compound of embodiment 47, having an IC_{50} value of ≤ 0.1 μM and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1.
49. 49. A USP30 Inhibitor Compound as disclosed and provided herein.
50. 50. The USP30 Inhibitor Compound of embodiment 49, having an IC_{50} value of ≤ 1 μM and > 0.001 μM as measured in a Ubiquitin-Rhodamine 110 Assay as described in Example 1.

EXAMPLES

General Methods

[0175] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[0176] Proton NMR spectra were recorded using a Bruker Plus 400 NMR Spectrometer. The deuterated solvent (DMSO-d_6) typically contained 0.03% to 0.05% v/v tetramethylsilane, which was used as the reference signal (set at δ 0.00 for 1H).

[0177] LCMS analyses were performed on a SHIMADZU LCMS consisting of an UFLC 20-AD and LCMS 2020 MS detector. The column used was a Shim-pack XR-ODS, 2.2 μm, 3.0 × 50 mm. The instrument uses reverse-phase conditions (acetonitrile / water, containing 0.05% ammonia).

Abbreviations

[0178] Unless otherwise noted, or where the context dictates otherwise, the following abbreviations shall be understood to have the following meanings:

δ
: chemical shift

ACN
: Acetonitrile

DIEA
: N,N-Diisopropylethylamine

DMF
: N,N-Dimethylformamide

DCM
: Dichloromethane or methylene chloride

h
: hour

^{1}H NMR
: proton nuclear magnetic resonance

HATU
: 2-(3H-[1,2,3]Triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate

HPLC
: high performance liquid chromatography

Hz
: Hertz

LCMS
: liquid chromatography/mass spectrometry

min
: minutes

MS
: mass spectrometry

ppm
: parts per million

RT
: retention time

SEMCl
: 2-chloromethyl 2-(trimethylsilyl)ethyl ether

TFA
: Trifluoroacetic acid

THF
: Tetrahydrofuran

XPhos-Pd
: Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

XPhos-Pd-G3
: (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methane sulfonate

Example 1: Ubiquitin-Rhodamine 110 Assay for USP30 Activity

[0179] The assay was performed in a final volume of 9 µL in assay buffer containing 20 mM Tris-HCl (pH 8.0, (1M Tris-HCl, pH 8.0 solution; Coming 46-031-CM)), 1 mM GSH (L-glutathione reduced, Sigma-Aldrich, G4251-100G), 0.03% BGG (0.22 µM filtered, Sigma, G7516-25G), and 0.01% Triton X-100 (Sigma, T9284-10L). Nanoliter quantities of 10-point, 3-fold serial dilution in DMSO were pre-dispensed into 1536 assay plates (Corning, #3724BC) for a final test concentration of 25 µM to 1.3 nM, top to lowest dose, respectively. Concentration and incubation times were optimized for the maximal signal-to-background while maintaining initial velocity conditions at a fixed substrate concentration. The final concentration of USP30 (human recombinant USP30, Boston Biochem, cat. # E-582) in the assay was 0.2 nM. Final substrate (Ub-Rh110; Ubiquitin-Rhodamine 110, UbiQ-126) concentration was 25 nM with [Ub-Rh110]<<Km. 3 µL of 2× USP30 was added to assay plates (pre-stamped with compound), preincubated for 30 minutes and then treated with 3 µL of 2× Ub-Rh110. Plates were incubated for 30 minutes at room temperature before addition of 3 µL of stop solution (final concentration of 10 mM citric acid (Sigma, 251275-500G)). Fluorescence was read on the Envision (excitation at 485 nm and emission at 535 nm; Perkin Elmer) or on the PheraSTAR (excitation at 485 nm and emission at 535 nm; BMG Labtech) fluorescence reader.

[0180] For all assay formats, data were reported as percent inhibition compared with control wells based on the following equation: % inh = 1 - ((FLU - AveLow) / (AveHigh - AveLow)) where FLU = measured Fluorescence, AveLow = average Fluorescence of no enzyme control (n=16), and AveHigh= average Fluorescence of DMSO control (n=16). IC_{50} values were determined by curve fitting of the standard 4 parameter logistic fitting algorithm included in the Activity Base software package: IDBS XE Designer Model205. Data is fitted using the Levenburg Marquardt algorithm.

[0181] The calculated IC_{50} values of the compounds described herein are reported in Table 3, where A represents an IC_{50} of < 0.1 µM, B represents an IC_{50} of 0.1 to 1.0 µM, and C represents an IC_{50} of > 1.0 µM. Compounds in the USP30 biochemical assay were deemed active if the IC_{50} was ≤ 1 µM.

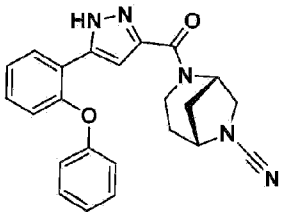
Table 3. IC_{50} Values of Compounds in Ubiquitin-Rhodamine 110 Assay

Compound	**IC_{50} (µM)**
1-a	B
1b	A
2-a	A
2-b	C
3-a	B

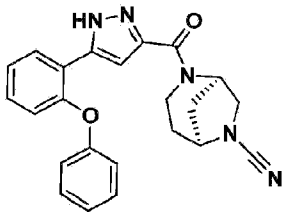
Compound	IC_{50} (μM)
3-b	A
4-a	B
4-b	B
5-a	A
5-b	B
6-a	A
6-b	B
7-a	A
7-b	B
8-a	B
8-b	B
9-a	C
9-b	C
13-a	A
13-b	A
20-a	A
20-b	A

Example 2: Preparation of (1S,5R)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile (1-a) and (1R,5S)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile (1-b)

[0182]

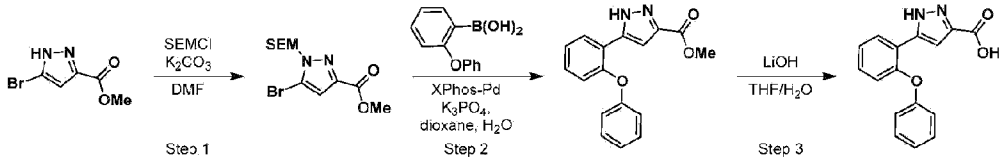


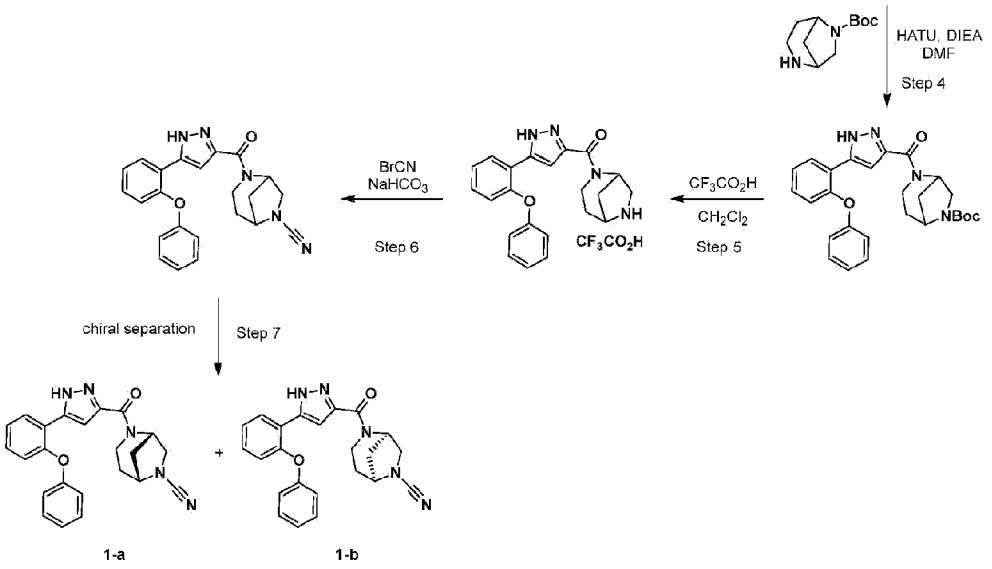
Compound 1-a



Compound 1-b

[0183] Compounds **1-a** and **1-b** were prepared by the following route:





Step 1. Methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0184] 2-Chloromethyl 2-(trimethylsilyl)ethyl ether (12.3 mL, 69.5 mmol) was added to a mixture of methyl 5-bromo-1H-pyrazole-3-carboxylate (5.00 g, 23.2 mmol) and K_2CO_3 (18.0 g, 130 mmol) in DMF (50 mL) at 0 °C in an ice/water bath. The resulting solution was stirred for 14 h at 25 °C. The reaction was quenched by the addition of water (100 mL). The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 15:1 petroleum ether/ethyl acetate) to afford methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate as a yellow oil (6.20 g, 79%). LCMS (ES, m/z) 335, 337 $[M+H]^+$.

Step 2. Methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0185] A solution of methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (6.20 g, 18.4 mmol), (2-phenoxyphenyl)boronic acid (4.96 g, 23.2 mmol), XPhos-Pd (2.90 g, 3.68 mmol) and K_3PO_4 (11.7 g, 55.2 mmol) in dioxane (120 mL) and H_2O (24 mL) was stirred for 15 h at 100 °C in an oil bath. After cooling to 25 °C, the solids were filtered out. The filtrate was concentrated under vacuum. The residue was diluted with water (50 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase chromatography (Column: XBridge Shield RP18 OBD Column, 5 μm, 30 × 150 mm; Mobile phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: ACN (5 % B to 72 % over 20 min); Detector: UV:220 and 254 nm) to afford methyl 5-(2-

phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate as a yellow solid (3.20 g, 41%). LCMS (ES, m/z) 425 $[M+H]^+$.

Step 3. 5-(2-Phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid

[0186] A solution of methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (1.40 g, 3.30 mmol) and LiOH (0.810 g, 33.8 mmol) in THF (60 mL) and H_2O (15 mL) was stirred for 4 h at 50 °C. The mixture was allowed to cool to 25 °C and concentrated under vacuum. The pH value of the residue was adjusted to 5-6 with 3 N hydrochloric acid. The solids were collected by filtration and dried in an oven to afford 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy] methyl]-1H-pyrazole-3-carboxylic acid as an off-white solid (1.05 g, 78%). LCMS (ES, m/z) 411 $[M+H]^+$.

Step 4. tert-butyl 2-[5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carboxylate

[0187] A solution of 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid (150 mg, 0.366 mmol), HATU (210 mg, 0.541 mmol), tert-butyl 2,6-diazabicyclo[3.2.1]octane-6-carboxylate (75.0 mg, 0.346 mmol) and DIEA (0.2 mL, 1.40 mmol) in DMF (2 mL) was stirred for 3 h at 25 °C. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting with 1/1 petroleum ether/ethyl acetate) to afford tert-butyl 2-[5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carboxylate as a white solid (100 mg, 45%). LCMS (ES, *m/z*): 605 $[M+H]^+$.

Step 5. 2-[5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane 2,2,2-trifluoroacetate

[0188] A solution of tert-butyl 2-[5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carboxylate (100 mg, 0.157 mmol) and TFA (1 mL) in DCM (2 mL) was stirred for 2 h at 25 °C. The resulting mixture was concentrated under vacuum to afford 2-[5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane 2,2,2-trifluoroacetate as a colorless oil (110 mg, crude). LCMS (ES, *m/z):* 375 $[M+H]^+$.

Step 6. 2-[5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile

[0189] Cyanogen bromide (17.8 mg, 0.170 mmol) was added to a 0 °C mixture of 2-[5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane 2,2,2-trifluoroacetate (80.0 mg, 0.170 mmol) and $NaHCO_3$ (82.0 mg, 0.957 mmol) in DMF (2 mL). The resulting mixture stirred for 16 h at 25 °C. The reaction was quenched by the addition of water (10 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 × 150 mm; Mobile Phase A: water (containing 10 mmol/L NH4HCO_3) and B: CH_3CN (30% to 55% in 8 min); Flow rate: 25 mL/min; Detector: 220 nm) to afford 2-[5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile as a white solid (40.0 mg, 59%). LCMS (ES, *m/z):* 400 $[M+H]^+$.

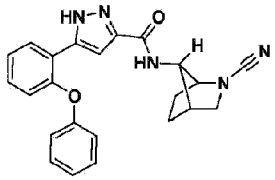
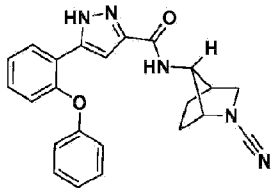
Step 7. (1S,SR)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile and (1R,5S)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile

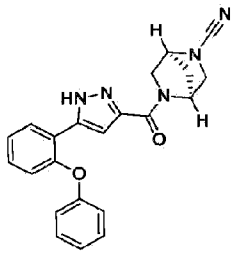
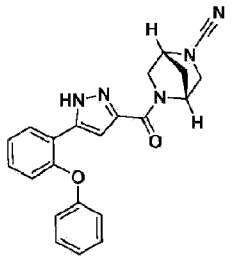
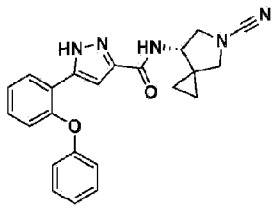
[0190] 2-[5-(2-Phenoxyphenyl)-1H-pyrazole-3-carbonyl]-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile (40.0 mg, 0.100 mmol) was separated by chiral-HPLC (Column: CHIRAL ART Cellulose-SB, 2 × 25 cm, 5um; Mobile Phase A: n-hexane and B: EtOH (hold 50% in 15 min); Flow rate: 20 mL/min; Detector: 254/220 nm; RT_1: 8.911 min and RT_2: 11.119 min). The first eluting isomer (RTi= 8.911 min) was collected and concentrated under vacuum, then lyophilized to obtain a compound for which the absolute stereochemistry was arbitrarily assigned as (1S,5R)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile **(1-a)** as a white solid (13.8 mg, 35%). LCMS (ES, *m/z):* 400 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.63 (br s, 1H), 7.86-7.85 (m, 1H), 7.44-7.29 (m, 4H), 7.13-6.90 (m, 5H), 5.49-5.18 (m, 1H), 4.65-4.31 (m, 1H), 4.18-4.17 (m, 1H), 3.65-3.46 (m, 3H), 3.08-3.03 (m, 1H), 1.86-1.72 (m, 4H). The second eluting isomer (RT_2= 11.119 min) was collected and concentrated under vacuum, then lyophilized to obtain a compound for which the absolute stereochemistry was arbitrarily assigned as (1R,SS)-2-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,6-diazabicyclo[3.2.1]octane-6-carbonitrile **(1-b)** as a white solid (14.8 mg, 37%). LCMS (ES, *m/z):* 400 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.63 (br s, 1H), 7.88-7.85 (m, 1H), 7.44-7.29 (m, 4H), 7.14-6.90 (m, 5H), 5.48-5.17 (m, 1H), 4.65-4.31 (m, 1H), 4.18-4.17 (m, 1H), 3.65-3.48 (m, 3H), 3.08-3.03 (m, 1H), 1.86-1.72 (m, 4H).

