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(71) Applicant: FORMA THERAPEUTICS, INC. [US/US];

500 Arsenal Street, Suite 100, Watertown, Massachusetts 02472 (US).

(72) Inventors: MARTIN, Matthew W.; c/o Forma Therapeutics, Inc., 500 Arsenal Street, Suite 100, Watertown, Massachusetts 02472 (US). BUCKMELTER, Alexandre Joseph; c/o Forma Therapeutics, Inc., 500 Arsenal Street, Suite 100, Watertown, Massachusetts 02472 (US).

(74) Agent: D'AMATO, Erica M. et al.; Choate, Hall & Stewart LLP, Two International Place, Boston, Massachusetts 02110 (US).

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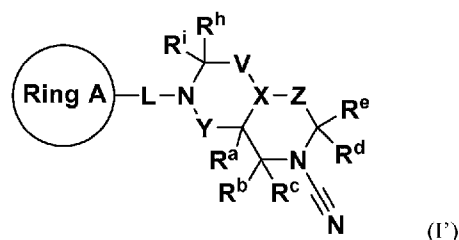
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(57) **Abstract:** The present disclosure relates to compounds of formula (I') and pharmaceutically acceptable salts thereof useful as inhibitors of Ubiquitin Specific Peptidase 30 (USP30), pharmaceutical compositions thereof, and methods of use thereof. Compounds as disclosed herein can be useful in the treatment of a disease or disorder involving mitochondrial dysfunction, including neurodegenerative diseases.



**FUSED BICYCLIC COMPOUNDS USEFUL AS UBIQUITIN-SPECIFIC
PEPTIDASE 30 INHIBITORS**

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/673,019, filed on May 17, 2018, U.S. Provisional Patent Application No. 62/687,599, filed on June 20, 2018, U.S. Provisional Patent Application No. 62/697,635, filed on July 13, 2018, and U.S. Provisional Patent Application No. 62/727,164, filed on September 5, 2018, the entire contents of each of which are hereby incorporated by reference.

TECHNICAL FIELD

[0002] The present disclosure provides novel compounds and pharmaceutical forms thereof useful for inhibiting Ubiquitin-Specific Peptidase 30, also known as Ubiquitin-Specific Protease 30 (USP30).

BACKGROUND

[0003] The ubiquitination system is a highly-regulated process which affects a wide variety of cellular activities and physiological processes. Dysregulation of this system is commonly associated with several human diseases, including cancer, neurodegenerative disorders, muscle dystrophies, and cardiomyopathies, amongst others (Popovic, et al., *Nature Medicine* **2014**, 20, 1242-1253). 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.

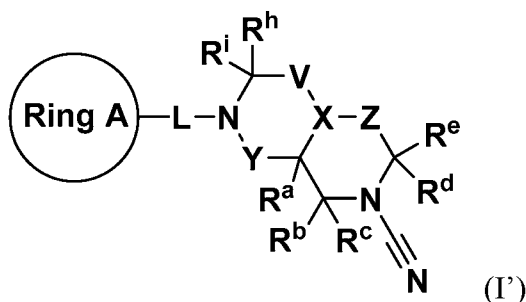
[0004] Ubiquitin regulates mitochondrial dynamics and biogenesis, affecting the abundance and function of these organelles. Mitochondria serve many functions to maintain cell health in mammals, including generating ATP. As mitochondria age they become damaged, losing their metabolic functionality and 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. In studies to determine what influences how mitochondria perform mitophagy, ubiquitination of mitochondrial proteins is believed to contribute to mitochondrial dynamics in mammalian cells, possibly by “flagging” those proteins for inactivation. USP30 is a deubiquitinating enzyme 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.

[0005] Many age-related diseases, particularly neurodegenerative disorders, have been linked to mitochondrial dysfunction and impairment of the ubiquitination system (Ross, et al., Int J Mol Sci. 2015, 16(8), 19458-19476). Inactivating mutations in PINK1 and Parkin impair mitophagy can result in accumulation of damaged mitochondria and neuronal toxicity, believed to lead to Parkinson's Disease. USP30 is a mitochondrial DUB that opposes the ligase activity of Parkin and is a negative regulator of mitophagy. USP30 inhibition is expected to promote mitophagy and restore mitochondrial health.

[0006] Accordingly, there is a need for compounds that can therapeutically inhibit USP30.

SUMMARY

[0007] The present disclosure provides compounds of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from a bond, C(O), and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is $-(CH_2)_n-$;

n is 0, 1, 2, or 3,

wherein each methylene unit of L is optionally substituted with one or two C₁-C₆ alkyl, and

wherein if n is 2 or 3, then one methylene unit of L is optionally replaced with a heteroatom

selected from nitrogen, oxygen, and sulfur;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

or R^b and R^c, or R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₆

cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

wherein an optionally substituted R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x group may be substituted with one or more R^l ;

Ring A is selected from C_3 - C_{13} cycloalkyl, 3- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C_{10} aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C_1 - C_6 aliphatic, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, optionally substituted C_{10} aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l ;

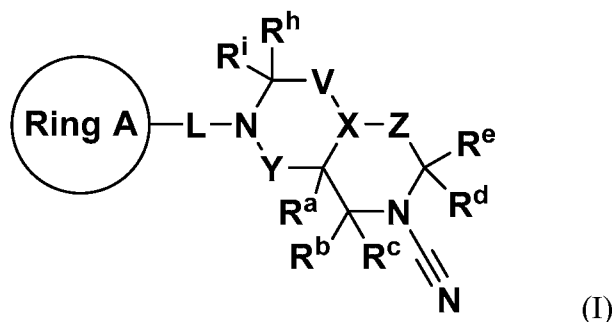
each R^l is independently selected from oxo, halogen, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C_1 - C_6 aliphatic, C_1 - C_6 haloaliphatic, $-(CH_2)_m(C_3-C_{10}\text{cycloalkyl})$, $-(CH_2)_m(3\text{- to }10\text{-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur})$, $-(CH_2)_m(C_6\text{aryl})$, $-(CH_2)_m(C_{10}\text{aryl})$, and $-(CH_2)_m(5\text{- to }10\text{-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur})$;

each R is independently selected from hydrogen, C_1 - C_6 aliphatic, C_1 - C_6 haloaliphatic, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

each R' is independently selected from C_1 - C_6 aliphatic, C_1 - C_6 haloaliphatic, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur; and

each m is independently 0, 1, or 2.

[0008] The present disclosure also relates to chemical entities chosen from compounds of Formula (I):



and pharmaceutically acceptable forms thereof, wherein:

V is selected from a bond and CR^fR^g

X is selected from N and CR^x ;

Y is selected from a bond, carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

Z is selected from a carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

L is $-\text{[(CH}_2\text{)]}_n-$, $n = 0, 1, 2, 3$, where if n is 2 or 3, then L can be optionally substituted or interrupted with one or two alkyls and/or heteroatoms;

each occurrence of R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x is independently selected from small lipophilic and/or electron withdrawing groups that exhibit activity in a USP30 biochemical assay; R^f and R^g can also be combined to form a carbonyl; R^j and R^k can also cyclize;

Ring A is selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group;

W is chosen from hydrogen, halogen, cyano groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl ester groups, 3- to 10-membered cycloalkyl and heterocycloalkyl groups, and 5 to 10-membered aryl and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R^l group, which can be the same or different;

R^l is independently selected from small lipophilic or electron withdrawing groups that exhibit activity in a USP30 biochemical assay.

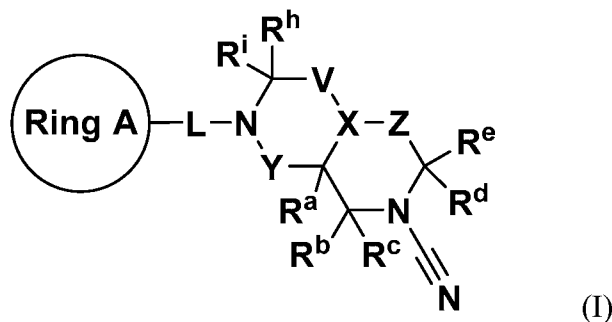
[0009] Additional objects and advantages will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice. The objects and advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0010] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims.

DETAILED DESCRIPTION

Compounds of Formula (I)

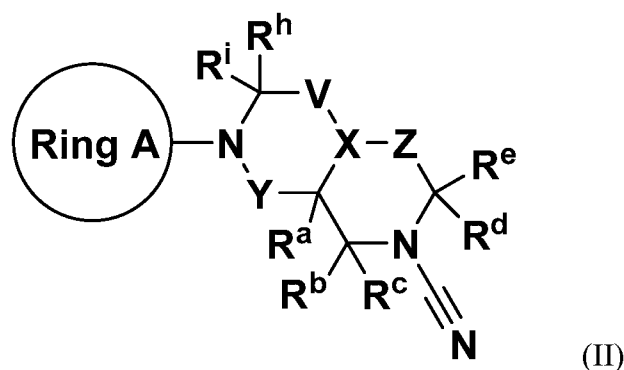
[0011] The present disclosure provides, among other things, chemical entities of Formula (I):



and pharmaceutically acceptable forms thereof, wherein:

V, X, Y, Z, L, R^a, R^b, R^c, R^d, R^e, R^h, Rⁱ, and Ring A are all as defined for Formula (I) above and described in classes and subclasses herein for Formula (I), both singly and in combination.

[0012] In some embodiments, chemical entities include those selected from compounds of Formula (II):



and pharmaceutically acceptable forms thereof, wherein:

V is selected from a bond and CR^fR^g .

X is selected from N and CH;

Y is selected from a bond, carbonyl (C=O), and CR^jR^k ,

Z is selected from a carbonyl (C=O), and CR^jR^k,

R^a is hydrogen;

one of R^b and R^c is hydrogen, and the other is selected from hydrogen, alkyl groups, and heteroalkyl groups, the groups optionally substituted with R¹;

one of R^d and R^e is hydrogen, and the other is selected from hydrogen, alkyl groups, and heteroalkyl groups, the groups optionally substituted with R¹;

one of R^f and R^g is hydrogen, and the other is selected from hydrogen, alkyl groups, and heteroalkyl groups, the groups optionally substituted with R^1 , or alternatively, R^f and R^g form a carbonyl; one of R^h and R^i is hydrogen, and the other is selected from hydrogen, alkyl groups, and heteroalkyl groups, the groups optionally substituted with R^1 ;

one of R^j and R^k is hydrogen, and the other is selected from hydrogen, alkyl groups, and heteroalkyl groups, the groups optionally substituted with R^1 ;

Ring A is selected from 5- to 10-membered cycloalkyl, heterocycloalkyl, and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group;

W is selected from hydrogen, halogen, cyano groups, alkyl groups, alkyl ester groups, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R^1 group, which can be the same or different; and

R^1 is independently selected from hydrogen, halogen, cyano, amides, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl esters, trifluoromethyl, and trifluoromethylester groups.