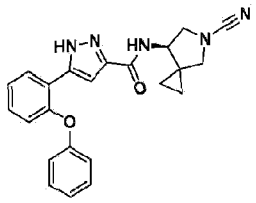
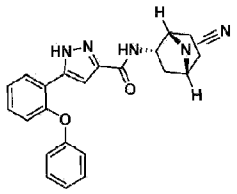
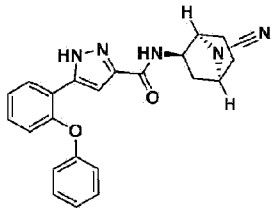
[0191] The compounds set forth in Table 4 were prepared by methods analogous to the

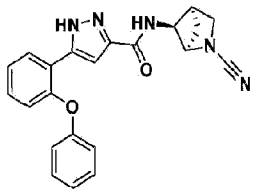
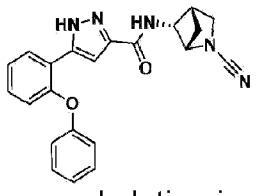
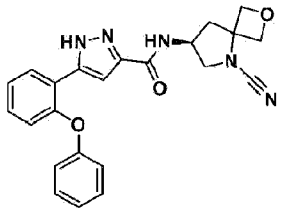
preparation of compounds 1-a and 1-b. Each pair of compounds listed in Table 4 (i.e., compounds 2-a and 2-b, compounds 3-a and 3-b, etc.) was obtained as a racemic mixture, and were then separated by chiral HPLC according to the procedure described in Example 2, Step 7, to obtain the individual compounds in substantially enantiomerically pure form. The first and second eluting enantiomer of each enantiomer pair is identified in Table 4. The absolute stereochemistry of each enantiomer was arbitrarily assigned.

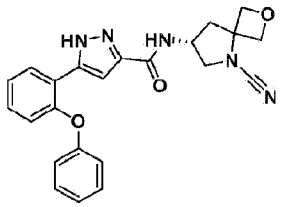
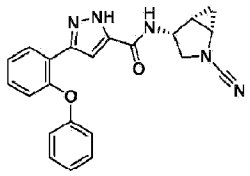
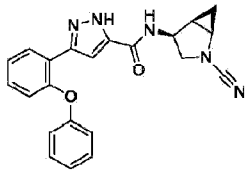
Table 4. Additional Compounds Prepared By Analogous Methods

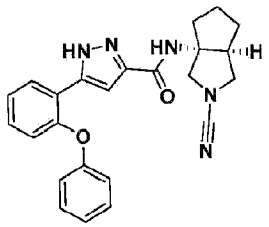
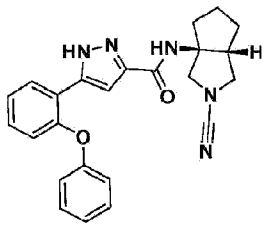
Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
2-a	 first eluting isomer	N-((1S,4S,7S)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.7-13.6 (m, 1H), 8.42-8.15 (m, 1H), 8.04-7.85(m, 1H), 7.42-7.29 (m, 4H), 7.15-7.10 (m, 1H), 7.02-6.95 (m, 4H), 4.06-4.04 (m, 1H), 3.84-3.82 (m, 1H), 3.52-3.49 (m, 1H), 3.10-3.06 (m, 1H), 2.67-2.62 (m, 1H), 1.97-1.88 (m, 1H), 1.84-1.71 (m, 2H), 1.54-1.48 (m, 1H).
2-b	 second eluting isomer	N-((1R,4R,7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm):13.8-13.6 (m, 1H), 8.57-8.15 (m, 1H), 8.02-7.86 (m, 1H), 7.40-7.22 (m, 4H), 7.15-7.11 (m, 1H), 7.01-6.97 (m, 4H), 4.06-4.04 (m, 1H), 3.83-3.81 (m, 1H), 3.53-3.50 (m, 1H), 3.09-3.06 (m, 1H), 2.71-2.60 (m, 1H), 1.97-1.88 (m, 1H), 1.84-1.71 (m, 2H), 1.54-1.48 (m, 1H).

Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
4-a	 first eluting isomer	(1S,4S)-5-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carbonitrile	386	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.7 (br s, 1H), 7.91-7.89 (m, 1H), 7.44-7.37(m, 3H), 7.32-7.29 (m, 1H), 7.15-7.12 (m, 1H), 7.03-6.99 (m, 4H), 5.50-5.40 (m, 0.5H), 4.87-4.86 (m, 0.5H), 4.46-4.43 (m, 1H), 4.06-3.88 (m, 1H), 3.65-3.51 (m, 2H), 3.36-3.34 (m, 1H), 1.99-1.85 (m, 2H).
4-b	 second eluting isomer	(1R,4R)-5-(5-(2-phenoxyphenyl)-1H-pyrazole-3-carbonyl)-2,5-diazabicyclo[2.2.1]heptane-2-carbonitrile	386	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.7 (br s, 1H), 7.91-7.89 (m, 1H), 7.44-7.37(m, 3H), 7.32-7.29 (m, 1H), 7.15-7.12 (m, 1H), 7.03-6.99 (m, 4H), 5.50-5.40 (m, 0.5H), 4.87-4.86 (m, 0.5H), 4.46-4.43 (m, 1H), 3.99-3.88 (m, 1H), 3.65-3.51 (m, 2H), 3.44-3.34 (m, 1H), 1.99-1.81 (m, 2H).
5-a	 first eluting isomer	(S)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.6 (br s, 1H), 8.41-8.38 (m, 1H), 7.92-7.85(m, 1H), 7.41-7.29 (m, 4H), 7.15-7.12 (m, 1H), 7.02-6.91 (m, 4H), 4.25-4.20 (m, 1H), 3.82-3.78 (m, 1H), 3.68-3.65 (m, 1H), 3.52-3.44 (m, 1H), 3.25-3.24 (m, 1H), 0.80-0.59 (m, 4H).

Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
5-b	 second eluting isomer	(R)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.6 (br s, 1H), 8.41-8.38 (m, 1H), 7.92-7.85(m, 1H), 7.41-7.29 (m, 4H), 7.15-7.12 (m, 1H), 7.02-6.91 (m, 4H), 4.25-4.20 (m, 1H), 3.82-3.78 (m, 1H), 3.68-3.65 (m, 1H), 3.48-3.40 (m, 1H), 3.26-3.24 (m, 1H), 0.80-0.59 (m, 4H).
7-a	 first eluting isomer	N-((1S,2S,4R)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm):13.7-13.6 (m, 1H), 8.62-8.51 (m, 1H), 8.05-7.87 (m, 1H), 7.45-7.25 (m, 4H), 7.19-7.12 (m, 1H), 7.04-6.95 (m, 4H), 4.27-4.13 (m, 3H), 2.22-2.08 (m, 1H), 1.83-1.65 (m, 4H).
7-b	 second eluting isomer	N-((1R,2R,4S)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	400	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm):13.7-13.6 (m, 1H), 8.62-8.51 (m, 1H), 8.03-7.86(m, 1H), 7.47-7.25 (m, 4H), 7.15-7.10 (m, 1H), 7.01-6.95 (m, 4H), 4.30-4.15 (m, 3H), 2.22-2.10 (m, 1H), 1.88-1.62 (m, 4H).

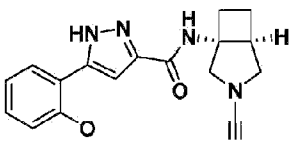
Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
8-a	 first eluting isomer	N-((1R,4R,5S)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	386	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.7 (br s, 1H), 7.94-7.88 (m, 2H), 7.41-7.28 (m, 4H), 7.16-7.12 (m, 1H), 7.03-6.92 (m, 4H), 4.20-4.19 (m, 1H), 3.83-3.82 (m, 1H), 3.45-3.43 (m, 1H), 2.94-2.92 (m, 1H), 1.78-1.76 (m, 1H), 1.32-1.29 (m, 1H).
8-b	 second eluting isomer	N-((1S,4S,5R)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	386	^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 13.6 (br s, 1H), 7.94-7.88 (m, 2H), 7.41-7.29 (m, 4H), 7.16-7.12 (m, 1H), 7.03-6.98 (m, 4H), 4.20-4.19 (m, 1H), 3.83-3.82 (m, 1H), 3.45-3.43 (m, 1H), 2.94-2.92 (m, 1H), 1.78-1.76 (m, 1H), 1.32-1.29 (m, 1H).
9-a	 first eluting isomer	N-[(7S)-5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl]-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	416	^{1}H-NMR (CD_3OD, 400 MHz) δ (ppm): 7.80-7.77 (m, 1H), 7.39-7.35 (m, 3H), 7.28-7.25 (m, 1H), 7.16-7.13 (m, 2H), 7.03-6.97 (m, 3H), 4.97-4.93 (m, 2H), 4.74-4.70 (m, 2H), 4.55-4.50 (m, 1H), 3.86-3.81 (m, 1H), 3.54-3.50 (m, 1H), 2.68-2.63 (m, 1H), 2.53-2.48 (m, 1H).

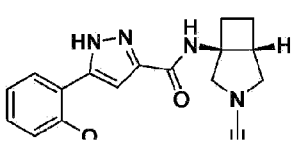
Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
9-b	 second eluting isomer	N-[(7R)-5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl]-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	416	^{1}H-NMR (CD_3OD, 400 MHz) δ (ppm): 7.80-7.77 (m, 1H), 7.39-7 35 (m, 3H), 7.28-7.25 (m, 1H), 7.16-7.13 (m, 2H), 7.03-6.97 (m, 3H), 4.97-4.90 (m, 2H), 4.74-4.70 (m, 2H), 4.55-4.51 (m, 1H), 3.86-3.82 (m, 1H), 3.54-3.50 (m, 1H), 2.68-2.63 (m, 1H), 2.53-2.48 (m, 1H).
13-a		N-((1S,4R,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide	386	^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.75-13.61 (m, 1H), 8.55-8.20 (m, 1H), 8.05-7.87 (m, 1H), 7.45-7.30 (m, 4H), 7.16-7.14 (m, 1H), 7.03-6.97 (m, 3H), 6.95-6.85 (m, 1H), 4.80-4.77 (m, 1H), 3.72-3.67 (m, 1H), 3.51-3.49 (m, 1H), 3.12-3.08 (m, 1H), 1.90-1.80 (m, 1H), 1.40-1.20 (m, 1H), 0.75-0.60 (m, 1H).
13-b		N-((1R,4S,5R)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazole-5-carboxamide		

Cmpd No.	Structure	IUPAC name	MS (ESI, m/z) $[M+H]^+$	^{1}H-NMR δ (ppm)
20-a		N-((3aR,6aS)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	414	^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.70-13.58 (m, 1H), 8.55-8.21 (m, 1H), 8.03-7.86 (m, 1H), 7.45-7.13 (m, 5H), 7.04-6.92 (m, 3H), 3.70-3.66 (m, 2H), 3.54-3.49 (m, 1H), 3.16-3.14 (m, 1H), 1.78-1.74 (m, 1H), 2.93-2.81 (m, 1H), 2.09-1.90 (m, 3H), 1.71-1.63 (m, 2H), 1.41-1.37 (m, 1H).
20-b		N-((3aS,6aR)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide	414	^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.62 (br s, 1H), 8.33 (br s, 1H), 7.94-7.93 (m, 1H), 7.42-7.30 (m, 3H), 7.28-7.26 (m, 1H), 7.16-7.14 (m, 1H), 7.12 (br s, 1H), 7.08-6.98 (m, 3H), 3.70-3.64 (m, 2H), 3.52-3.50 (m, 1H), 3.16-3.13 (m, 1H), 2.91-2.89 (m, 1H), 2.05-1.89 (m, 3H), 1.73-1.63 (m, 2H), 1.41-1.37 (m, 1H).

Example 3: Preparation of N-((1R,5S)-3-cvano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (6-a) and N-((1S,5R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (6-b)

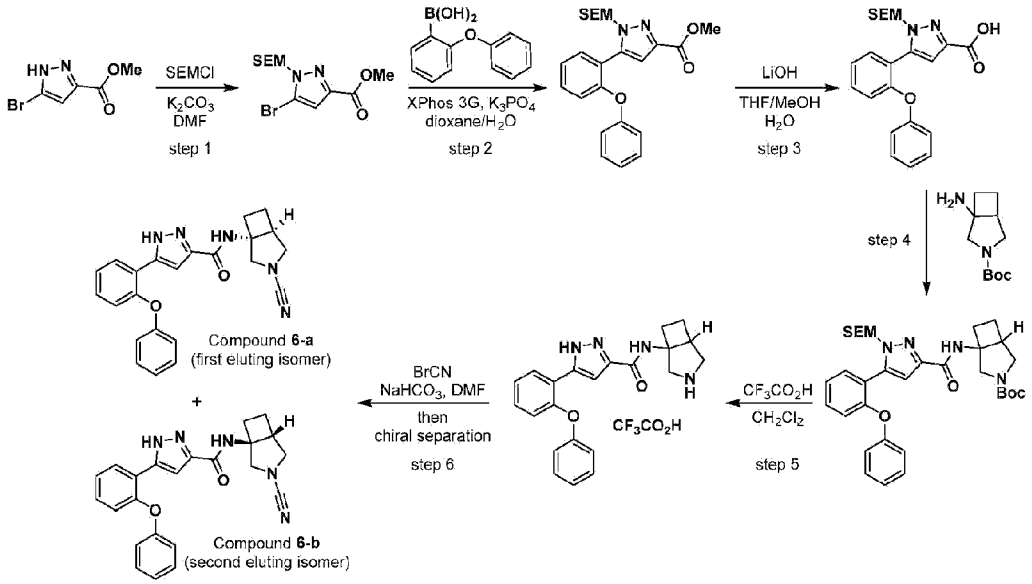
[0192]





Compound **6-a** Compound **6-b**

[0193] Compounds **6-a** and **6-b** were prepared by the following route:



Step 1. Methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0194] 2-(Trimethylsilyl)ethoxymethyl chloride (12.2 mL, 68.8 mmol) was added dropwise to a 0 °C solution of methyl 5-bromo-1H-pyrazole-3-carboxylate (5.00 g, 24.5 mmol) and potassium carbonate (18.0 g, 130 mmol) in DMF (10 mL). The resulting mixture was stirred for 14 h at 25 °C. The reaction was quenched with water (20 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 15:1 petroleum ether/ethyl acetate) to afford methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (6.20 g, 76%) as a yellow oil. LCMS (ES, m/z): 335, 337 $[M+H]^+$.