[0013] In at least one embodiment of Formulas (I) and (II), V is selected from CR^fR^g . In at least one embodiment, V is a bond.

[0014] In at least one embodiment of Formulas (I) and (II), X is N. In at least one embodiment, X is CR^x , wherein R^x is hydrogen. In some embodiments, X is N.

[0015] In at least one embodiment of Formula (I), L is $-(CH_2)_n-$, and $n = 0$. In at least one embodiment, L is $-(CH_2)_n-$, and $n = 1$. In at least one embodiment, L is $-(CH_2)_n-$, and $n = 2$. In at least one embodiment, L is $-(CH_2)_n-$, $n = 2$, and L is substituted with an alkyl. In at least one embodiment, L is $-(CH_2)_n-$, $n = 2$, and L is both substituted with an alkyl and interrupted with a heteroatom. In some embodiments, L is $-(CH_2)_n-$, and $n = 0$.

[0016] In at least one embodiment of Formulas (I) and (II), Y is a bond. In at least one embodiment, Y is a carbonyl ($C=O$). In at least one embodiment, Y is CR^jR^k , wherein R^j and R^k are as defined herein for Formula (I). In some embodiments, Y is a carbonyl ($C=O$). In some embodiments, Y is CR^jR^k wherein R^j and R^k are selected from hydrogen, halogen, and alkyl groups.

[0017] In at least one embodiment of Formulas (I) and (II), Z is a carbonyl ($C=O$). In at least one embodiment, Z is CR^jR^k , wherein R^j and R^k are as defined herein for Formula (I). In some embodiments, Z is a carbonyl ($C=O$). In some embodiments, Z is CR^jR^k wherein R^j and R^k are selected from hydrogen, halogen, and alkyl groups.

[0018] As defined above for Formula (I), each occurrence of R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x is independently selected from small lipophilic and/or electron withdrawing groups

that exhibit activity in a USP30 biochemical assay. Examples of such groups include hydrogen, halogens, hydroxy groups, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and branched alkyl groups optionally interrupted with heteroatoms, and/or optionally substituted with R^1 .

[0019] In at least one embodiment of Formulas (I) and (II), R^a is selected from hydrogen and halogens. In at least one embodiment, R^a is hydrogen.

[0020] In at least one embodiment of Formulas (I) and (II), R^b and R^c are each independently selected from hydrogen, alkyl or heteroalkyl. In at least one embodiment, one of R^b and R^c is hydrogen, and the other is selected from optionally substituted alkyl or heteroalkyl (e.g., C_1 - C_6 alkyl or C_1 - C_6 heteroalkyl), optionally substituted with R^1 . In at least one embodiment, one of R^b and R^c is hydrogen, and the other is C_1 - C_6 (linear or branched) alkyl or C_1 - C_6 (linear or branched) heteroalkyl groups. In at least one embodiment, R^b and R^c are each independently selected from hydrogen and C_1 - C_6 alkyl. In at least one embodiment, R^b and R^c are each hydrogen.

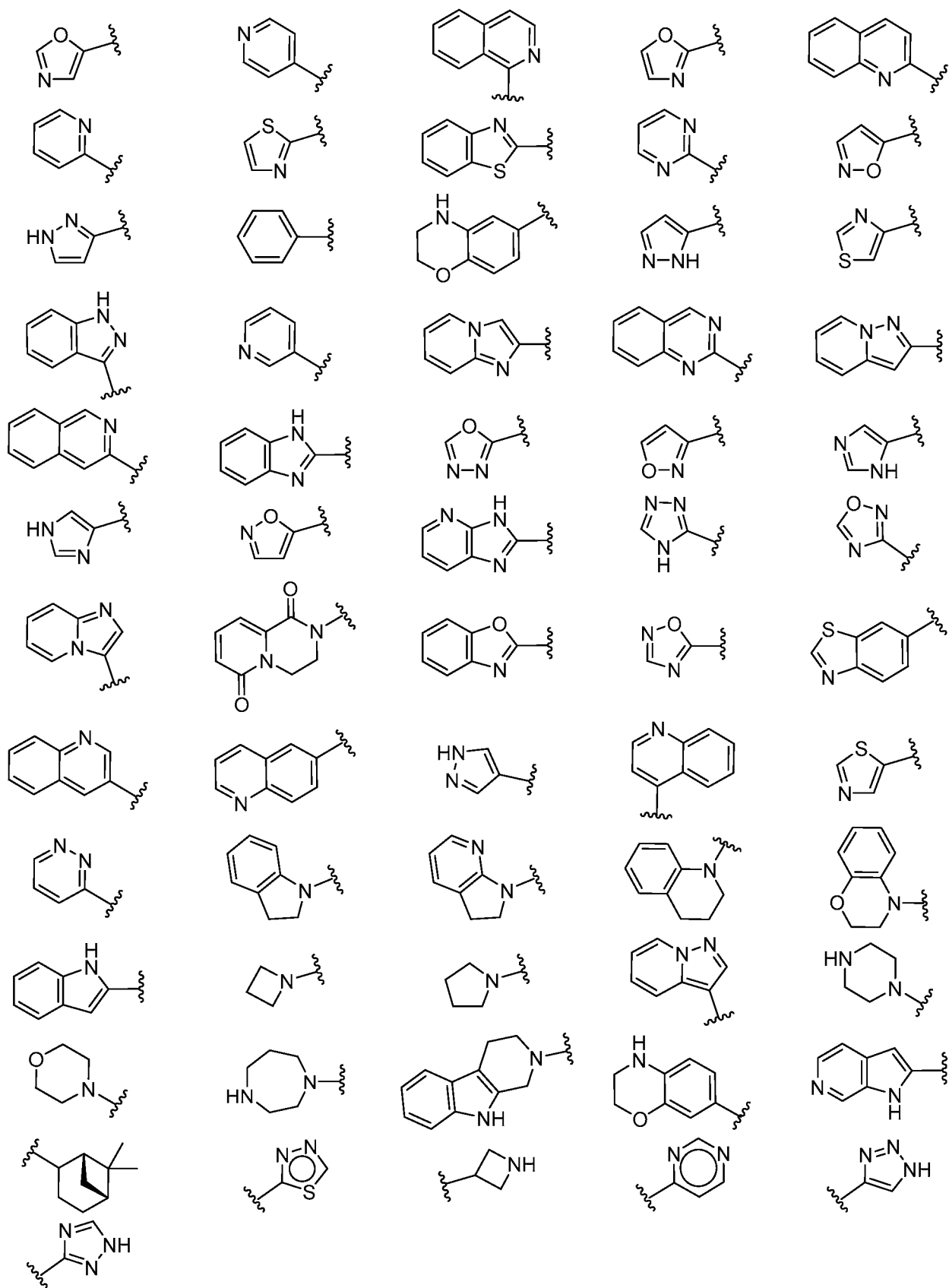
[0021] In at least one embodiment of Formulas (I) and (II), R^d and R^e are each independently selected from hydrogen, alkyl or heteroalkyl. In at least one embodiment, one of R^d and R^e is hydrogen, and the other is selected from optionally substituted alkyl or heteroalkyl (e.g., C_1 - C_6 alkyl or C_1 - C_6 heteroalkyl), optionally substituted with R^1 . In at least one embodiment, one of R^d and R^e is hydrogen, and the other is C_1 - C_6 (linear or branched) alkyl or C_1 - C_6 (linear or branched) heteroalkyl groups. In at least one embodiment, R^d and R^e are each independently selected from hydrogen and C_1 - C_6 alkyl. In at least one embodiment, R^d and R^e are each hydrogen.

[0022] In at least one embodiment of Formulas (I) and (II), R^f and R^g are each independently selected from hydrogen and halogens. In some embodiments, when X is N, R^f and R^g are each independently hydrogen. In some embodiments, when X is CH, R^f and R^g are each independently selected from hydrogen and halogens. In at least one embodiment, one of R^f and R^g is hydrogen, and the other is selected from halogens, hydroxy groups, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and branched alkyl groups optionally interrupted with heteroatoms, and/or optionally substituted with R^1 . In at least one embodiment, R^f and R^g can also combine to form a carbonyl. In at least one embodiment, one of R^f and R^g is hydrogen, and the other is selected from hydrogen, halogen, cyano, and alkyl groups. In at least one embodiment, R^f and R^g are each independently selected from hydrogen and halogens. In at least one embodiment, R^f and R^g are each hydrogen.

[0023] In at least one embodiment of Formulas (I) and (II), R^h and R^i are each independently selected from hydrogen, optionally substituted alkyl or heteroalkyl (e.g., C_1 - C_6 alkyl or C_1 - C_6 heteroalkyl) and halogens. In at least one embodiment, one of R^h and R^i is hydrogen, and the other is selected from halogens, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and branched alkyl groups (e.g., C_1 - C_6 alkyl) optionally interrupted with heteroatoms, and/or optionally substituted with R^l . In at least one embodiment, one of R^h and R^i is hydrogen, and the other is selected from hydrogen, halogen, cyano, and alkyl groups. In at least one embodiment, R^h and R^i are each independently selected from hydrogen and halogens. In at least one embodiment, R^h and R^i are each hydrogen.

[0024] In at least one embodiment of Formulas (I) and (II), R^j and R^k are each independently selected from hydrogen, optionally substituted alkyl or heteroalkyl (e.g., C_1 - C_6 alkyl or C_1 - C_6 heteroalkyl) and halogens. In at least one embodiment, one of R^j and R^k is hydrogen, and the other is selected from halogens, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and branched alkyl groups optionally interrupted with heteroatoms, and/or optionally substituted with R^l . In at least one embodiment, one of R^j and R^k is hydrogen, and the other is selected from hydrogen, halogen, cyano, and alkyl groups (e.g., C_1 - C_6 alkyl). In at least one embodiment, R^j and R^k are each independently selected from hydrogen and halogens. In at least one embodiment, R^j and R^k are each hydrogen.

[0025] In at least one embodiment of Formulas (I) and (II), Ring A is selected from 4- to 13-membered cycloalkyl and heterocycloalkyl groups, and 5- to 10-membered aryl and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group. In at least one embodiment, Ring A is selected from 5- to 10-membered cycloalkyl and heterocycloalkyl groups, and 5- to 10-membered heteroaryl groups, the groups being unsubstituted or substituted with at least one W group. In at least one embodiment, Ring A is chosen from aromatic and heteroaromatic groups, such as thiazole, isoxazole, oxazole, pyrimidine, pyridine, phenyl, benzoxazole, benzimidazole, benzothiazole, the groups being unsubstituted or substituted with at least one W group. By way of non-limiting example, Ring A can also be selected from the groups of Table A:

Table A:

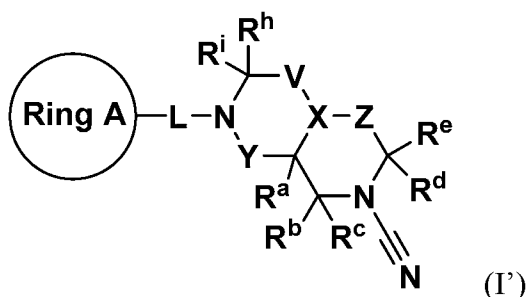
[0026] In Table A, a wavy line represents the attachment point of Ring A to Formula (I) or (II). In some embodiments of Formulas (I) and (II), Ring A is selected from 5- and 6-membered heterocyclic and heteroaromatic rings substituted with at least one W group.