Step 2. Methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0195] A solution of methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (6.20 g, 18.5 mmol), (2-phenoxyphenyl)boronic acid (4.96 g, 23.2 mmol), XPhos-Pd-G3 (3.12 g, 36.9 mmol) and potassium phosphate tribasic (25.4 mg, 37.1 mmol) in dioxane (120 mL) and water (24 mL) was stirred for 15 h at 100 °C in an oil bath. The mixture was

cooled to 25 °C. The resulting mixture was concentrated under vacuum. The residue was diluted with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by reverse phase chromatography (Column: XBridge Shield RP18 OBD Column, 5 μm, 30 × 150 mm; Mobile phase, A: water (containing 0.05% ammonium hydrogen) and B: acetonitrile (5 % B to 72 % over 20 min); Detector: UV 220 and 254 nm) to afford methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate as a yellow solid (3.20 g, 41%). LCMS (ES, m/z): 425 $[M+H]^+$.

Step 3. 5-(2-Phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid

[0196] A solution of methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (1.40 g, 3.30 mmol) and lithium hydroxide (810 mg, 34.0 mmol) in THF (60.0 mL), water (15.0 mL), and methanol (300 mL) was stirred for 4 h at 50 °C. The mixture was cooled to 25 °C and concentrated under vacuum. The pH value of the residue was adjusted to 3-4 with 3 N aqueous hydrochloric acid solution. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (eluting with 2:1 petroleum ether/ethyl acetate) to afford 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid as an off-white solid (1.00 g, 74%). LCMS (ES, m/z): 411 $[M+H]^+$.

Step 4. tert-Butyl 1-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.2.0]heptane-3-carboxylate

[0197] A solution of 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid (300 mg, 0.723 mmol), tert-butyl 1-amino-3-azabicyclo[3.2.0]heptane-3-carboxylate (154 mg, 0.723 mmol), HATU (275 mg, 0.723 mmol) and N,N-diisopropylethylamine (0.239 mL, 1.45 mmol) in DMF (2 mL) was stirred for 40 min at 25 °C. The reaction was quenched with water (5 mL). The resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (eluting with 4:1 petroleum ether/ethyl acetate) to afford tert-butyl 1-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.2.0]heptane-3-carboxylate as an off-white solid (350 mg, 80%). LCMS (ES, m/z): 605 $[M+H]^+$.

Step 5. N-(3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate

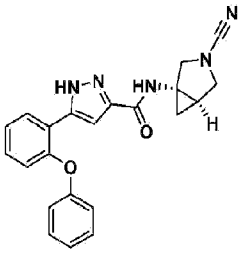
[0198] A solution of tert-butyl 1-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.2.0]heptane-3-carboxylate (350 mg, 0.579 mmol) in trifluoroacetic acid (1 mL) and dichloromethane (3 mL) was stirred for 30 min at 25 °C. The resulting mixture was concentrated under vacuum to afford N-(3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate as a brown oil (360 mg, crude). LCMS (ES, m/z): 375 $[M+H]^+$.

Step 6. N-((1R,5S)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (6-a) and N-((1S,5R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (6-b)

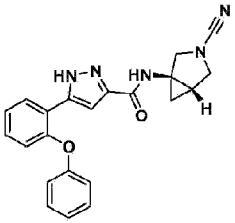
[0199] Cyanogen bromide (72.8 mg, 0.687 mmol) was added dropwise to a 0 °C solution of N-(3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate (350 mg, 0.763 mmol) and sodium bicarbonate (785 mg, 9.25 mmol) in DMF (2 mL). The mixture was stirred for 1 h at 25 °C. The solids were filtered out. The filtrate was directly purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 30 × 150 mm; Mobile phase, A: water (containing 0.05% ammonium hydrogen) and B: acetonitrile (35% B to 65 % over 7 min); Detector: UV 220 and 254 nm) to afford N-(3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide as a white solid (70.0 mg). This material was separated by chiral-HPLC (Column: Chiralpak IG, 2*25 cm, 5 μm; Mobile Phase, A: MTBE and B: EtOH (hold 15% in 24 min); Flow rate: 20 mL/min; Detector: 220/254 nm). The first elutinig isomer was collected, and the absolute stereochemistry was arbitrarily assigned as (1R,5S): N-((1R,5S)-3-cyano-3-azabicyclo[32.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (RTi=10.9 min) as a white solid **(6-a,** 28.5 mg, 10%). LCMS (ES, m/z): 400 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.68-13.62 (m, 1H), 8.92-8.61 (m, 1H), 8.03-7.86 (m, 1H), 7.42-7.23 (m, 4H), 7.21-7.12 (m, 1H), 7.03-6.89 (m, 4H) , 3.73-3.70 (m, 1H), 3.68-3.56 (m, 1H), 3.39-3.31 (m, 2H), 3.08-3.05 (m, 1H), 2.34-2.31 (m, 1H), 2.20-2.08 (m, 2H), 1.61-1.58 (m, 1H). The second eluting isomer was collected, and the absolute stereochemistry was arbitrarily assigned as (1S,5R): N-((1S,5R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (RT_2=12.7 min) as a white solid **(6-b,** 20.6 mg, 8%). LCMS (ES, m/z): 400 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.68-13.62 (m, 1H), 8.92-8.61 (m, 1H), 8.03-7.86 (m, 1H), 7.42-7.29 (m, 4H), 7.21-7.12 (m, 1H), 7.04-6.89 (m, 4H), 3.73-3.70 (m, 1H), 3.68-3.54 (m, 1H), 3.39-3.31 (m, 2H), 3.08-3.05 (m, 1H), 2.34-2.31 (m, 1H), 2.20-2.08 (m, 2H), 1.61-1.58 (m, 1H). Alternatively, the absolute stereochemistry of the first and second eluting isomers could have been arbitrarily assigned as (1S,5R) and (1R,5S), respectively.

Example 4: Preparation of N-((1S,5R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (3-a) and N-((1R,5S)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (3-b)

[0200]

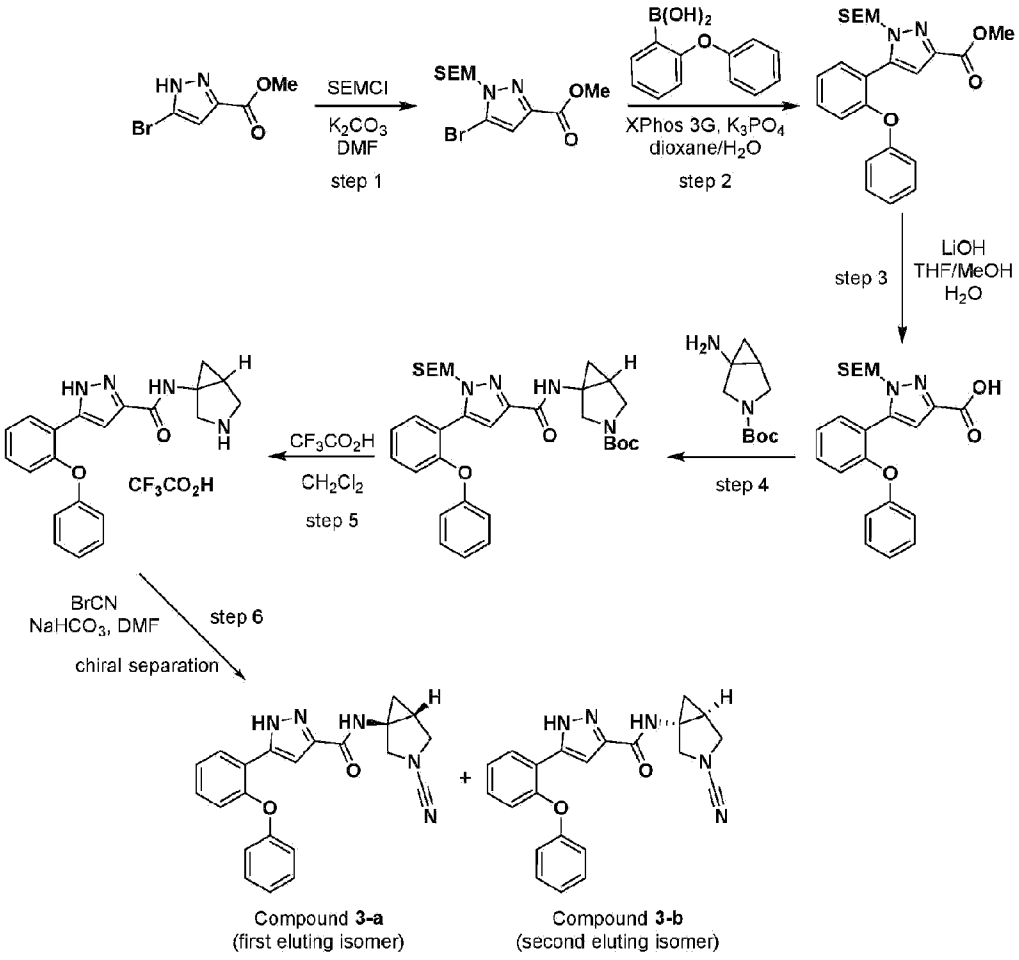


Compound **3-a**



Compound **3-b**

[0201] Compounds **3-a** and **3-b** were prepared by the following route:



Step 1. Methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0202] 2-(Trimethylsilyl)ethoxymethyl chloride (12.2 mL, 68.8 mmol) was added dropwise to a 0 °C solution of methyl 5-bromo-1H-pyrazole-3-carboxylate (5.00 g, 24.5 mmol) and potassium carbonate (18.0 g, 130 mmol) in DMF (10 mL). The resulting mixture stirred for 14 h at 25 °C.

The reaction was quenched with water (20 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 15:1 petroleum ether/ethyl acetate) to afford methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (6.20 g, 76%) as a yellow oil. LCMS (ES, m/z): 335, 337 $[M+H]^+$.

Step 2. Methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate

[0203] A solution of methyl 5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (6.20 g, 18.5 mmol), (2-phenoxyphenyl)boronic acid (4.96 g, 23.2 mmol), XPhos-Pd-G3 (3.12 g, 36.9 mmol) and potassium phosphate tribasic (25.4 mg, 37.1 mmol) in dioxane (120 mL) and water (24 mL) was stirred for 15 h at 100 °C in an oil bath. The mixture was cooled to 25 °C. The resulting mixture was concentrated under vacuum. The residue was diluted with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by reverse phase chromatography (Column: XBridge Shield RP18 OBD Column, 5 μm, 30 × 150 mm; Mobile phase, A: water (containing 0.05% ammonium hydrogen) and B: acetonitrile (5 % B to 72 % over 20 min); Detector: UV 220 and 254 nm) to afford methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate as a yellow solid (3.20 g, 41%). LCMS (ES, m/z): 425 $[M+H]^+$.

Step 3. 5-(2-Phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid

[0204] A solution of methyl 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylate (1.40 g, 3.30 mmol) and lithium hydroxide (810 mg, 34.0 mmol) in THF (60.0 mL), water (15.0 mL), and methanol (30.0 mL) was stirred for 4 h at 50 °C. The mixture was cooled to 25 °C and concentrated under vacuum. The pH value of the residue was adjusted to 3-4 with 3 N aqueous hydrochloric acid solution. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (eluting with 2:1 petroleum ether/ethyl acetate) to afford 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid as an off-white solid (1.00 g, 74%). LCMS (ES, m/z): 411 $[M+H]^+$.

Step 4. tert-butyl-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate

[0205] A solution of 5-(2-phenoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazole-3-carboxylic acid (300 mg, 0.723 mmol), tert-butyl 1-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (145 mg, 0.723 mmol), HATU (278 mg, 0.723 mmol) and N,N-diisopropylethylamine (0.242 mL, 1.47 mmol) in DMF (3 mL) was stirred for 30 min at 25 °C. The reaction was quenched with water (10 mL) at 25 °C. The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (eluting with 4:1 petroleum ether/ethyl acetate) to afford tert-butyl 1-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate as an off-white solid (280 mg, 67%). LCMS (ES, m/z): 591 $[M+H]^+$.

Step 5. N-(3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate

[0206] A solution of tert-butyl 1-(5-(2-phenoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (280 mg, 0.475 mmol) in trifluoroacetic acid (1 mL) and dichloromethane (3 mL) was stirred for 2 h at 25 °C. The resulting mixture was concentrated under vacuum to afford N-(3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate as a yellow oil (285 mg, crude). LCMS (ES, m/z): 361 $[M+H]^+$.

Step 6. N-((1S,SR)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-S-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (3-a) and N-((1R,5S)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (3-b)

[0207] Cyanogen bromide (58.5 mg, 0.552 mmol) was added dropwise to a 0 °C solution of N-(3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide 2,2,2-trifluoroacetate (280 mg, 0.613mmol) and sodium bicarbonate (653 mg, 7.69 mmol) in DMF (2 mL). The mixture was stirred for 1 h at 25 °C. The reaction was cooled to 0 °C and quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 30 × 150 mm; Mobile phase, A: water (containing 0.05% ammonium hydrogen) and B: acetonitrile (28 % B to 48 % over 7 min); Detector: UV 220 and 254 nm) to afford N-(3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide as a white solid (60.0 mg). This material was separated by chiral-HPLC (Column: Chiralpak IG, 2*25 cm, 5 μm; Mobile Phase, A: MTBE and B: EtOH (hold 30% in 10.5 min); Flow rate: 13 mL/min; Detector: 220/254 nm). The first eluting isomer was collected, and the absolute stereochemistry was arbitrarily assigned as (1S,5R): N-((1S,SR)-3-

cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (RT1=6.45 min) as a pink solid (3-a, 30.3 mg, 14%). LCMS (ES, m/z): 386 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.72-13.64 (m, 1H), 9.08-8.70 (m, 1H), 8.05-7.85 (m, 1H), 7.44-7.29 (m, 4H), 7.20-7.12 (m, 1H), 7.04-6.87 (m, 4H), 3.69-3.66 (m, 1H), 3.57-3.48 (m, 3H), 1.78-1.74 (m, 1H), 1.17-1.14 (m, 1H), 0.87-0.82 (m, 1H). The second eluting isomer was collected, and the absolute stereochemistry was arbitrarily assigned as (1R,5S); N-((1R,5S)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazole-3-carboxamide (RT2=8.97 min) (3-b, 29.9 mg, 14%) as a white solid. LCMS (ES, m/z): 386 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 13.72-13.64 (m, 1H), 9.08-8.70 (m, 1H), 8.05-7.85 (m, 1H), 7.44-7.29 (m, 4H), 7.22-7.12 (m, 1H), 7.04 -6.87 (m, 4H), 3.69-3.66 (m, 1H), 3.57-3.51 (m, 3H), 1.78-1.74 (m, 1H), 1.17-1.14 (m, 1H), 0.87-0.82 (m, 1H). Alternatively, the absolute stereochemistry of the first and second eluting isomers could have been arbitrarily assigned as (1R,5S) and (1S,5R), respectively.

[0208] Many modifications and variations of the embodiments described herein may be made without departing from the scope of the claims, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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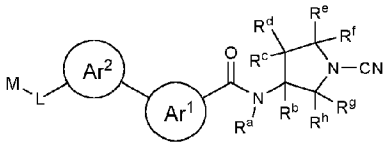
- **NAKAMURA et al.**Mol Biol Cell, 2008, vol. 19, 51903-1911 [0011]
- **BINGOL et al.**Nature, 2014, vol. 510, 7505370-5 [0011]
- **S. M. BERGE et al.**pharmaceutically acceptable salts in detailJ. Pharmaceutical Sciences, 1977, vol. 66, 1-19 [0025]
- Remington's Pharmaceutical SciencesMack Publishing Co.19900000 [0164]
- **T. W. GREENEP. G. M. WUTS**Protective Groups in Organic SynthesisWiley19990000 [0172]

Patentkrav

1. Forbindelse med formel (I):



(I);

eller et farmaceutisk acceptabelt salt deraf, hvor

R^a, R^b, R^c, R^d, R^e, R^f, R^g og R^h er defineret som følger:

(i) R^a og R^b danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_4-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^c, R^d, R^e, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(ii) R^a og R^e danner en C_1-C_2-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_2-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^b, R^c, R^d, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(iii) R^a og R^g danner en C_1-C_3-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_3-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^b, R^c, R^d, R^e, R^f og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(iv) R^b og R^c danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_4-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^d, R^e, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(v) R^b og R^e danner en C_1-C_3-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_3-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^c, R^d, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(vi) R^b og R^g danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_4-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^c, R^d, R^e, R^f og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(vii) R^c og R^d sammen med atomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl, hvor nævnte 3-6-leddet cycloalkyl eller heterocycloalkyl er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^b, R^e, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(viii) R^c og R^d sammen danner =O; og R^a, R^b, R^e, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(ix) R^c og R^e danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_4-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^b, R^d, R^f, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(x) R^c og R^g danner en C_1-C_3 alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_3-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^b, R^d, R^e, R^f og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(xi) R^e og R^f sammen med atomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl, hvor nævnte 3-6-leddet cycloalkyl eller heterocycloalkyl er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^b, R^c, R^d, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(xii) R^e og R^f sammen danner =O; og R^a, R^b, R^c, R^d, R^g og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(xiii) R^e og R^g danner en C_1-C_3-alkylengruppe mellem atomerne, til hvilke de er bundet, hvor nævnte C_1-C_3-alkylengruppe er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-

halogenalkyl; og R^a, R^b, R^c, R^d, R^f og R^h er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(xiv) R^g og R^h sammen med atomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl, hvor nævnte 3-6-leddet cycloalkyl eller heterocycloalkyl er substitueret med 0-4 substituenter valgt fra gruppen bestående af halogen, C_1-C_3-alkyl og C_1-C_3-halogenalkyl; og R^a, R^b, R^c, R^d, R^e og R^f er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; eller

(xv) R^g og R^h sammen danner =O; og R^a, R^b, R^c, R^d, R^e og R^f er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl; og

Ar^1 er phenylen eller 5-6-leddet heteroarylen, hvor nævnte phenylen eller heteroarylen er substitueret med *m* R^1-grupper; og

Ar^2 er phenylen eller 5-10-leddet heteroarylen, hvor nævnte phenylen eller heteroarylen er substitueret med *n* R^2-grupper;

L er -O-, -S-, -NR^3-, -$C(R^4)_2$-, -$S(O)_2$- eller -S(O)-;

M er 3-6-leddet cycloalkyl, phenyl eller 5-6-leddet heteroaryl, hvor nævnte cycloalkyl, phenyl eller heteroaryl er substitueret med p R^5-grupper;

hver forekomst af R^1, R^2 og R^5 er uafhængigt halogen, cyano, NO_2, oxo, hydroxyl, -R^6, -OR^6, C_1-C_6-alkyl, C_1-C_6-halogenalkyl, C_1-C_6-hydroxyalkyl, -C_1-C_6-alkylen-R^6, C_1-C_6-alkoxy, C_1-C_6-halogenalkoxy, -C_0-C_3-alkylen-NR^6R^7, -C_0-C_3-alkylen-NR^7R^8, -C_0-C_3-alkylen-$C(O)NR^6R^7$, -C_0-C_3-alkylen-$C(O)NR^7R^8$, -C_0-C_3-alkylen-$NR^7C(O)R^6$, -C_0-C_3-alkylen-$NR^7C(O)R^8$, -C_0-C_3-alkylen-$NR^7S(O)_2R^6$, -C_0-C_3-alkylen-$C(O)R^6$, -C_0-C_3-alkylen-$C(O)R^7$, -C_0-C_3-alkylen-SR^6, -C_0-C_3-alkylen-$S(O)R^6$, -C_0-C_3-alkylen-$S(O)_2R^6$, -C_0-C_3-alkylen-$S(O)_2R^7$, -C_0-C_3-alkylen-$S(O)_2NR^6R^7$, -C_0-C_3-alkylen-$S(O)_2NR^7R^8$, -C_0-C_3-alkylen-$NR^7C(O)NR^8R^9$, -C_0-C_3-alkylen-$NR^7S(O)_2NR^8R^9$, -C_0-C_3-alkylen-$C(O)OR^7$, -C_0-C_3-alkylen-$C(O)OR^6$, -C_0-C_3-alkylen-$OC(O)R^7$, -C_0-C_3-alkylen-$OC(O)R^6$, -C_0-C_3-alkylen-$NR^7C(O)OR^8$ eller -C_0-C_3-alkylen-$NR^7S(O)_2R^8$;

R^3 er H, C_1-C_6-alkyl eller C_1-C_6-halogenalkyl;

hvert R^4 er uafhængigt H, C_1-C_6-alkyl eller C_1-C_6-halogenalkyl, eller to R^4-grupper sammen med carbonatomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl;

hvert R^6 er 5-10-leddet heteroaryl, 4-10-leddet heterocycloalkyl, 6-10-leddet aryl eller 3-8-leddet cycloalkyl, hvor nævnte heteroaryl, heterocycloalkyl, aryl eller cycloalkyl er eventuelt substitueret med 1-5

substituenter uafhængigt valgt fra gruppen bestående af halogen, oxo, C_1-C_6-alkyl, C_1-C_6-halogenalkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy, C_1-C_6-halogenalkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, 5-10-leddet heteroaryl, 4-10-leddet heterocycloalkyl, 6-10-leddet aryl, 3-8-leddet cycloalkyl, -$NR^{10}C(O)NR^{11}R^{12}$, - $NR^{10}R^{11}$, -$C(O)R^{10}$, -$NR^{10}C(O)R^{11}$, -$NR^{10}C(O)OR^{11}$, -$S(O)_2R^{10}$, -$C(O)NR^{10}R^{11}$, -$C(O)OR^{10}$, - $S(O)_2NR^{10}R^{11}$, -$NR^{10}S(O)_2R^{11}$, -OR^{10}, -$OC(O)R^{10}$, -$OS(O)_2R^{10}$, -$OC(O)NR^{10}R^{11}$, - $OC(O)OR^{10}$, -$OS(O)_2NR^{10}R^{11}$, -$C(O)NR^{10}C(O)NR^{11}R^{12}$, -$C(O)C(O)R^{10}$, -$C(O)NR^{10}C(O)R^{11}$, -$C(O)NR^{10}C(O)OR^{11}$, -$C(O)S(O)_2R^{10}$, -$C(O)C(O)NR^{10}R^{11}$, -$C(O)C(O)OR^{10}$, -$C(O)S(O)_2NR^{10}R^{11}$, -$C(O)NR^{10}S(O)_2R^{11}$, -$C_1$-$C_6$-alkylen-$R^{10}$, -$C_1$-$C_6$-alkylen-$NR^{10}C(O)NR^{11}R^{12}$, -$C_1$-$C_6$-alkylen-$NR^{10}R^{11}$, -$C_1$-$C_6$-alkylen-$C(O)R^{10}$, -$C_1$-$C_6$-alkylen-$NR^{10}C(O)R^{11}$, -$C_1$-$C_6$-alkylen-$NR^{10}C(O)OR^{11}$, -$C_1$-$C_6$-alkylen-$S(O)_2R^{10}$, -$C_1$-$C_6$-alkylen-$C(O)NR^{10}R^{11}$, -$C_1$-$C_6$-alkylen-$C(O)OR^{10}$, -$C_1$-$C_6$-alkylen-$S(O)_2NR^{10}R^{11}$, -$C_1$-$C_6$-alkylen-$NR^{10}S(O)_2R^{11}$, -$C_1$-$C_6$-alkenylen-$R^{10}$, -$C_1$-$C_6$-alkenylen-$NR^{10}C(O)NR^{11}R^{12}$, -$C_1$-$C_6$-alkenylen-$NR^{10}R^{11}$, -$C_1$-$C_6$-alkenylen-$C(O)R^{10}$, -$C_1$-$C_6$-alkenylen-$NR^{10}C(O)R^{11}$, -$C_1$-$C_6$-alkenylen-$NR^{10}C(O)OR^{11}$, -$C_1$-$C_6$-alkenylen-$S(O)_2R^{10}$, -$C_1$-$C_6$-alkenylen-$C(O)NR^{10}R^{11}$, -$C_1$-$C_6$-alkenylen-$C(O)OR^{10}$, -$C_1$-$C_6$-alkenylen-$S(O)_2NR^{10}R^{11}$ og -C_1-C_6-alkenylen-$NR^{10}S(O)_2R^{11}$;

hvert R^7, R^8 og R^9 er uafhængigt hydrogen eller C_1-C_6-alkyl;

hvert R^{10}, R^{11} og R^{12} er uafhængigt hydrogen, C_1-C_6-alkyl, 5-10-leddet heteroaryl, 4-10 leddet heterocycloalkyl, 6-10 leddet aryl eller 3-8 leddet cycloalkyl;

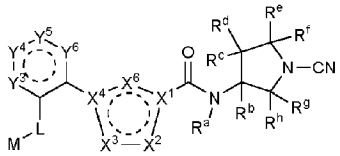
m er 0-4;

n er 0-4; og

p er 0-4.

2. Forbindelsen ifølge krav 1, hvor forbindelsen er:

(a) med formel (I-B):



(I-B)

eller et farmaceutisk acceptabelt salt deraf, hvor:

X^1 er C eller N;

X^2 er CH, CR^1, O, S, N, NH eller NR^1, så vidt valensen tillader det;

X^3 er CH, CR^1, O, S, N, NH eller NR^1, så vidt valensen tillader det;

X^4 er C eller N;

X^6 er CH, CR^1, O, S, N, NH eller NR^1, så vidt valensen tillader det;

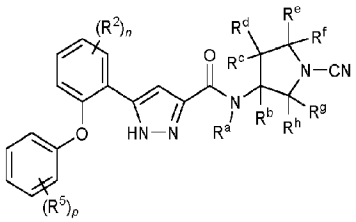
Y^3 er CH, CR^2 eller N;

Y^4 er CH, CR^2 eller N;

Y^5 er CH, CR^2 eller N;

Y^6 er CH, CR^2 eller N; og/eller

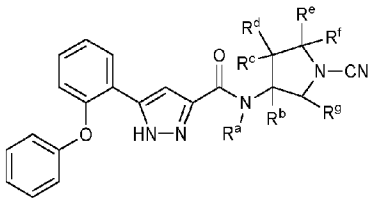
(b) med formel (I-C):



(I-C)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(c) med formel (I-E):



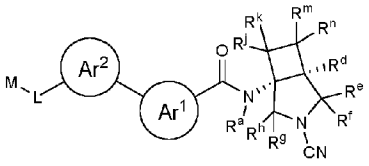
(I-E)

eller et farmaceutisk acceptabelt salt deraf.

3. Forbindelsen ifølge krav 1 eller krav 2, hvor R^b og R^c danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet, og R^a, R^d, R^e, R^f, R^g og R^h er hver hydrogen.