[0027] In at least one embodiment of Formulas (I) and (II), W is selected from hydrogen, halogen, cyano groups, C₁-C₆ alkyl groups, C₁-C₆ alkyl ester groups, 4- to 7-membered cycloalkyl groups, 5- and 6-membered heterocycloalkyl groups, and 6- to 10-membered aryl and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R¹ group, which can be the same or different. In at least one embodiment, W is selected from hydrogen, halogen, cyano groups, isopropyl groups, t-butyl groups, cyclobutyl groups, cyclohexane groups, phenyl groups, and indazolpyridinyl groups, the groups being unsubstituted, or substituted with at least one R¹ group, which can be the same or different. In at least one embodiment, W is an alkyl group substituted with R¹ being halogen, such as trifluoromethyl groups.

[0028] As defined above for Formula (I), R¹ is independently selected from small lipophilic or electron withdrawing groups that exhibit activity in a USP30 biochemical assay. Examples of such groups include hydrogen, halogen, hydroxy groups, cyano groups, amides, amines, C₁-C₆ alkyl groups, C₁-C₆ alkyl esters, C₁-C₆ alkyl amines, C₁-C₆ alkyl alcohols, C₃-C₆ cycloalkyl groups, S(O)₂ groups, and trifluoromethyl and trifluoromethylester groups. In at least one embodiment, R¹ is independently selected from hydrogen, halogen, cyano, amides, C₁-C₆ alkyl groups, C₁-C₆ alkyl esters, C₁-C₆ alkyl amines, C₁-C₆ alkyl alcohols, C₃-C₆ cycloalkyl groups, S(O)₂ groups, and trifluoromethyl and trifluoromethylester groups. In at least one embodiment, R¹ is independently selected from hydrogen, halogen, cyano, amides, C₁-C₆ alkyl groups, C₁-C₆ alkyl esters, trifluoromethyl, and trifluoromethylester groups.

Compounds of Formula (I')

[0029] The present disclosure also provides compounds of Formula (I'):



wherein V, X, Y, Z, L, R^a, R^b, R^c, R^d, R^e, R^h, Rⁱ, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0030] In some embodiments, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from a bond, C(O), and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is $-(CH_2)_n-$;

n is 0, 1, 2, or 3,

wherein each methylene unit of L is optionally substituted with one or two C₁-C₆ alkyl, and

wherein if n is 2 or 3, then one methylene unit of L is optionally replaced with a heteroatom

independently selected from nitrogen, oxygen, and sulfur;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from

hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl;

or R^j and R^k combine with the carbon to which they are attached to form an optionally substituted

C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

wherein an optionally substituted R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x group may be substituted with one or more R^l;

Ring A is selected from C₄-C₁₃ cycloalkyl, 4- to 13-membered heterocycloalkyl containing 1 to 3

heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C₁₀ aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, -CN, -C(O)OR, optionally substituted C₁-C₆ alkyl,

optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered

heterocycloalkyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

optionally substituted phenyl, optionally substituted C₁₀ aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l;

each R^1 is independently selected from oxo, halogen, -OR, -NR₂, -CN, -C(O)OR, -C(O)OCF₃, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C₁-C₆ alkyl optionally substituted with -OH, trifluoromethyl, and C₃-C₆cycloalkyl;

each R is independently selected from hydrogen and C₁-C₆ alkyl; and

each R' is independently selected from C₁-C₆ alkyl.

[0031] In some embodiments, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from C(O) and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is -(CH₂)_n;

n is 0, 1, or 2,

wherein each methylene unit of L is optionally substituted with one C₁-C₆ alkyl, and

wherein if n is 2, then one methylene unit of L is optionally replaced with an oxygen;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, and C₁-C₆ alkyl;

Ring A is selected from C₃-C₁₀ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, -OR, -CN, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_m(C₃-C₁₀cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(C₆aryl);

each R is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and phenyl; and

each m is independently 0 or 1.

[0032] In some embodiments, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from C(O) and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is $-(CH_2)_n-$;

n is 0;

R^a is selected from hydrogen, halogen, and C₁-C₆ alkyl;

R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen;

Ring A is 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, $-(CH_2)_m$ (3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and $-(CH_2)_m$ (C₆aryl);

each R is phenyl; and

each m is 1.

[0033] In some embodiments, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, wherein:

V is selected from C(O) and CR^fR^g;

X is N;

Y is C(O);

Z is selected from C(O) and CR^jR^k;

L is $-(CH_2)_n-$;

n is 0;

R^a is hydrogen;

R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen;

Ring A is 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

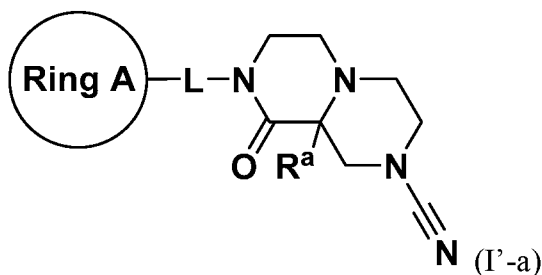
each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R¹;

each R¹ is independently selected from halogen, -OR, -CN, and -(CH₂)_m(C₆aryl);

each R is phenyl; and

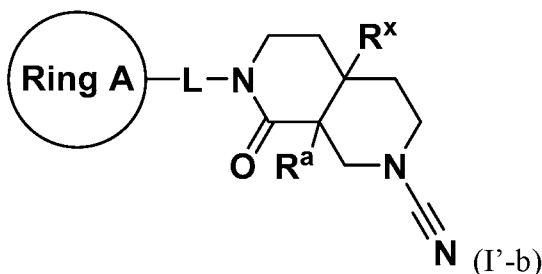
each m is 1.

[0034] In some embodiments, the present disclosure provides compounds of Formula (I'-a):



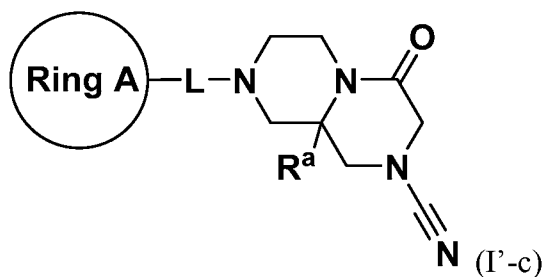
or a pharmaceutically acceptable salt thereof, wherein L, R^a, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0035] In some embodiments, the present disclosure provides compounds of Formula (I'-b):



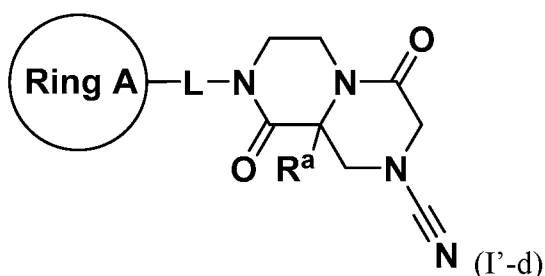
or a pharmaceutically acceptable salt thereof, wherein L, R^a, R^x, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0036] In some embodiments, the present disclosure provides compounds of Formula (I'-c):



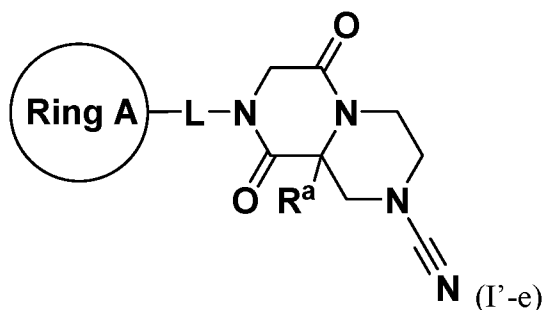
or a pharmaceutically acceptable salt thereof, wherein L, R^a, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0037] In some embodiments, the present disclosure provides compounds of Formula (I'-d):



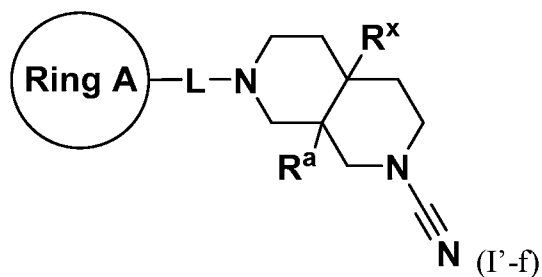
or a pharmaceutically acceptable salt thereof, wherein L, R^a, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0038] In some embodiments, the present disclosure provides compounds of Formula (I'-e):



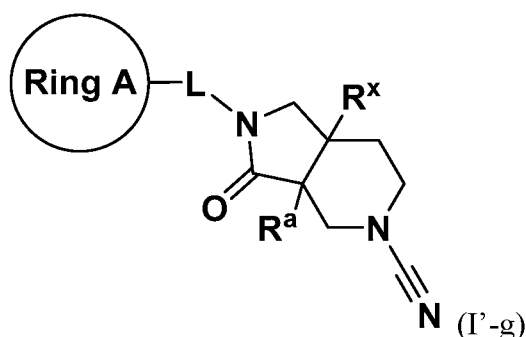
or a pharmaceutically acceptable salt thereof, wherein L, R^a, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0039] In some embodiments, the present disclosure provides compounds of Formula (I'-f):



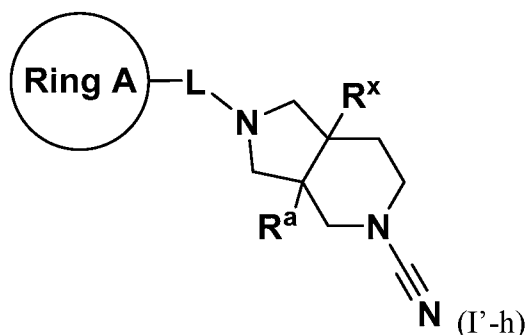
or a pharmaceutically acceptable salt thereof, wherein L , R^a , R^x , and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0040] In some embodiments, the present disclosure provides compounds of Formula (I'-g):



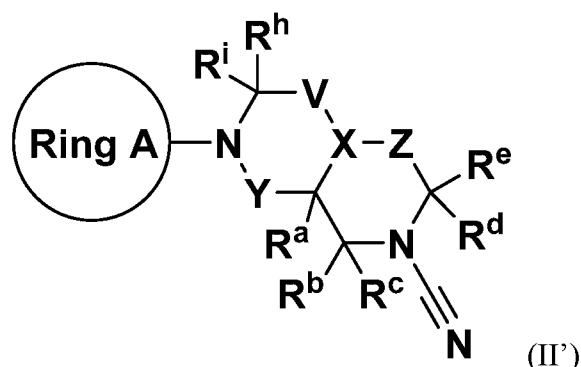
or a pharmaceutically acceptable salt thereof, wherein L , R^a , R^x , and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0041] In some embodiments, the present disclosure provides compounds of Formula (I'-h):



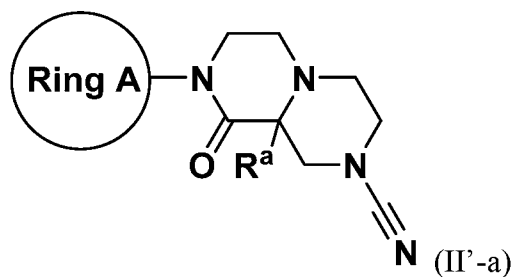
or a pharmaceutically acceptable salt thereof, wherein L , R^a , R^x , and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0042] In some embodiments, the present disclosure provides compounds of Formula (II'):



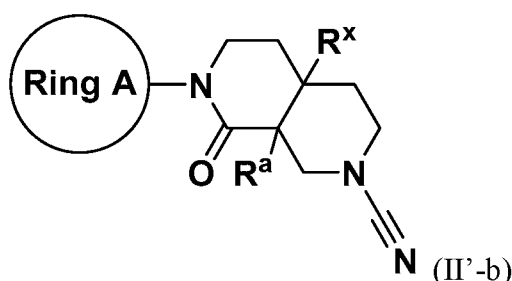
or a pharmaceutically acceptable salt thereof, wherein V, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^h, Rⁱ, and Ring A are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0043] In some embodiments, the present disclosure provides compounds of Formula (II'-a):



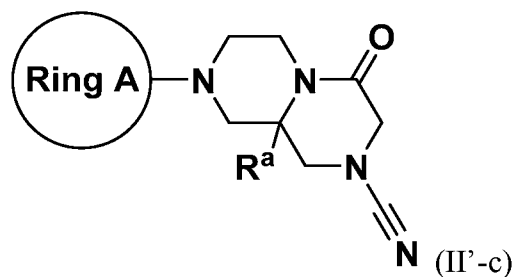
or a pharmaceutically acceptable salt thereof, wherein R^a and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0044] In some embodiments, the present disclosure provides compounds of Formula (II'-b):



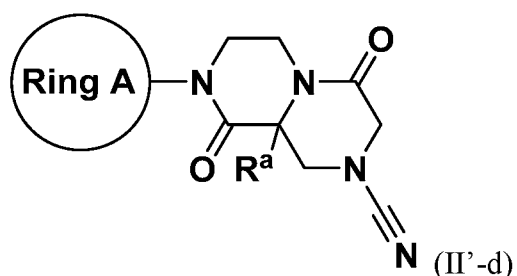
or a pharmaceutically acceptable salt thereof, wherein R^a, R^x, and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0045] In some embodiments, the present disclosure provides compounds of Formula (II'-c):



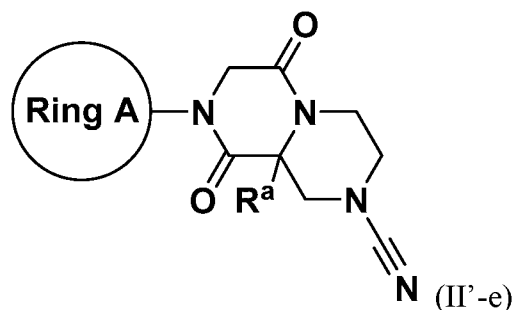
or a pharmaceutically acceptable salt thereof, wherein R^a and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0046] In some embodiments, the present disclosure provides compounds of Formula (II'-d):



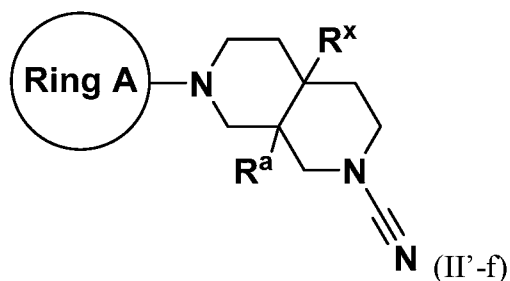
or a pharmaceutically acceptable salt thereof, wherein R^a and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0047] In some embodiments, the present disclosure provides compounds of Formula (II'-e):



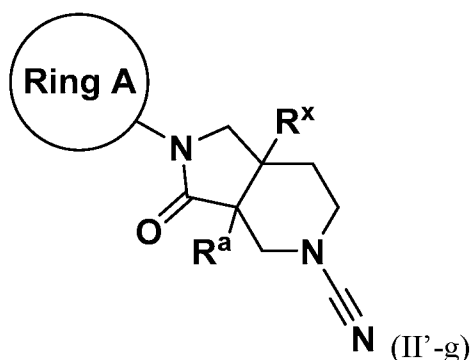
or a pharmaceutically acceptable salt thereof, wherein R^a and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0048] In some embodiments, the present disclosure provides compounds of Formula (II'-f):



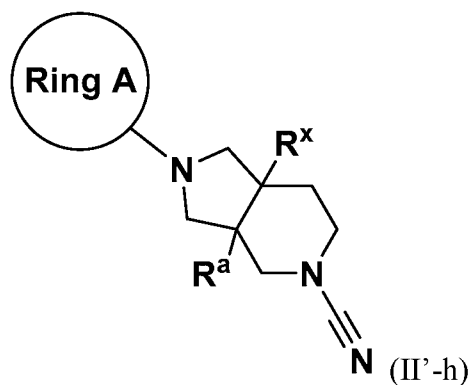
or a pharmaceutically acceptable salt thereof, wherein R^a , R^x , and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0049] In some embodiments, the present disclosure provides compounds of Formula (II'-g):



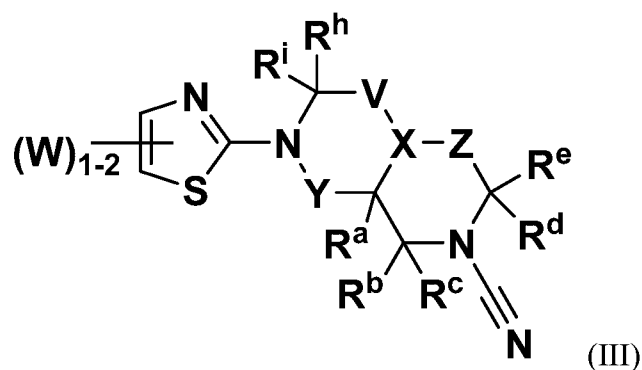
or a pharmaceutically acceptable salt thereof, wherein R^a , R^x , and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0050] In some embodiments, the present disclosure provides compounds of Formula (II'-h):



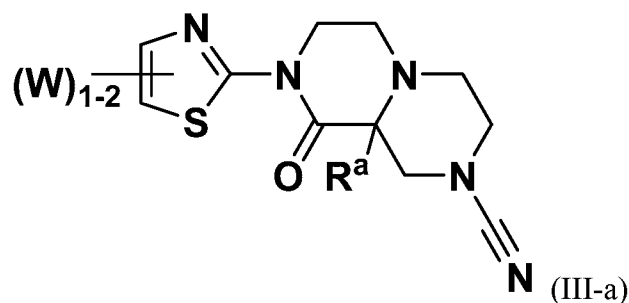
or a pharmaceutically acceptable salt thereof, wherein R^a , R^x , and Ring A are both as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0051] In some embodiments, the present disclosure provides compounds of Formula (III):



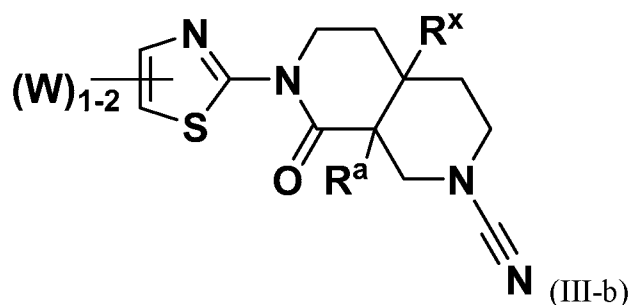
or a pharmaceutically acceptable salt thereof, wherein V, X, Y, Z, R^a , R^b , R^c , R^d , R^e , R^h , R^i , and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0052] In some embodiments, the present disclosure provides compounds of Formula (III-a):



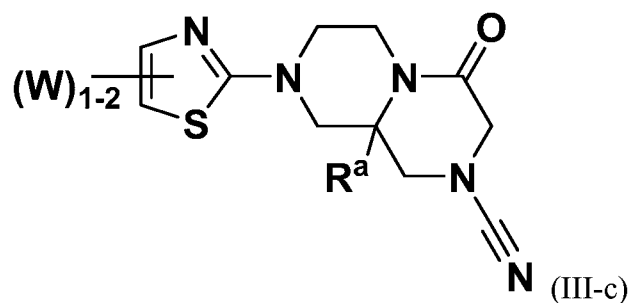
or a pharmaceutically acceptable salt thereof, wherein R^a and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0053] In some embodiments, the present disclosure provides compounds of Formula (III-b):



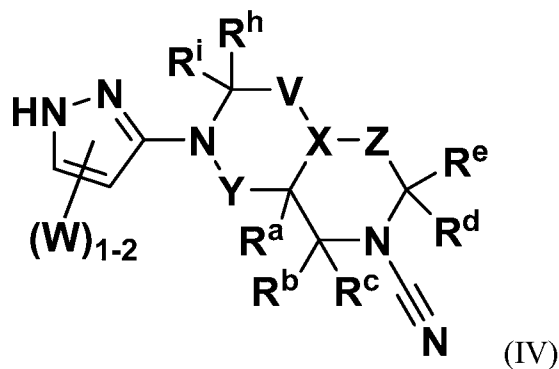
or a pharmaceutically acceptable salt thereof, wherein R^a , R^x , and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0054] In some embodiments, the present disclosure provides compounds of Formula (III-c):



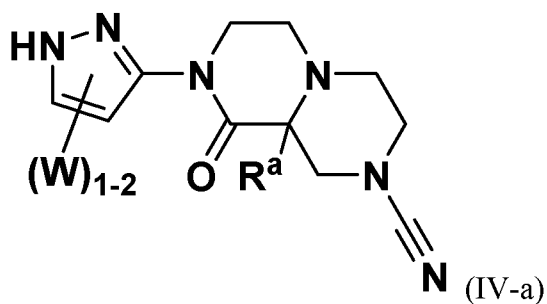
or a pharmaceutically acceptable salt thereof, wherein R^a and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0055] In some embodiments, the present disclosure provides compounds of Formula (IV):