4. Forbindelsen ifølge et hvilket som helst af kravene 1-3, hvor forbindelsen er:

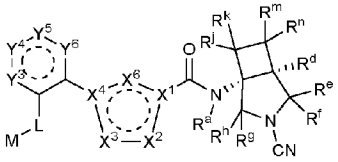
(a) med formel (I-1):



(I-1)

eller et farmaceutisk acceptabelt salt deraf, hvor R^j, R^k, R^m og R^n er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl, eventuelt hvor:

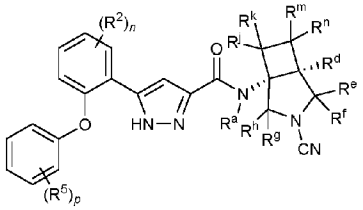
(i) forbindelsen er med formel (I-B-1):



(I-B-1)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(ii) forbindelsen er med formel (I-C-1):

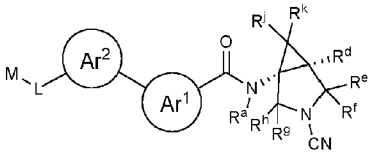


(I-C-1)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(iii) R^a, R^d, R^e, R^f, R^g, R^h, R^j, R^k, R^m og R^n er hver hydrogen; eller

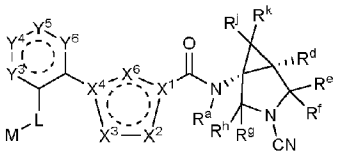
(b) med formel (I-2):



(I-2)

eller et farmaceutisk acceptabelt salt deraf, hvor R^j og R^k er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl, eventuelt hvor:

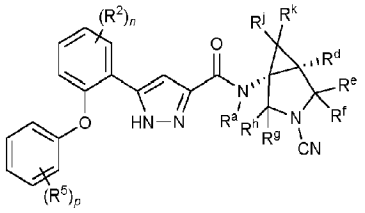
(i) forbindelsen er med formel (I-B-2):



(I-B-2)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(ii) forbindelsen er med formel (I-C-2):

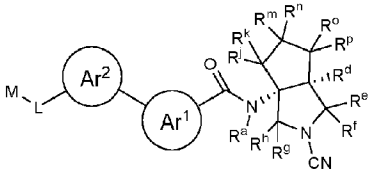


(I-C-2)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(iii) R^a, R^d, R^e, R^f, R^g, R^h, R^j og R^k er hver hydrogen; eller

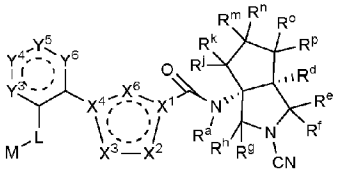
(c) med formel (I-3):



(I-3)

eller et farmaceutisk acceptabelt salt deraf, hvor R^j R^k, R^m, R^n, R^o og R^p er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl, eventuelt hvor:

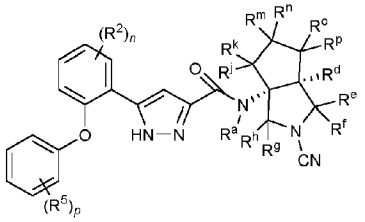
(i) forbindelsen er med formel (I-B-3):



(I-B-3)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(ii) forbindelsen er med formel (I-C-3):



(I-C-3)

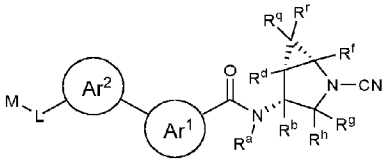
eller et farmaceutisk acceptabelt salt deraf; og/eller

(iii) R^a, R^d, R^e, R^f, R^g, R^h, R^j, R^k, R^m, R^n, R^o og R^p er hver hydrogen.

5. Forbindelsen ifølge krav 1 eller krav 2, hvor:

(a) R^c og R^e danner en C_1-C_4-alkylengruppe mellem atomerne, til hvilke de er bundet; og R^a, R^b, R^d, R^f, R^g og R^h er hver hydrogen; og/eller

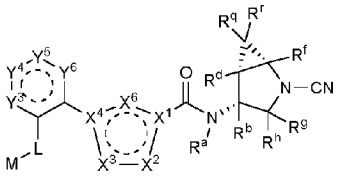
(b) forbindelsen er med formel (I-4):



(I-4)

eller et farmaceutisk acceptabelt salt deraf, hvor R^q og R^r er hver uafhængigt hydrogen, halogen, C_1-C_3-alkyl eller C_1-C_3-halogenalkyl, eventuelt hvor:

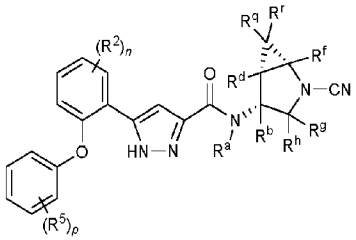
(i) forbindelsen er med formel (I-B-4):



(I-B-4)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(ii) forbindelsen er med formel (I-C-4):



(I-C-4)

eller et farmaceutisk acceptabelt salt deraf; og/eller

(iii) R^a, R^b, R^d, R^f, R^g, R^h, R^q og R^r er hver hydrogen.

6. Forbindelsen ifølge krav 1 eller krav 2, hvor:

(a) R^a og R^e danner en C_1-C_2-alkylengruppe mellem atomerne, til hvilke de er bundet; og R^b, R^c, R^d, R^f, R^g og R^h er hver hydrogen; eller

(b) R^c og R^d sammen med atomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl; og R^a, R^b, R^e, R^f, R^g og R^h er hver hydrogen; eller

(c) R^c og R^g danner en C_1-C_3-alkylengruppe mellem atomerne, til hvilke de er bundet; og R^a, R^b, R^d, R^e, R^f og R^h er hver hydrogen; eller

(d) R^e og R^f sammen med atomet, til hvilket de er bundet, danner en 3-6-leddet cycloalkyl eller heterocycloalkyl; og R^a, R^b, R^c, R^d, R^g og R^h er hver hydrogen; eller

(e) R^e og R^g danner en C_1-C_3-alkylengruppe mellem atomerne, til hvilke de er bundet; og R^a, R^b, R^c, R^d, R^f og R^h er hver hydrogen.

7. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor Ar^1 er:

(a) 5-6-leddet heteroarylen, eventuelt hvor Ar^1 er 5-leddet heteroarylen; eller

(b) phenylen.

8. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor Ar^2 er:

(a) 5-10-leddet heteroarylen; eller

(b) phenylen; eller

(c) phenylen eller 5-6-leddet heteroarylen.

9. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor L er:

(a) -O-, -S- eller -NH-; eller

(b) -O-.

10. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor:

(a) M er phenyl substitueret med *p* R^5-grupper,

eventuelt hvor M er phenyl; og/eller

(b) hver forekomst af R^1, R^2 og R^5 er uafhængigt valgt fra halogen, cyano, hydroxyl, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-halogenalkyl og C_1-C_6-hydroxyalkyl; og/eller

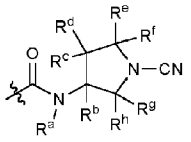
(c) *m* er 0; og/eller

(d) *n* er 0; og/eller

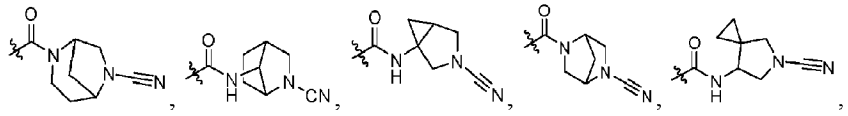
(e) *p* er 0 eller 1,

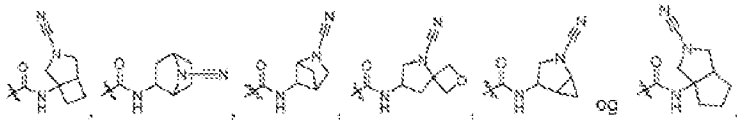
eventuelt hvor *p* er 0.

11. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor

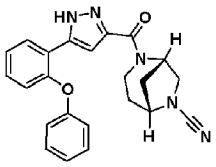
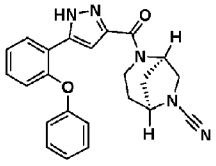
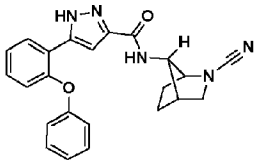
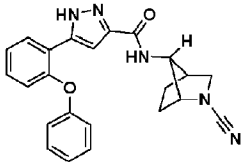


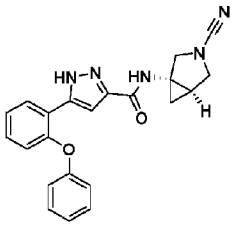
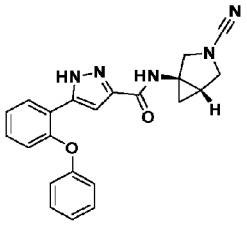
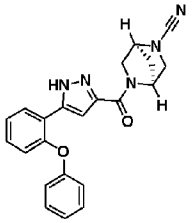
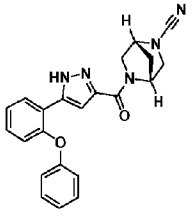
er valgt fra:

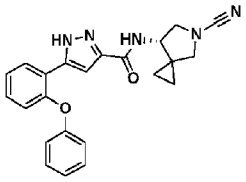
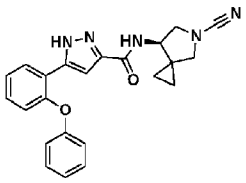
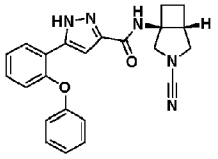
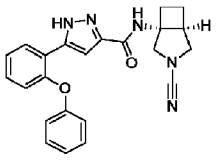


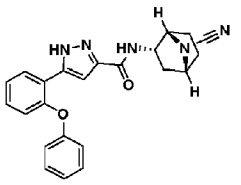
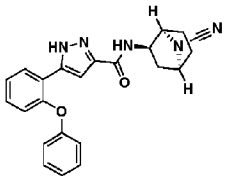
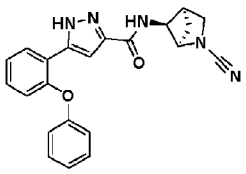
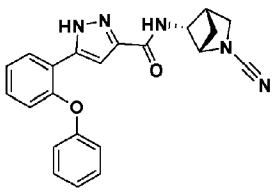


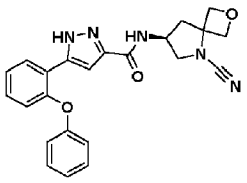
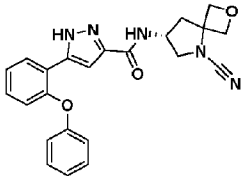
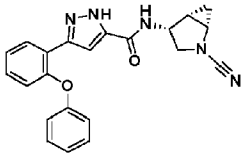
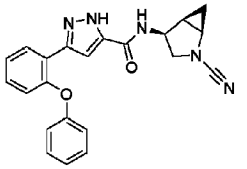
12. Forbindelse ifølge krav 1 eller farmaceutisk acceptabelt salt deraf, hvor forbindelsen er valgt fra:

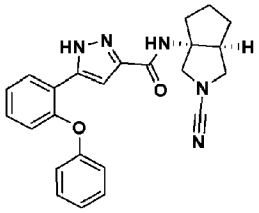
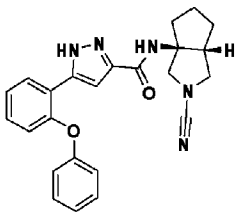
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
1-a	
	(1S,5R)-2-(5-(2-phenoxyphenyl)-1H-pyrazol-3-carbonyl)-2,6-diazabicyclo[3.2.1]octan-6-carbonitril
1-b	
	(1R,5S)-2-(5-(2-phenoxyphenyl)-1H-pyrazol-3-carbonyl)-2,6-diazabicyclo[3.2.1]octan-6-carbonitril
2-a	
	N-((1S,4S,7S)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
2-b	
	N-((1R,4R,7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
3-a	
	N-((1S, 5R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
3-b	
	N-((1R, 5S)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
4-a	
	(1S,4S)-5-(5-(2-phenoxyphenyl)-1H-pyrazol-3-carbonyl)-2,5-diazabicyclo[2.21]heptan-2-carbonitril
4-b	

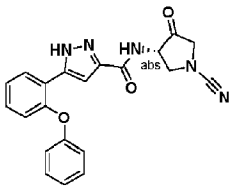
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
	(1R,4R)-5-(5-(2-phenoxyphenyl)-1H-pyrazol-3-carbonyl)-2,5-diazabicyclo[2.2. 1]heptan-2-carbonitril
5-a	
	(S)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
5-b	
	(R)-N-(5-cyano-5-azaspiro[2.4]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
6-a	
	N-((1R,5S)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
6-b	

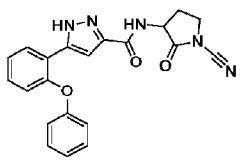
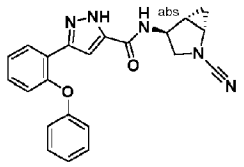
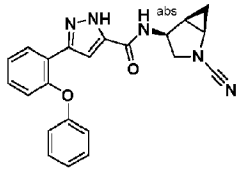
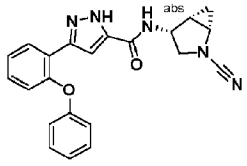
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
	N-((1S,5R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
7-a	
	N-((1S,2S,4R)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
7-b	
	N-((1R,2R,4S)-7-cyano-7-azabicyclo[2.2.1]heptan-2-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
8-a	
	N-[(1R,4R,5S)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl]-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
8-b	

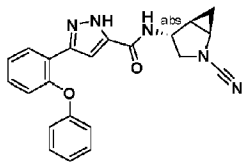
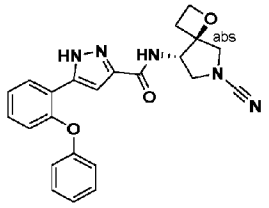
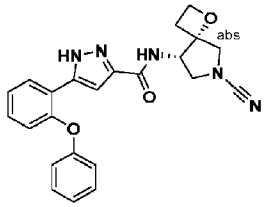
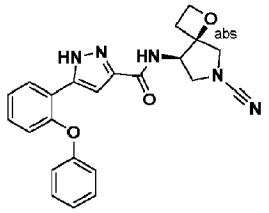
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
	N-((1S,4S,5R)-2-cyano-2-azabicyclo[2.1.1]hexan-5-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
9-a	
	(S)-N-(5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
9-b	
	(R)-N-(5-cyano-2-oxa-5-azaspiro[3.4]octan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
13-a	
	N-((1S,4R,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid
13-b	
	N-((1R,4S,SR)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid

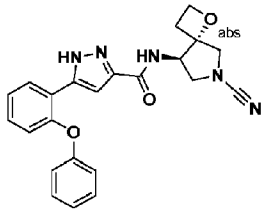
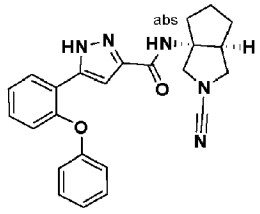
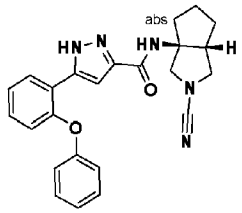
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
20-a	
	N-((3aR,6aS)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
20-b	
	N-((3aS,6aR)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid

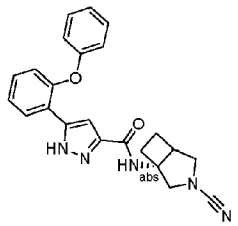
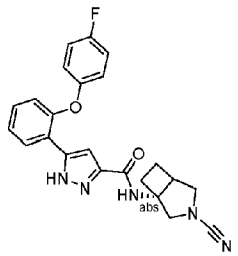
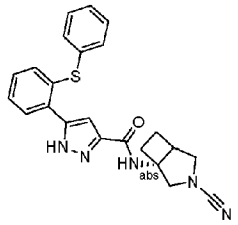
, eller hvor forbindelsen er valgt fra:

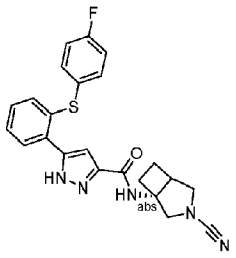
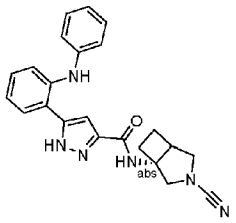
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
10	
	(S)-N-(1-cyano-4-oxopyrrolidin-3-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
11	
	N-(1-cyano-2-oxopyrrolidin-3-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
12	
	N-((1S,4S,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid
13	
	N-((1R,4S,SR)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid
14	
	N-((1S,4R,5S)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
15	
	N-((1R,4R,SR)-2-cyano-2-azabicyclo[3.1.0]hexan-4-yl)-3-(2-phenoxyphenyl)-1H-pyrazol-5-carboxamid
16	
	N-((4S,8S)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
17	
	N-((4R,8S)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
18	
	N-((4S,8R)-6-cyano-1-oxa-6-azaspiro[3.4]octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
19	
	N-((4R, 8R)-6-cyano-1-oxa-6-azaspiro[3.4] octan-8-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
20	
	N-((3aR,6aS)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
21	
	N-((3aS,6aR)-2-cyanohexahydrocyclopenta[c]pyrrol-3a(1H)-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
22	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
23	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-(4-fluorphenoxy)phenyl)-1H-pyrazol-3-carboxamid
24	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-(phenylthio)phenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
25	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-((4-fluorphenyl)thio)phenyl)-1H-pyrazol-3-carboxamid
26	
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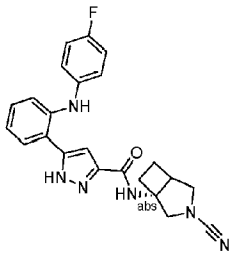
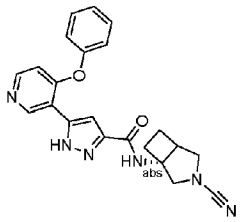
27	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(2-((4-fluorphenyl)amino)phenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
28	
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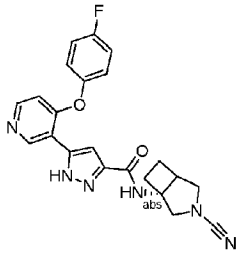
29	
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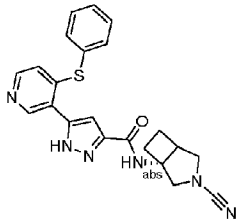
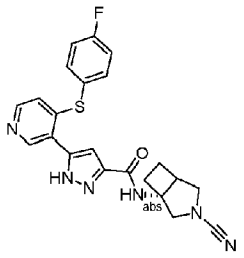
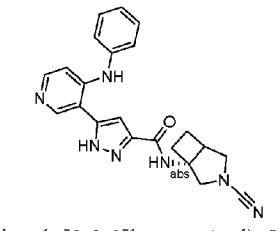
30	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(4-(phenylthio)pyridin-3-yl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
31	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(4-((4-fluorphenyl)thio)pyridin-3-yl)-1H-pyrazol-3 – carboxamid
32	
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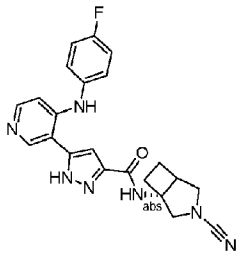
33	
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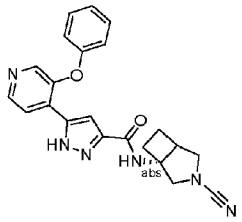
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
34	
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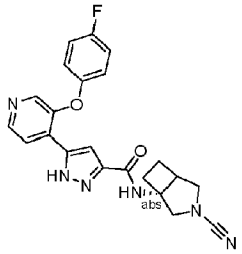
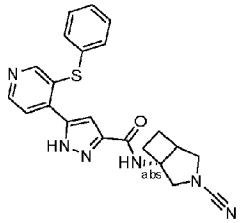
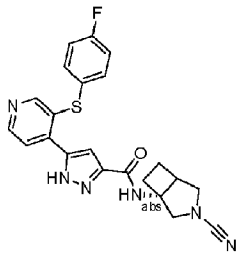
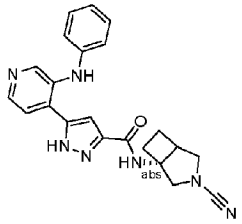
35	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-(4-fluorphenoxy)pyridin-4-yl)-1H-pyrazol-3-carboxamid
36	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-(phenylthio)pyridin-4-yl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
37	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-((4-fluorphenyl)thio)pyridin-4-yl)-1H-pyrazol-3-carboxamid
38	
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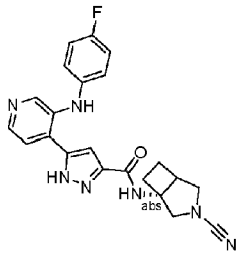
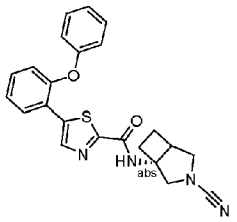
39	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-((4-fluorphenyl)amino)pyridin-4-yl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
40	
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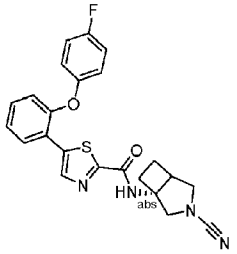
41	
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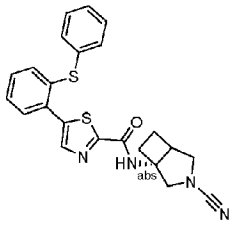
42	
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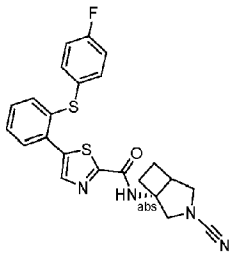
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
43	
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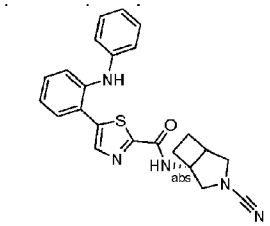
44	
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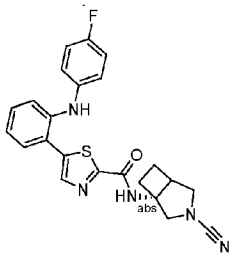
45	
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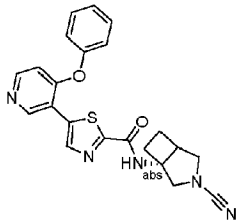
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
46	
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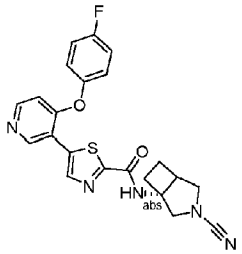
47	
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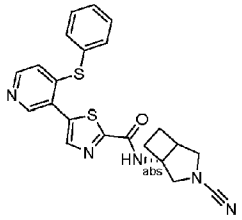
48	
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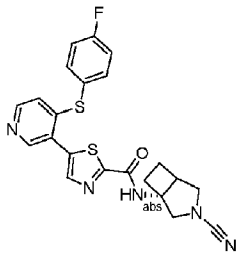
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
49	
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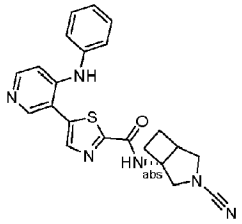
50	
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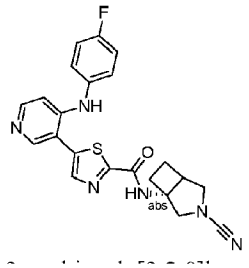
51	
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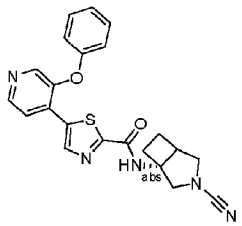
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
52	
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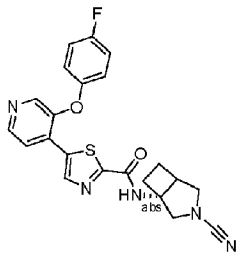
53	
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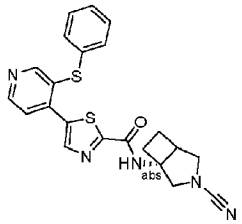
54	
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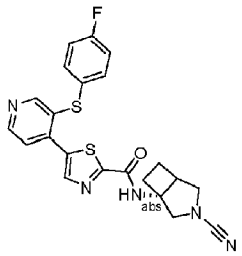
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
55	
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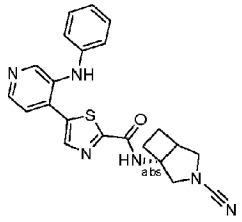
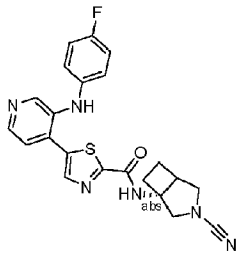
56	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-5-(3-(phenylamino)pyridin-4-yl)thiazol-2-carboxamid
57	
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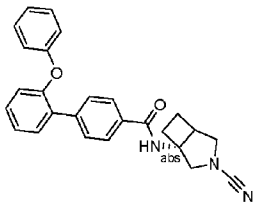
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
58	
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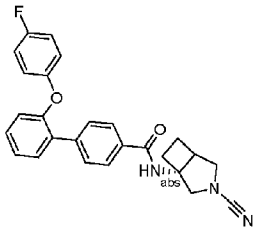
59	
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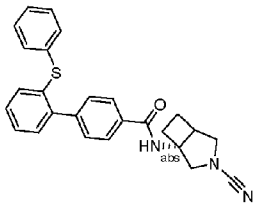
60	
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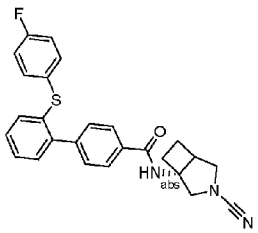
61	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
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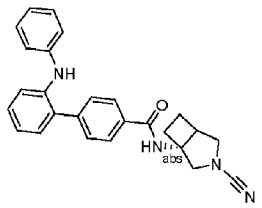
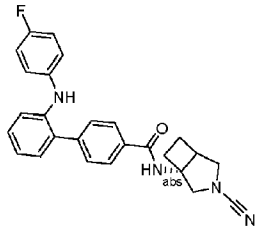
62	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-2'-(phenylamino)-[1,1'-biphenyl]-4-carboxamid
63	
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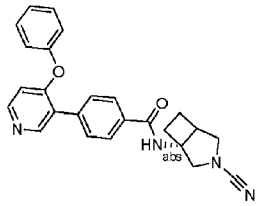
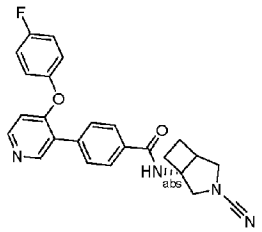
64	
	N-((1R)-3-cyano-3-azabicyclo[3.2.0]heptan-1-yl)-4-(4-phenoxypyridin-3-yl)benzamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
65	
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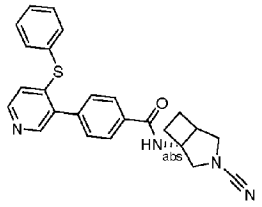
66	
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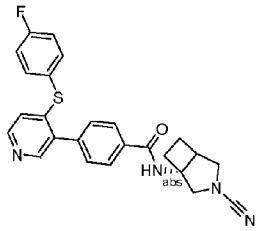
67	
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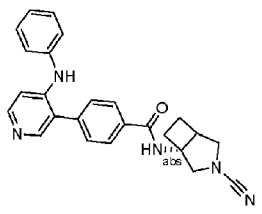
68	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
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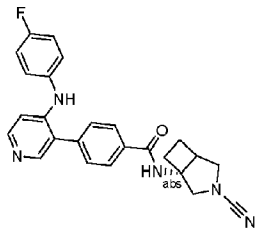
69	
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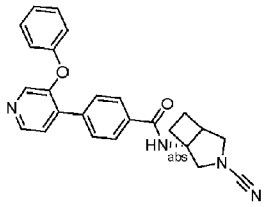
70	
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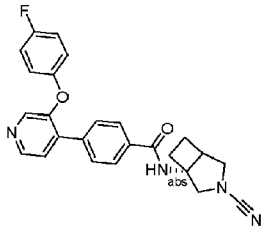
71	
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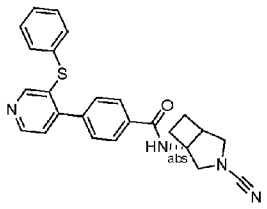
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
72	
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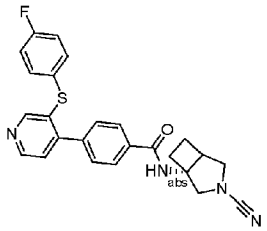
73	
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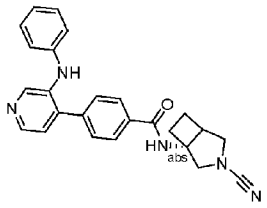
74	
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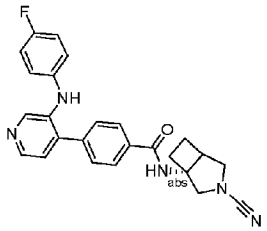
75	

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
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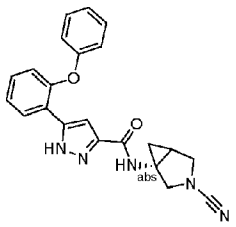
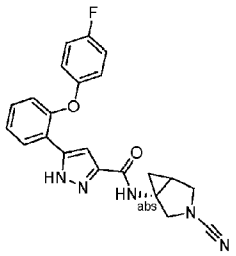
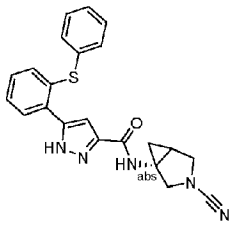
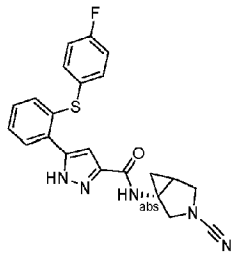
76	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
77	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-(4-fluorphenoxy)phenyl)-1H-pyrazol-3-carboxamid
78	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(2-(phenylthio)phenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
79	
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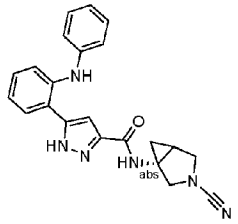
80	
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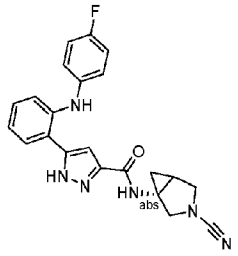
81	
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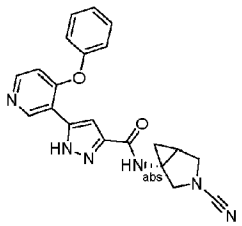
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
82	
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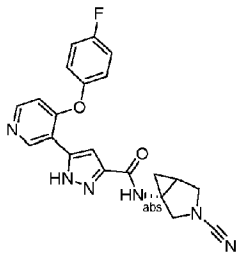
83	
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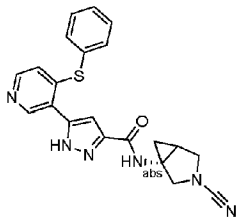
84	
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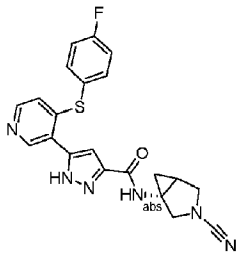
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
85	
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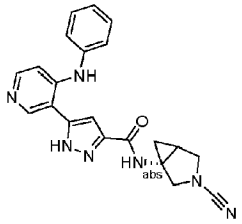
86	
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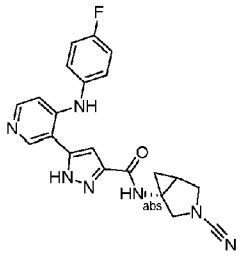
87	
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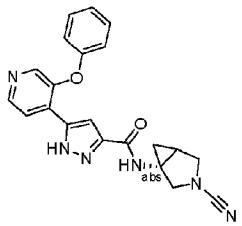
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
88	
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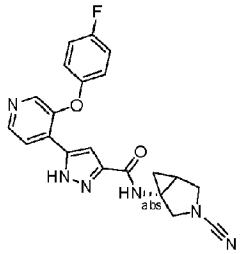
89	
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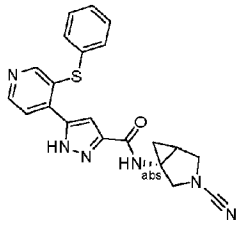
90	
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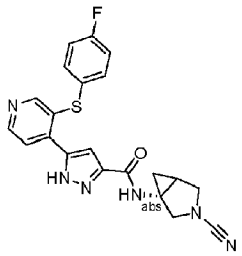
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
91	
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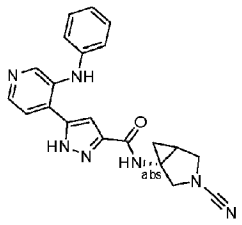
92	
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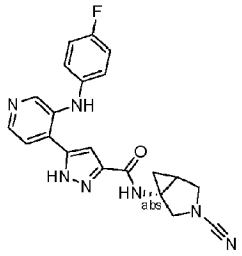
93	
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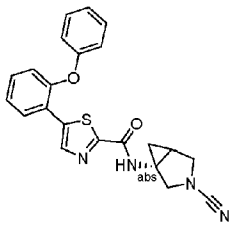
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
94	
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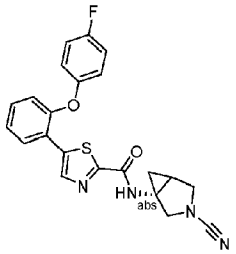
95	
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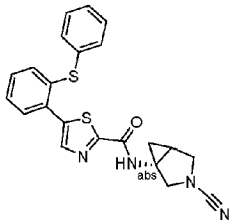
96	
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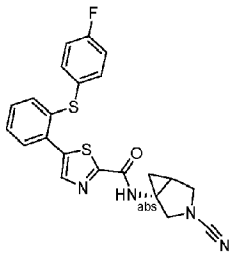
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
97	
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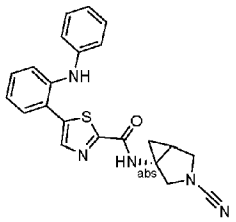
98	
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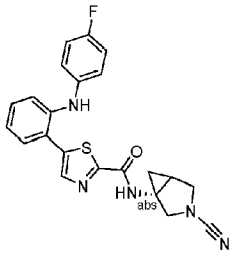
99	
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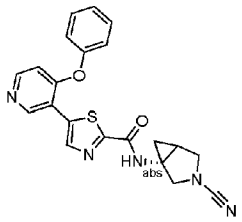
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
100	
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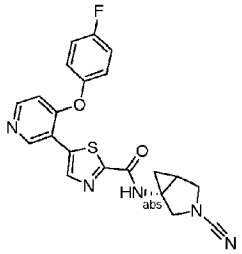
101	
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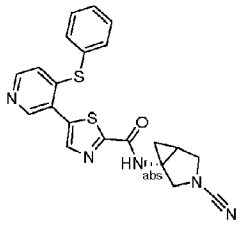
102	
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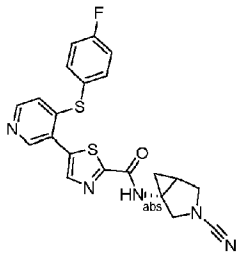
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
103	
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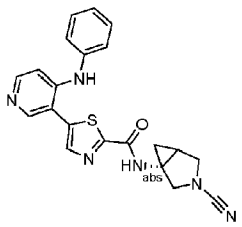
104	
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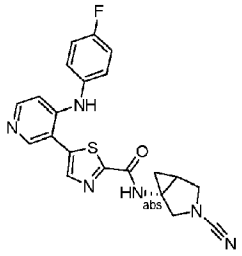
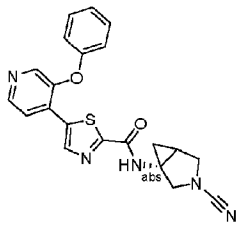
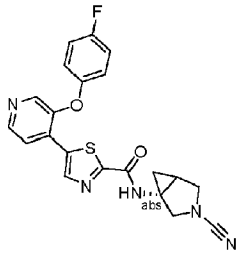
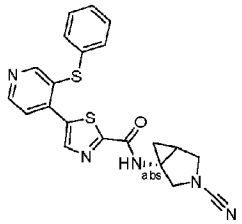
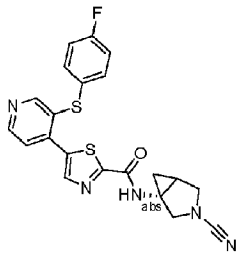
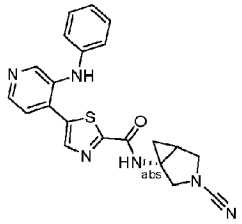
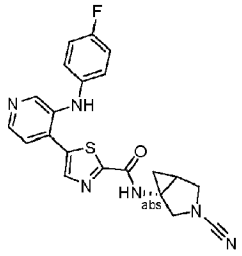
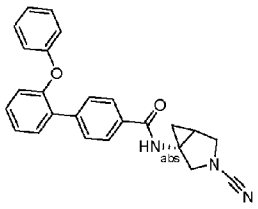
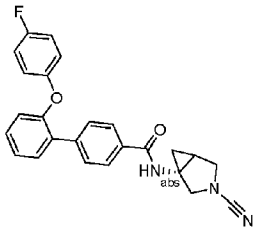
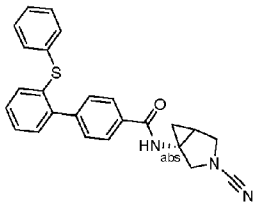
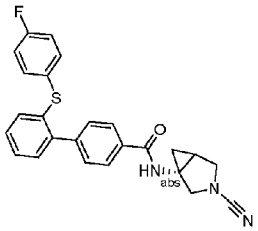
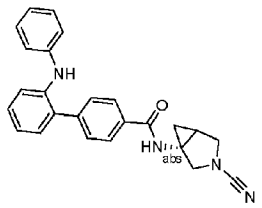
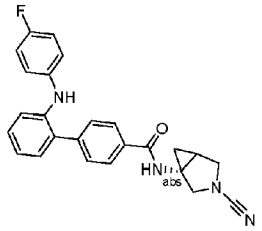
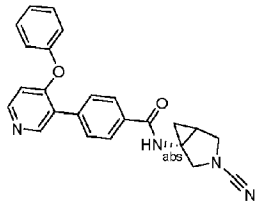
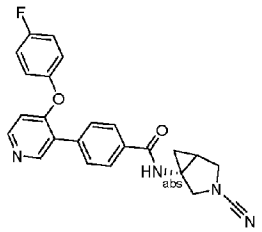
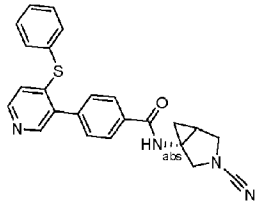
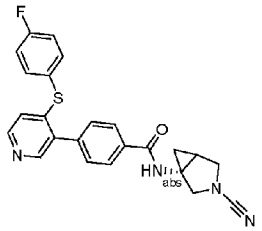
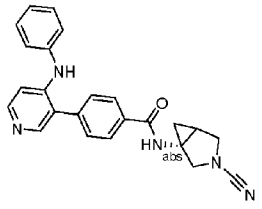
105	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(4-((4-fluorphenyl)amino)pyridin-3-yl)thiazol-2-carboxamid

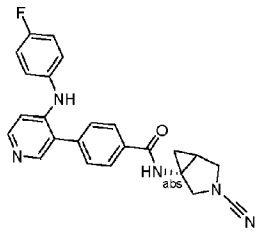
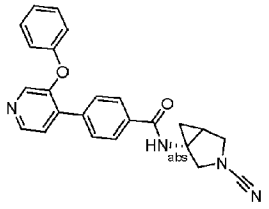
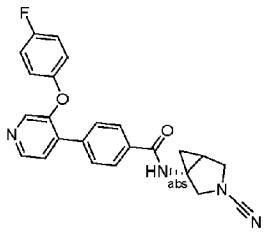
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
106	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-phenoxypyridin-4-yl)thiazol-2-carboxamid
107	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-(4-fluorphenoxy)pyridin-4-yl)thiazol-2-carboxamid
108	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-(phenylthio)pyridin-4-yl)thiazol-2-carboxamid

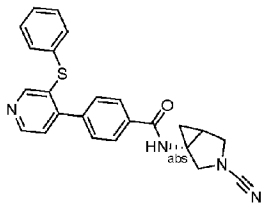
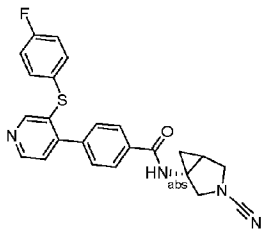
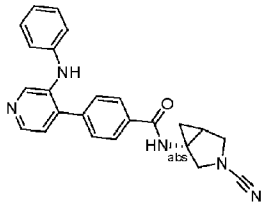
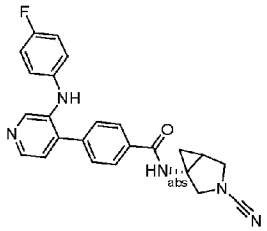
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
109	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-((4-fluorphenyl)thio)pyridin-4-yl)thiazol-2-carboxamid
110	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-(phenylamino)pyridin-4-yl)thiazol-2-carboxamid
111	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-5-(3-((4-fluorphenyl)amino)pyridin-4-yl)thiazol-2-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
112	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-phenoxy-[1,1'-biphenyl]-4-carboxamid
113	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-(4-fluorphenoxy)-[1,1'-biphenyl]-4-carboxamid
114	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-(phenylthio)-[1,1'-biphenyl]-4-carboxamid
115	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-((4-fluorphenyl)thio)-[1,1'-biphenyl]-4-carboxamid
116	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-(phenylamino)-[1,1'-biphenyl]-4-carboxamid
117	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-2'-((4-fluorphenyl)amino)-[1,1'-biphenyl]-4-carboxamid
118	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-phenoxypyridin-3-yl)benzamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
119	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-(4-fluorphenoxy)pyridin-3-yl)benzamid
120	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-(phenylthio)pyridin-3-yl)benzamid
121	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-((4-fluorphenyl)thio)pyridin-3-yl)benzamid
122	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-(phenylamino)pyridin-3-yl)benzamid
123	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(4-((4-fluorphenyl)amino)pyridin-3-yl)benzamid
124	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(3-phenoxypyridin-4-yl)benzamid
125	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(3-(4-fluorphenoxy)pyridin-4-yl)benzamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
126	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(3-(phenylthio)pyridin-4-yl)benzamid
127	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(3-((4-fluorphenyl)thio)pyridin-4-yl)benzamid
128	
	N-((1R)-3-cyano-3-azabicyclo[3.1.0]hexan-1-yl)-4-(3-(phenylamino)pyridin-4-yl)benzamid
129	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
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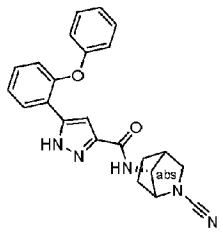
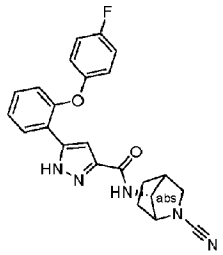
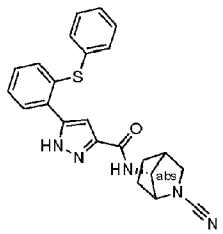
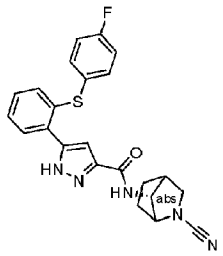
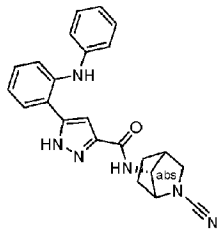
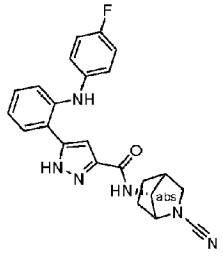
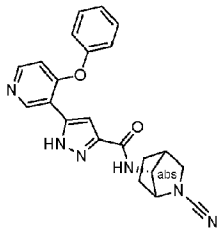
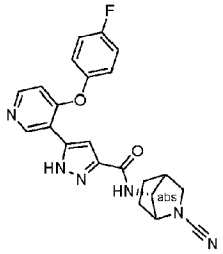
130	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)-1H-pyrazol-3-carboxamid
131	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(4-fluorphenoxy)phenyl)-1H-pyrazol-3-carboxamid
132	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(phenylthio)phenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
133	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-((4-fluorphenyl)thio)phenyl)-1H-pyrazol-3-carboxamid
134	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(phenylamino)phenyl)-1H-pyrazol-3-carboxamid
135	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-((4-fluorphenyl)amino)phenyl)-1H-pyrazol-3-carboxamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
136	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-phenoxypyridin-3-yl)-1H-pyrazol-3-carboxamid
137	
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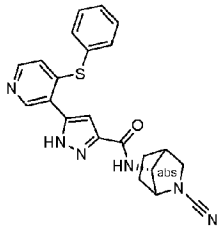
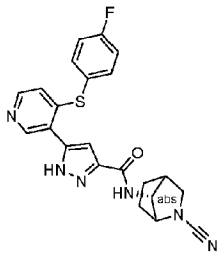
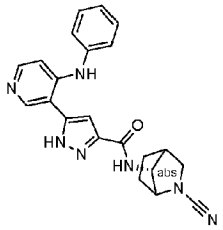
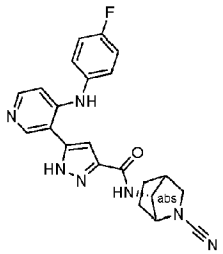
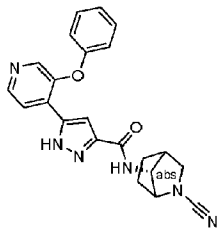
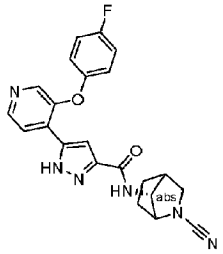
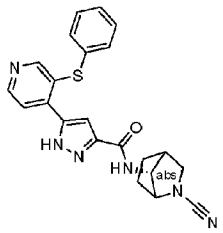
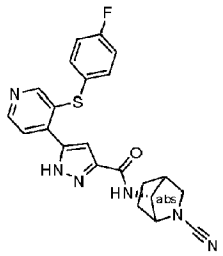
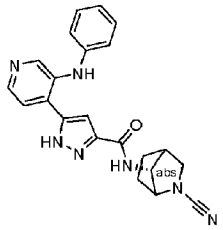
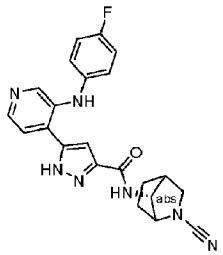
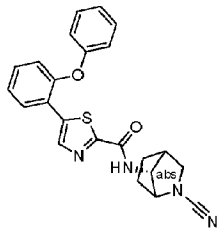
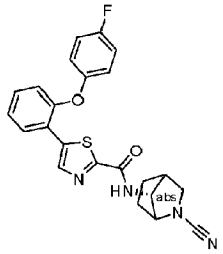
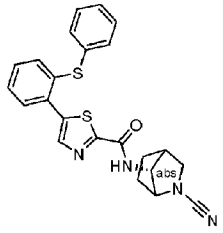
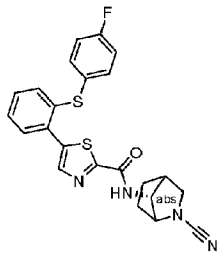
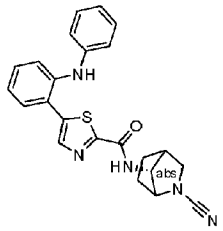
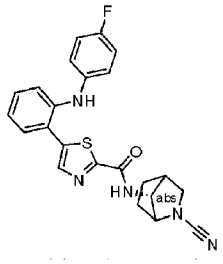
138	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(phenylthio)pyridin-3-yl)-1H-pyrazol-3-carboxamid