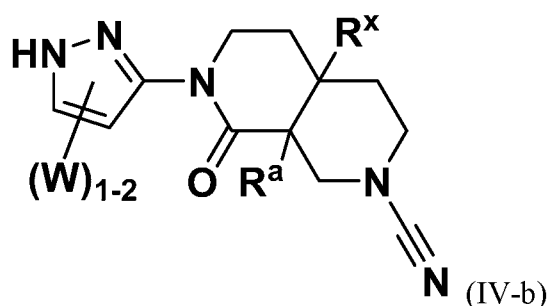
or a pharmaceutically acceptable salt thereof, wherein V, X, Y, Z, R^a , R^b , R^c , R^d , R^e , R^h , R^i , and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0056] In some embodiments, the present disclosure provides compounds of Formula (IV-a):



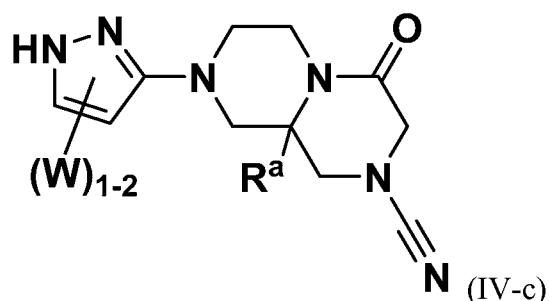
or a pharmaceutically acceptable salt thereof, wherein R^a and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0057] In some embodiments, the present disclosure provides compounds of Formula (IV-b):



or a pharmaceutically acceptable salt thereof, wherein R^a , R^x , and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0058] In some embodiments, the present disclosure provides compounds of Formula (IV-c):



or a pharmaceutically acceptable salt thereof, wherein R^a and W are all as defined for Formula (I') above and described in classes and subclasses herein for Formula (I'), both singly and in combination.

[0059] In some embodiments of Formulas (I'), (II'), (III) and (IV), V is selected from a bond, $C(O)$, and CR^fR^g . In some embodiments, V is a bond. In some embodiments, V is $C(O)$. In some embodiments, V is CR^fR^g . In some embodiments, V is CH_2 .

[0060] In some embodiments of Formulas (I'), (II'), (III) and (IV), X is selected from N and CR^x . In some embodiments, X is N . In some embodiments, X is CR^x . In some embodiments, X is CH .

[0061] In some embodiments of Formulas (I'), (II'), (III) and (IV), Y is selected from a bond, $C(O)$, and CR^jR^k . In some embodiments, Y is a bond. In some embodiments, Y is $C(O)$. In some embodiments, Y is CR^jR^k . In some embodiments, Y is CH_2 .

[0062] In some embodiments of Formulas (I'), (II'), (III) and (IV), Z is selected from $C(O)$ and CR^jR^k . In some embodiments, Z is $C(O)$. In some embodiments, Z is CR^jR^k . In some embodiments, Z is CH_2 .

[0063] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (III) and (IV), L is $-(CH_2)_n-$. In some embodiments, each methylene unit of L is optionally

substituted with one or two C₁-C₆ alkyl. In some embodiments, each methylene unit of L is optionally substituted with methyl. In some embodiments, one methylene unit of L is optionally substituted with methyl. In some embodiments, L is selected from $-(CH_2)_0-$, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, and $-CH_2CH(CH_3)O-$. It will be appreciated that L is a covalent bond when L is $-(CH_2)_0-$.

[0064] In some embodiments, L is $-CH_2-$. In some embodiments, L is $-CH_2CH_2-$. In some embodiments, L is $-CH_2CH(CH_3)-$. In some embodiments, L is $-CH_2CH(CH_3)O-$.

[0065] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (III) and (IV), n is 0. In some embodiments, when n is 0, Ring A is attached via a carbon atom. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, when n is 2 or 3, one methylene unit of L is optionally replaced with a heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, when n is 2, one methylene unit of L is optionally replaced with a heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, when n is 2, one methylene unit of L is optionally replaced with oxygen.

[0066] In some embodiments of Formulas (I'), (II'), (III) and (IV), each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^b and R^c, or R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x group may be substituted with one or more R^l.

[0067] In some embodiments of Formulas (I'), (II'), (III) and (IV), each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x group may be substituted with one or more R^l.

[0068] In some embodiments of (I'), (II'), (III) and (IV), each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OH, -NR₂, -CN,

optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments, each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^a is selected from hydrogen, halogen, and C₁-C₆ alkyl, and R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen. In some embodiments, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen.

[0069] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), R^a is hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^a may be substituted with one or more R¹. In some embodiments, R^a is selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments R^a is selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^a is selected from hydrogen and halogen. In some embodiments, R^a is hydrogen. In some embodiments, R^a is halogen. In some embodiments, R^a is fluoro. In some embodiments, R^a is C₁-C₆ alkyl. In some embodiments, R^a is methyl.

[0070] In some embodiments of (I'), (II'), (III) and (IV), R^b and R^c are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^b and R^c combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^b and R^c group may be substituted with one or more R¹.

[0071] In some embodiments of (I'), (II'), (III) and (IV), R^b and R^c are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^b and R^c group may be substituted with one or more R¹. In some embodiments, R^b and R^c combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

[0072] In some embodiments of (I'), (II'), (III) and (IV), R^b and R^c are each independently selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments, R^b and R^c are each independently selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^b and R^c are each independently selected from hydrogen and C₁-C₆ alkyl optionally substituted with R¹. In some embodiments, R^b and R^c are each independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, at least one of R^b and R^c is hydrogen. In some embodiments, at least one of R^b and R^c is hydrogen, and the other of R^b and R^c is C₁-C₆ alkyl optionally substituted with R¹. In some embodiments, R^b and R^c are each hydrogen.

[0073] In some embodiments of (I'), (II'), (III) and (IV), R^d and R^e are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^d and R^e combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^d and R^e group may be substituted with one or more R¹.

[0074] In some embodiments of (I'), (II'), (III) and (IV), R^d and R^e are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^d and R^e group may be substituted with one or more R¹. In some embodiments, R^d and R^e combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

[0075] In some embodiments of (I'), (II'), (III) and (IV), R^d and R^e are each independently selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments, R^d and R^e are each independently selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^d and R^e are each independently selected from hydrogen and C₁-C₆ alkyl optionally substituted with R¹. In some embodiments, R^d and R^e are each independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, at least one of R^d and R^e is hydrogen. In some embodiments, at least one of R^d and R^e is hydrogen, and the other of R^d and R^e

R^e is C₁-C₆ alkyl optionally substituted with R¹. In some embodiments, R^d and R^e are each hydrogen.

[0076] In some embodiments of (I'), (II'), (III) and (IV), R^f and R^g are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^f and R^g combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^f and R^g group may be substituted with one or more R¹.

[0077] In some embodiments of (I'), (II'), (III) and (IV), R^f and R^g are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^f and R^g group may be substituted with one or more R¹. In some embodiments, R^f and R^g combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

[0078] In some embodiments of (I'), (II'), (III) and (IV), R^f and R^g are each independently selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments, R^f and R^g are each independently selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^f and R^g are each independently selected from hydrogen and halogen. In some embodiments, R^f and R^g are each independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, at least one of R^f and R^g is hydrogen. In some embodiments, at least one of R^f and R^g is hydrogen, and the other of R^f and R^g is halogen, -CN, or C₁-C₆ alkyl. In some embodiments, R^f and R^g are each hydrogen.

[0079] In some embodiments of (I'), (II'), (III) and (IV), R^h and Rⁱ are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^h and Rⁱ combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from

nitrogen, oxygen, and sulfur, wherein an optionally substituted R^h and R^i group may be substituted with one or more R^l .

[0080] In some embodiments of (I'), (II'), (III) and (IV), R^h and R^i are each independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^h and R^i group may be substituted with one or more R^l . In some embodiments, R^h and R^i combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

[0081] In some embodiments of (I'), (II'), (III) and (IV), R^h and R^i are each independently selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C₁-C₆ alkyl, or cyclopropyl. In some embodiments, R^h and R^i are each independently selected from hydrogen, halogen, and C₁-C₆ alkyl. In some embodiments, R^h and R^i are each independently selected from hydrogen and halogen. In some embodiments, R^h and R^i are each independently selected from hydrogen, halogen, and C₁-C₆ alkyl optionally substituted with R^l . In some embodiments, R^h and R^i are each independently selected from hydrogen and C₁-C₆ alkyl. In some embodiments, at least one of R^h and R^i is hydrogen. In some embodiments, at least one of R^h and R^i is hydrogen, and the other of R^h and R^i is hydrogen, halogen, -CN, and C₁-C₆ alkyl. In some embodiments, R^h and R^i are each hydrogen.

[0082] In some embodiments of (I'), (II'), (III) and (IV), each occurrence of R^j and R^k is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, or R^j and R^k combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted R^j and R^k group may be substituted with one or more R^l .

[0083] In some embodiments of (I'), (II'), (III) and (IV), each occurrence of R^j and R^k is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an

optionally substituted R^h and R^i group may be substituted with one or more R^l . In some embodiments, R^j and R^k combine with the carbon to which they are attached to form an optionally substituted C_3 - C_6 cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

[0084] In some embodiments of (I'), (II'), (III) and (IV), each occurrence of R^j and R^k is independently selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C_1 - C_6 alkyl, or cyclopropyl. In some embodiments, each occurrence of R^j and R^k is independently selected from hydrogen, halogen, and C_1 - C_6 alkyl. In some embodiments, each occurrence of R^j and R^k is independently selected from hydrogen and halogen. In some embodiments, each occurrence of R^j and R^k is independently selected from hydrogen, halogen, and C_1 - C_6 alkyl optionally substituted with R^l . In some embodiments, each occurrence of R^j and R^k is independently selected from hydrogen and C_1 - C_6 alkyl. In some embodiments, at least one of R^j and R^k is hydrogen. In some embodiments, at least one of R^j and R^k is hydrogen, and the other of R^j and R^k is hydrogen, halogen, -CN, and C_1 - C_6 alkyl. In some embodiments, R^j and R^k are each hydrogen.

[0085] In some embodiments of (I'), (I'-b), (I'-f), (I'-g), (I'-h), (II'), (II'-b), (II'-f), (II'-g), (II'-h), (III), (III-b), (IV), and (IV-b), R^x is selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C_1 - C_6 aliphatic, optionally substituted C_3 - C_6 cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, R^x is selected from hydrogen, halogen, -OH, -NR₂, -CN, optionally substituted C_1 - C_6 alkyl, or cyclopropyl. In some embodiments, R^x is selected from hydrogen, halogen, and C_1 - C_6 alkyl. In some embodiments, R^x is hydrogen.

[0086] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), and (II'-h), Ring A is selected from C_3 - C_{13} cycloalkyl, 3- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C_{10} aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is selected from C_3 - C_{10} cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W.

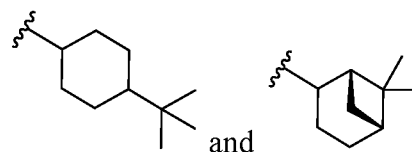
[0087] In some embodiments, Ring A is selected from C_4 - C_{13} cycloalkyl, 4- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C_{10}

aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is selected from C₅-C₁₀ cycloalkyl, 5- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W.

[0088] In some embodiments, Ring A is selected from Table A above.

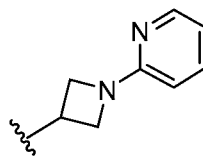
[0089] In some embodiments, Ring A is unsubstituted. In some embodiments, Ring A is substituted with one or more W.

[0090] In some embodiments, Ring A is C₃-C₁₃ cycloalkyl, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is optionally substituted C₄-C₁₃ cycloalkyl. In some embodiments, Ring A is optionally substituted C₃-C₁₀ cycloalkyl. In some embodiments, Ring A is optionally substituted C₆-C₇ cycloalkyl. In some embodiments, Ring A is optionally substituted cyclohexyl or bicyclo[3.1.1]heptanyl.



[0091] In some embodiments, Ring A is selected from:

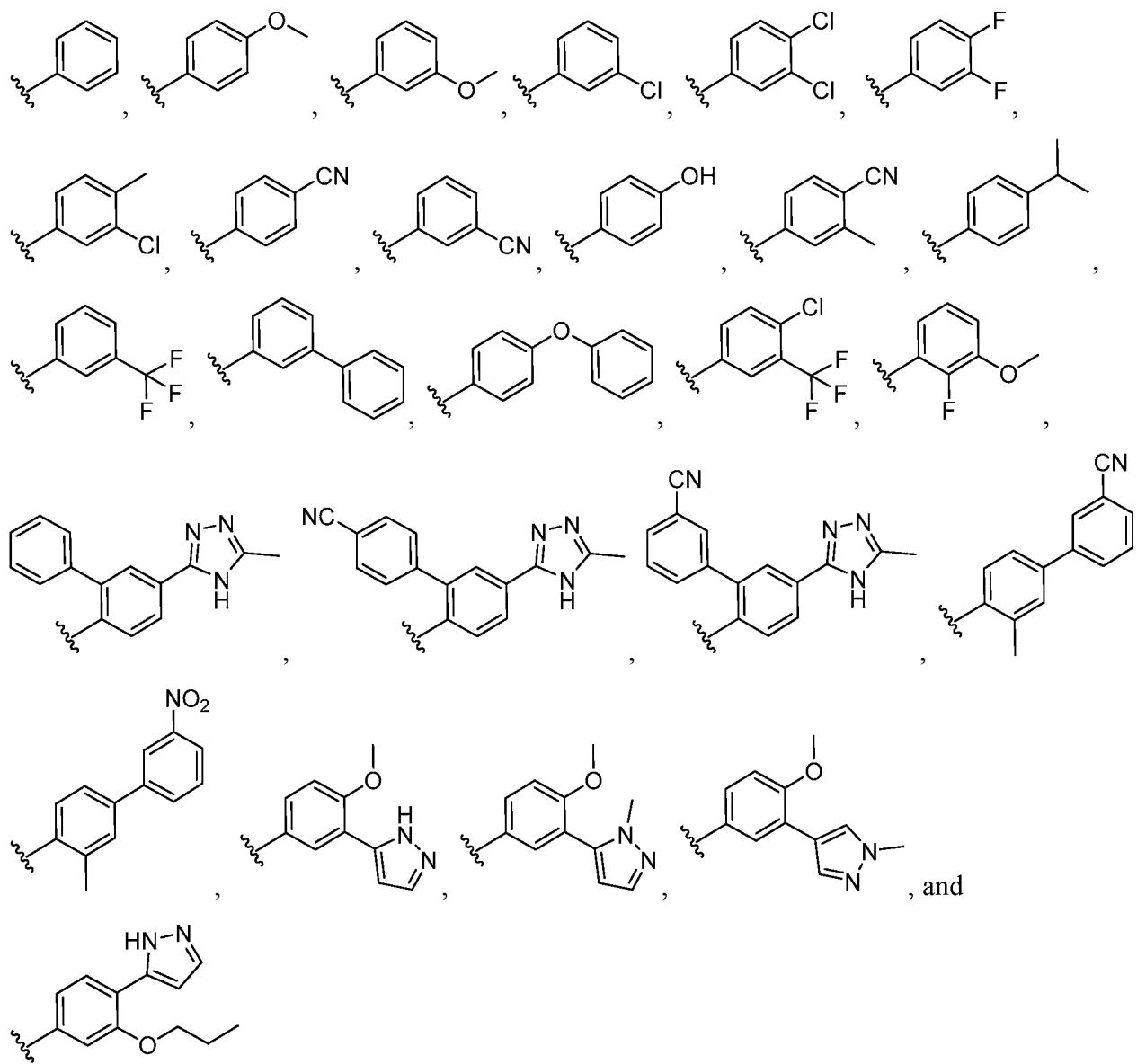
[0092] In some embodiments, Ring A is 3- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is optionally substituted 4- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted 4-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted azetidiny.



[0093] In some embodiments, Ring A is:

[0094] In some embodiments, Ring A is phenyl or C₁₀ aryl, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is optionally substituted phenyl. In some embodiments, Ring A is optionally substituted phenyl. In some embodiments, Ring A is optionally substituted C₁₀ aryl.

[0095] In some embodiments, Ring A is selected from:



[0096] In some embodiments, Ring A is 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W. In some embodiments, Ring A is 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W.

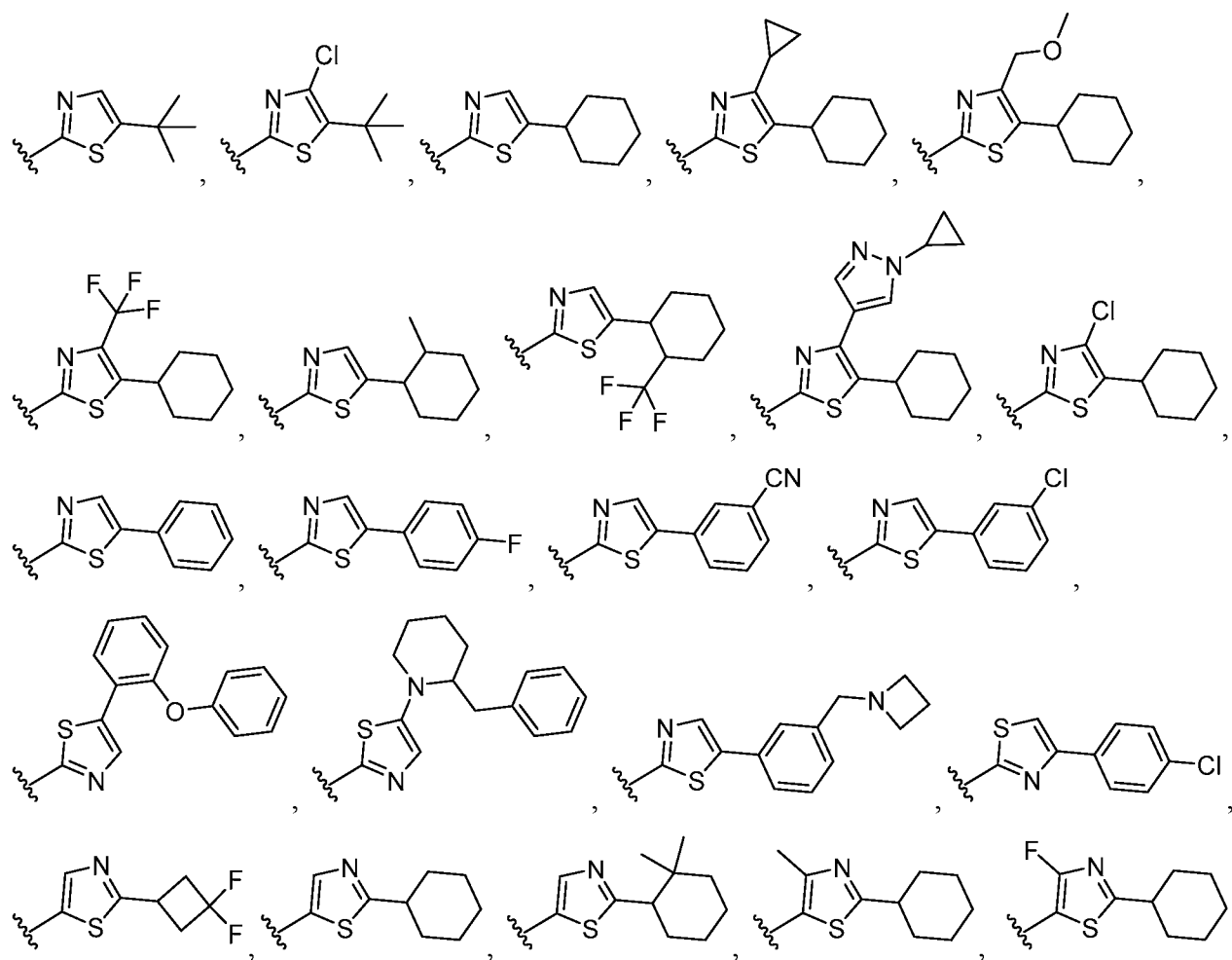
[0097] In some embodiments, Ring A is optionally substituted 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted thiazolyl, isoxazolyl, oxazolyl, pyrazolyl, imidazolyl, triazolyl, thiadiazolyl, or oxadiazolyl. In some embodiments, Ring A is optionally substituted thiazolyl or pyrazolyl.