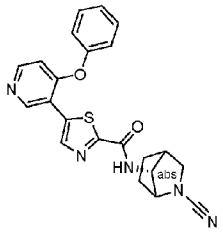
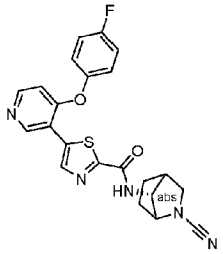
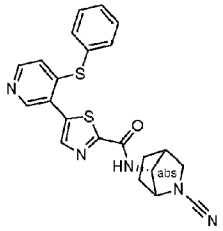
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
139	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-((4-fluorphenyl)thio)pyridin-3-yl)-1H-pyrazol-3-carboxamid
140	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(phenylamino)pyridin-3-yl)-1H-pyrazol-3-carboxamid
141	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-((4-fluorphenyl)amino)pyridin-3-yl)-1H-pyrazol-3-carboxamid

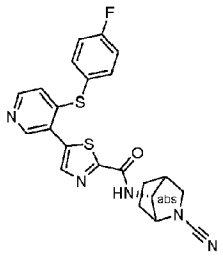
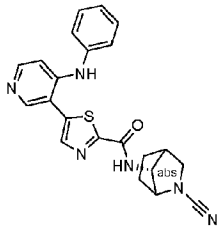
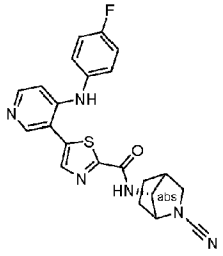
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
142	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-phenoxypyridin-4-yl)-1H-pyrazol-3-carboxamid
143	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(4-fluorphenoxy)pyridin-4-yl)-1H-pyrazol-3-carboxamid
144	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(phenylthio)pyridin-4-yl)-1H-pyrazol-3-carboxamid

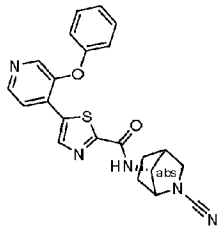
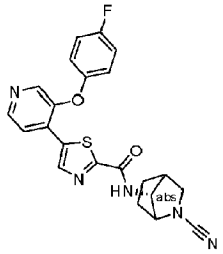
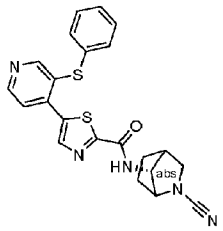
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
145	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-((4-fluorphenyl)thio)ppridin-4-yl)-1H-pyrazol-3-carboxamid
146	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(phenylamino)pyridin-4-yl)-1H-pyrazol-3-carboxamid
147	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-((4-fluorphenyl)amino)pyridin-4-yl)-1H-pyrazol-3-carboxamid

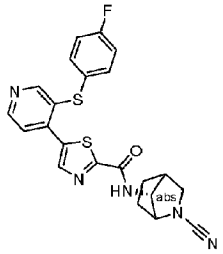
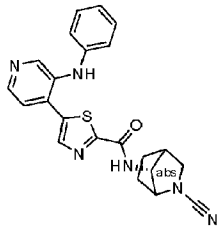
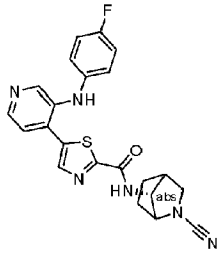
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
148	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-phenoxyphenyl)thiazol-2-carboxamid
149	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(4-fluorphenoxy)phenyl)thiazol-2-carboxamid
150	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(phenylthio)phenyl)thiazol-2-carboxamid

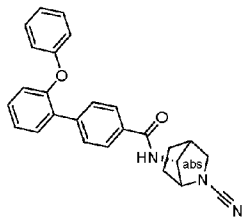
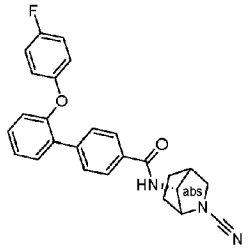
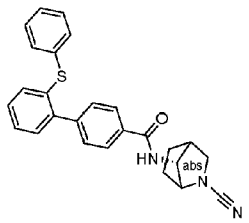
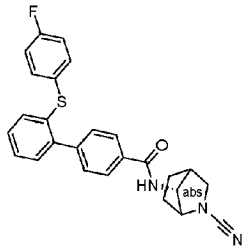
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
151	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-((4-fluorphenyl)thio)phenyl)thiazol-2-carboxamid
152	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-(phenylamino)phenyl)thiazol-2-carboxamid
153	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(2-((4-fluorphenyl)amino)phenyl)thiazol-2-carboxamid

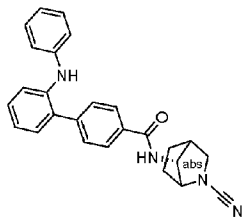
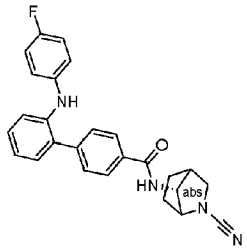
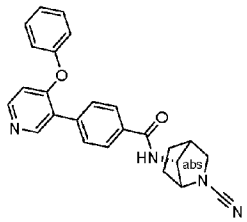
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
154	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-phenoxypyridin-3-yl)thiazol-2-carboxamid
155	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(4-fluorphenoxy)pyridin-3-yl)thiazol-2-carboxamid
156	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(phenylthio)pyridin-3-yl)thiazol-2-carboxamid

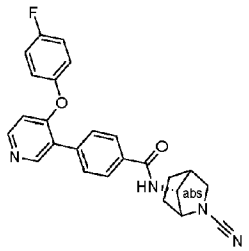
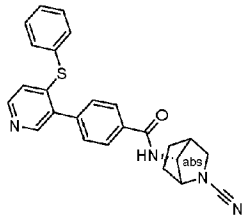
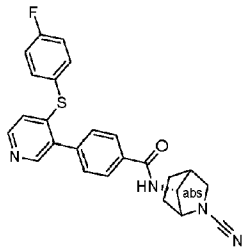
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
157	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-((4-fluorphenyl)thio)pyridin-3-yl)thiazol-2-carboxamid
158	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-(phenylamino)pyridin-3-yl)thiazol-2-carboxamid
159	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(4-((4-fluorphenyl)amino)pyridin-3-yl)thiazol-2-carboxamid

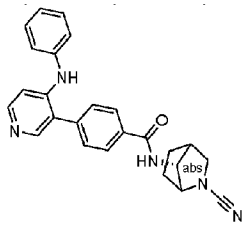
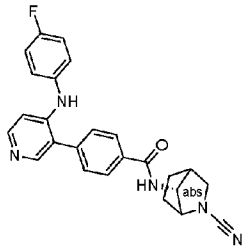
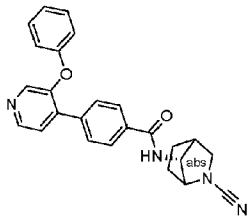
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
160	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-phenoxypyridin-4-yl)thiazol-2-carboxamid
161	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(4-fluorphenoxy)pyridin-4-yl)thiazol-2-carboxamid
162	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(phenylthio)pyridin-4-yl)thiazol-2-carboxamid

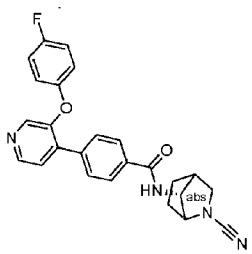
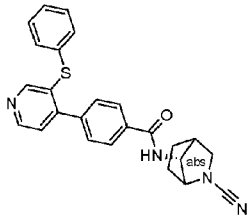
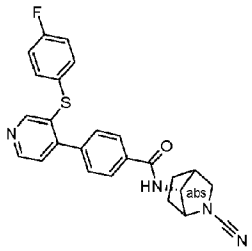
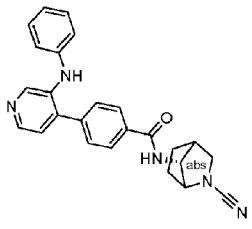
Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
163	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-((4-fluorphenyl)thio)pyridin-4-yl)thiazol-2-carboxamid
164	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-(phenylamino)pyridin-4-yl)thiazol-2-carboxamid
165	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-5-(3-((4-fluorphenyl)amino)pyridin-4-yl)thiazol-2-carboxamid

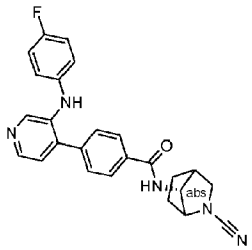
Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
166	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-phenoxy-[1,1'-biphenyl]-4-carboxamid
167	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-(4-fluorphenoxy)-[1,1'-biphenyl]-4-carboxamid
168	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-(phenylthio)-[1,1'-biphenyl]-4-carboxamid
169	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-((4-fluorphenyl)thio)-[1,1'-biphenyl]-4-carboxamid
170	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-(phenylamino)-[1,1'-biphenyl]-4-carboxamid
171	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-2'-((4-fluorphenyl)amino)-[1,1'-biphenyl]-4-carboxamid
172	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-phenoxypyridin-3-yl)benzamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
173	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-(4-fluorphenoxy)pyridin-3-yl)benzamid
174	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-(phenylthio)pyridin-3-yl)benzamid
175	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-((4-fluorphenyl)thio)pyridin-3-yl)benzamid

Forbindelses-nummer	**Forbindelsesstruktur og kemisk navn**
176	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-(phenylamino)pyridin-3-yl)benzamid
177	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(4-((4-fluorphenyl)amino)pyridin-3-yl)benzamid
178	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-phenoxypyridin-4-yl)benzamid

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
179	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-(4-fluorphenoxy)pyridin-4-yl)benzamid
180	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-(phenylthio)pyridin-4-yl)benzamid
181	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-((4-fluorphenyl)thio)pyridin-4-yl)benzamid
182	

Forbindelses-nummer	Forbindelsesstruktur og kemisk navn
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-(phenylamino)pyridin-4-yl)benzamid
183	
	N-((7R)-2-cyano-2-azabicyclo[2.2.1]heptan-7-yl)-4-(3-((4-fluorphenyl)amino)pyridin-4-yl)benzamid

13. Farmaceutisk sammensætning omfattende forbindelsen ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf og en farmaceutisk acceptabel bærer.

14. Forbindelse ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning ifølge krav 13 til anvendelse i en fremgangsmåde til at inhibere USP30 hos en patient, som har behov derfor, omfattende indgivelse til patienten af en terapeutisk effektiv mængde af forbindelsen ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf eller den farmaceutiske sammensætning ifølge krav 13.

15. Forbindelse ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf eller en farmaceutisk sammensætning ifølge krav 13 til anvendelse i en fremgangsmåden til behandling af en neurodegenerativ lidelse hos en patient, som har behov derfor, omfattende indgivelse til patienten af en terapeutisk effektiv mængde af forbindelsen ifølge et hvilket som helst af kravene 1-12, eller et farmaceutisk acceptabelt salt deraf eller den farmaceutiske

sammensætning ifølge krav 13,

eventuelt hvor den neurodegenerative lidelse er Parkinsons sygdom.