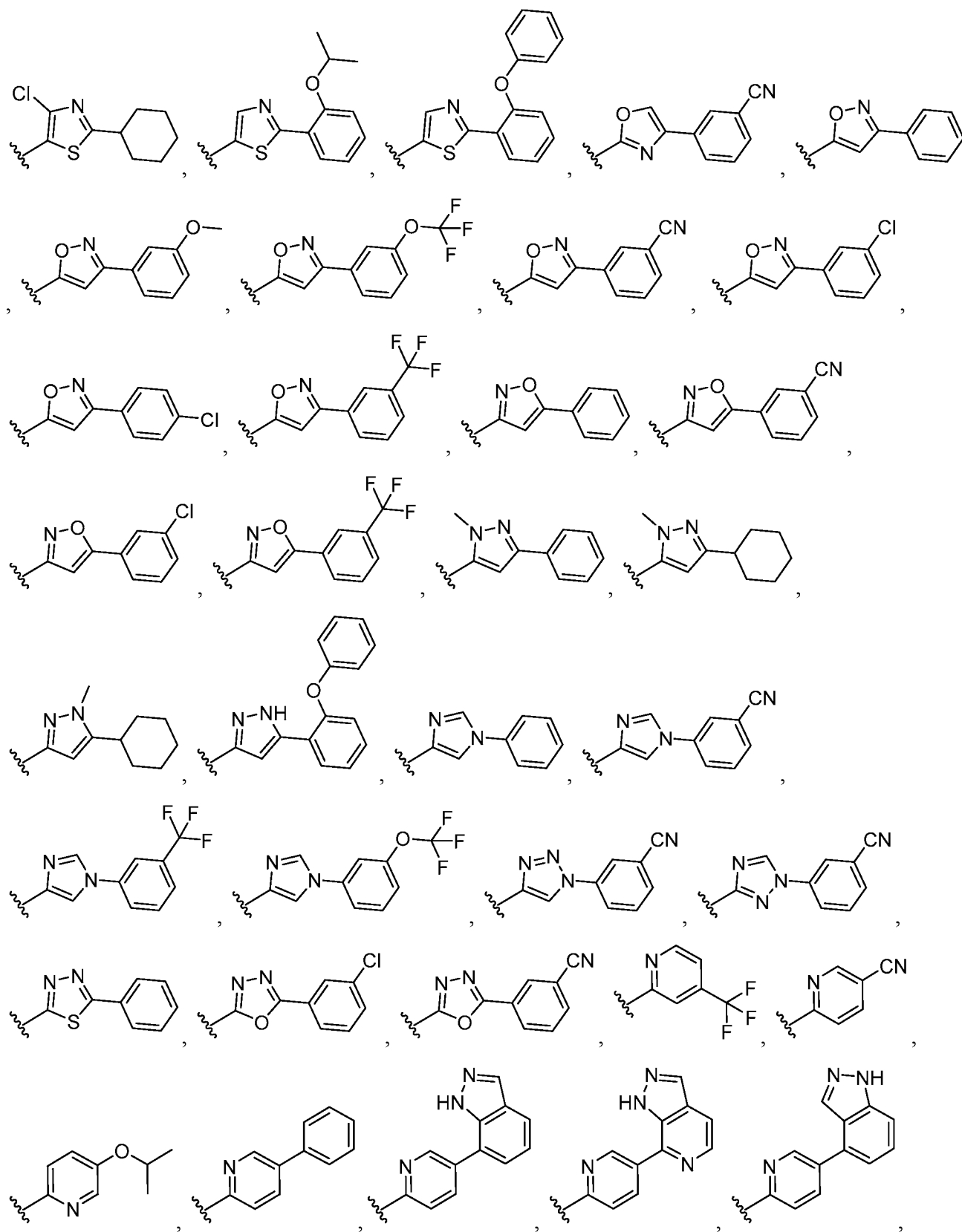
[0098] In some embodiments, Ring A is optionally substituted 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some embodiments, Ring A is optionally substituted pyrimidinyl.

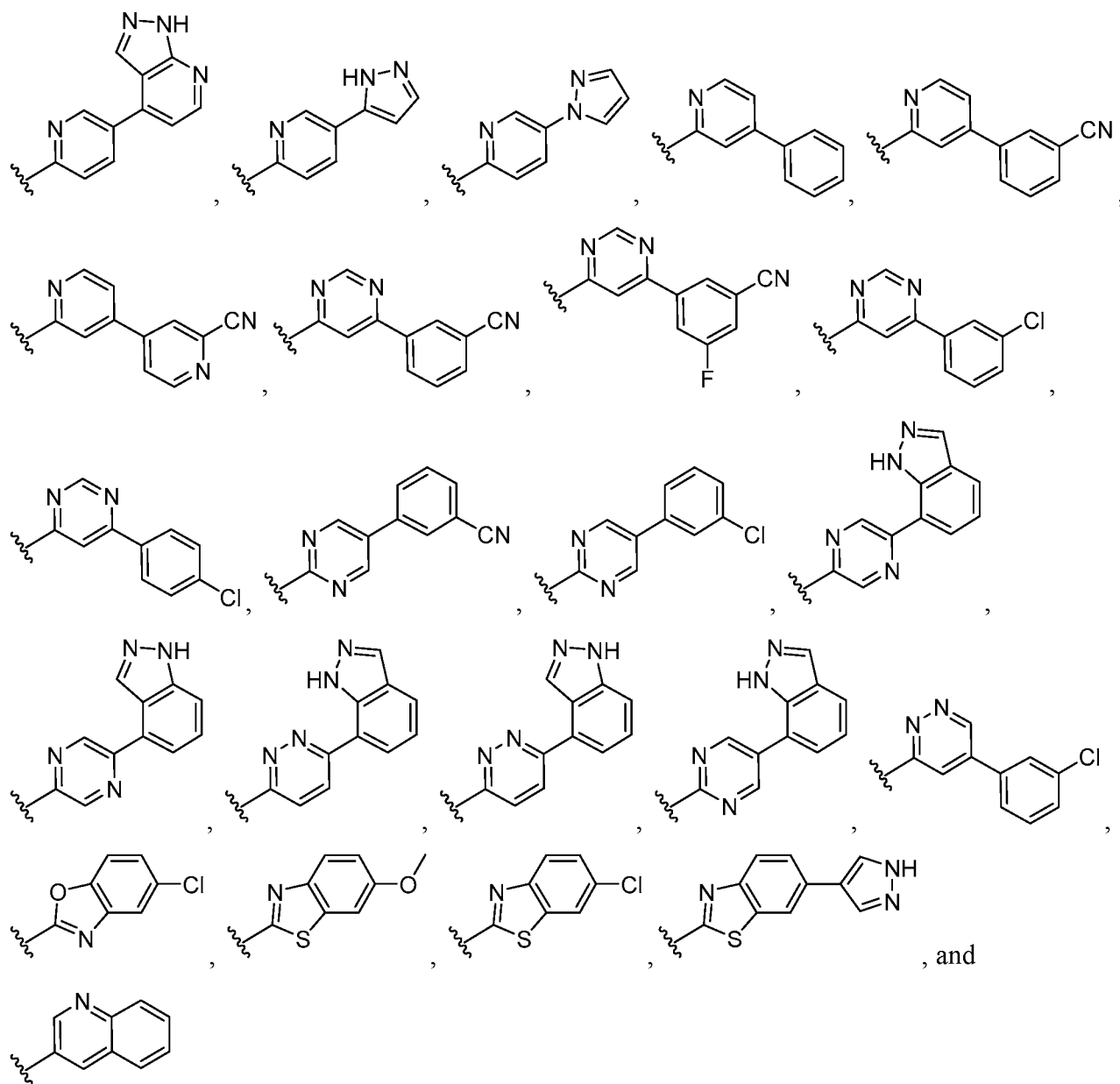
[0099] In some embodiments, Ring A is optionally substituted 9-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is optionally substituted benzoxazolyl or benzothiazolyl.

[0100] In some embodiments, Ring A is optionally substituted 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring A is quinolinyl.

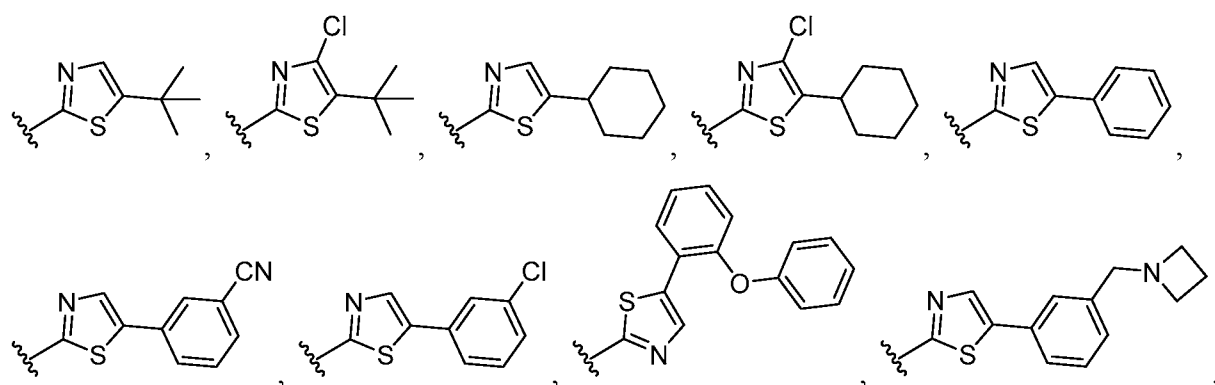
[0101] In some embodiments, Ring A is selected from:

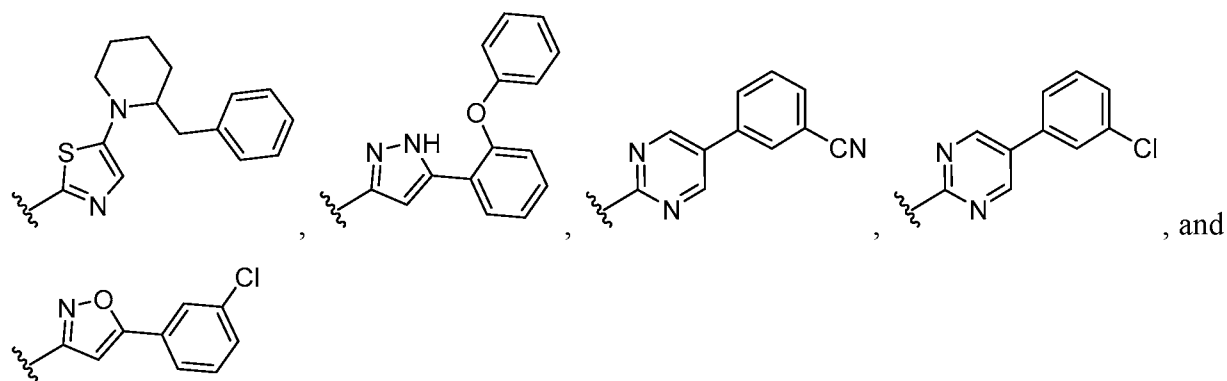






[0102] In some embodiments, Ring A is selected from:





[0103] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), each W is independently selected from halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, optionally substituted C₁₀ aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted W group may be substituted with one or more R¹. In some embodiments, each W is independently selected from halogen, -OR, -CN, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted W group may be substituted with one or more R¹. In some embodiments, each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R¹. In some embodiments, each W is independently selected from halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, optionally substituted 5- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl.

[0104] In some embodiments, each W is independently selected from halogen, -CN, -C(O)OR, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from

nitrogen, oxygen, and sulfur, optionally substituted phenyl, optionally substituted C₁₀ aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein an optionally substituted W group may be substituted with one or more R¹.

[0105] In some embodiments, W is unsubstituted. In some embodiments, W is substituted with one or more R¹.

[0106] In some embodiments, W is halogen. In some embodiments, W is fluoro. In some embodiments, W is chloro.

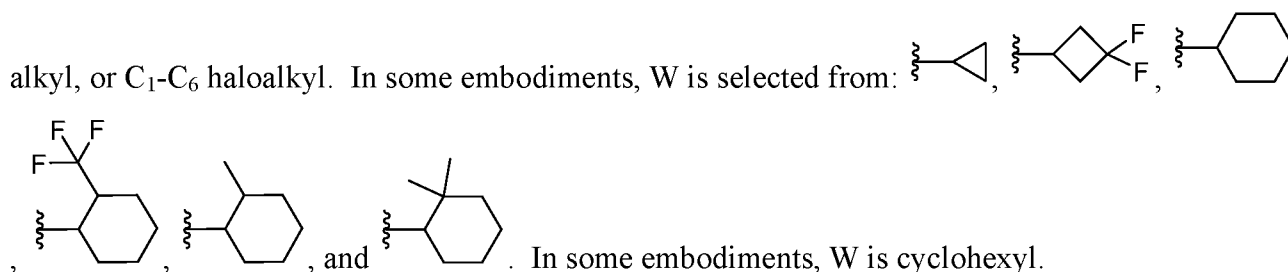
[0107] In some embodiments, W is –OR. In some embodiments, W is –OH. In some embodiments, W is –OR and R is C₁-C₆ alkyl. In some embodiments, W is selected from –OCH₃, –OCH₂CH₂CH₃, and –OCH(CH₃)₂. In some embodiments, W is –OR and R is phenyl.

[0108] In some embodiments, W is –CN.

[0109] In some embodiments, W is optionally substituted C₁-C₆ aliphatic. In some embodiments, W is optionally substituted C₁-C₆ alkyl. In some embodiments, W is C₁-C₆ alkyl optionally substituted with one or more halogen or –OR. In some embodiments, W is selected from methyl, iso-propyl, tert-butyl, –CH₂OCH₃, and –CF₃. In some embodiments, W is tert-butyl.

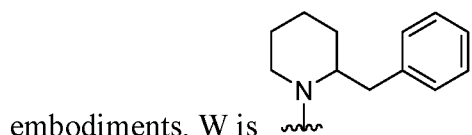
[0110] In some embodiments, W is optionally substituted C₃-C₁₀ cycloalkyl. In some embodiments, W is optionally substituted C₄-C₇ cycloalkyl. In some embodiments, W is optionally substituted cyclopropyl, cyclobutyl, or cyclohexyl. In some embodiments, W is optionally substituted C₃-C₆ cycloalkyl, wherein W is optionally substituted with one or more halogen, C₁-C₆

alkyl, or C₁-C₆ haloalkyl. In some embodiments, W is selected from:

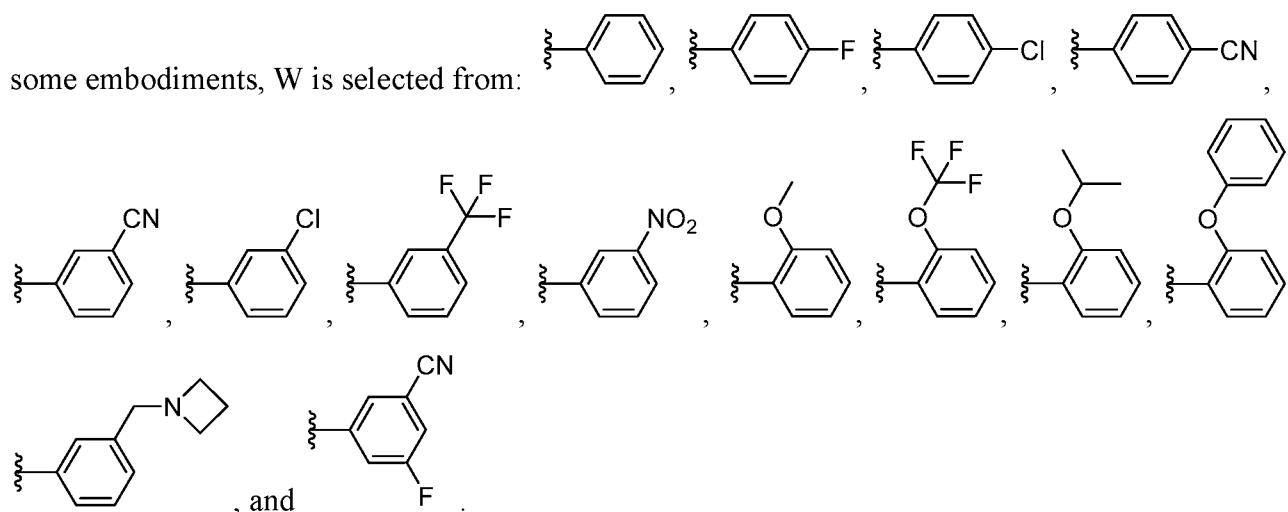


[0111] In some embodiments, W is optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is optionally substituted 5- to 6-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is optionally substituted 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some

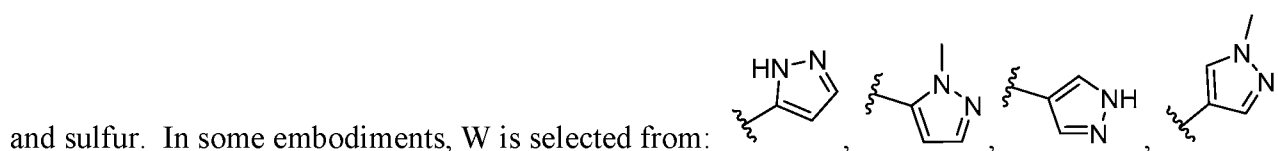
embodiments, W is optionally substituted piperidinyl (e.g., 2-benzylpiperidinyl). In some

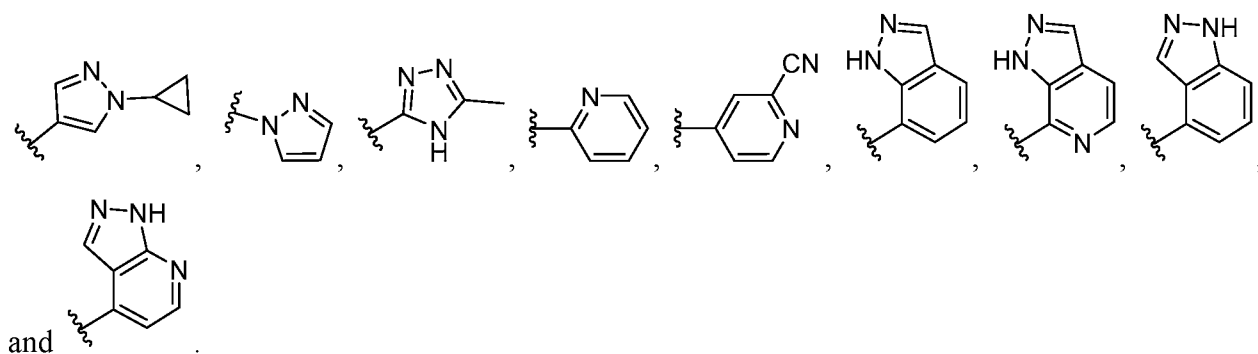


[0112] In some embodiments, W is optionally substituted phenyl or C₁₀ aryl. In some embodiments, W is optionally substituted phenyl. In some embodiments, W is optionally substituted phenyl. In some embodiments, W is phenyl optionally substituted with one or more halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and -CH₂(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur). In some embodiments, W is selected from phenyl, 3-cyanophenyl, 3-chlorophenyl, 2-phenoxyphenyl, and 3-(azetidin-1-ylmethyl)phenyl. In



[0113] In some embodiments, W is optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is optionally substituted 6- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted with one or more C₁-C₆ alkyl (e.g., methyl) or -CN. In some embodiments, W is optionally substituted 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is optionally substituted 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, W is optionally substituted 9-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen,





[0114] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), each R¹ is independently selected from oxo, halogen, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, -(CH₂)_m(C₃-C₁₀ cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), -(CH₂)_m(phenyl), -(CH₂)_m(C₁₀aryl), and -(CH₂)_m(5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur). In some embodiments, each R¹ is independently selected from halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_m(C₃-C₁₀ cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl). In some embodiments, each R¹ is independently selected from halogen, -OR, -CN, -(CH₂)_m(3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl).

[0115] In some embodiments, each R¹ is independently selected from oxo, halogen, -OR, -NR₂, -CN, -C(O)OR, -C(O)OCF₃, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C₁-C₆ alkyl optionally substituted with -OH, trifluoromethyl, and C₃-C₆ cycloalkyl.

[0116] In some embodiments, R¹ is halogen. In some embodiments, R¹ is fluoro. In some embodiments, R¹ is chloro.

[0117] In some embodiments, R¹ is -OR. In some embodiments, R¹ is -OR, and R is selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, and phenyl. In some embodiments, R¹ is -OCH₃, -OCF₃, -OCH(CH₃)₂, or -OPh.

[0118] In some embodiments, R¹ is -CN. In some embodiments, R¹ is -NO₂.

[0119] In some embodiments, R¹ is C₁-C₆ aliphatic. In some embodiments, R¹ is C₁-C₆ alkyl. In some embodiments, R¹ is methyl.

[0120] In some embodiments, R¹ is C₁-C₆ haloaliphatic. In some embodiments, R¹ is C₁-C₆ haloalkyl. In some embodiments, R¹ is -CF₃.

[0121] In some embodiments, R^1 is $-(CH_2)_m(C_3-C_{10} \text{ cycloalkyl})$. In some embodiments, R^1 is $C_3-C_{10} \text{ cycloalkyl}$. In some embodiments, R^1 is $C_3-C_6 \text{ cycloalkyl}$. In some embodiments, R^1 is cyclopropyl.

[0122] In some embodiments, R^1 is $-(CH_2)_m(3\text{- to } 10\text{-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur})$. In some embodiments, R^1 is $-CH_2(3\text{- to } 10\text{-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur})$. In some embodiments, R^1 is $-(CH_2)_m(3\text{- to } 6\text{-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur})$. In some embodiments, R^1 is $-CH_2(\text{azetidiny})$.

[0123] In some embodiments, R^1 is $-(CH_2)_m(\text{phenyl})$. In some embodiments, R^1 is $-CH_2(\text{phenyl})$. In some embodiments, R^1 is benzyl.

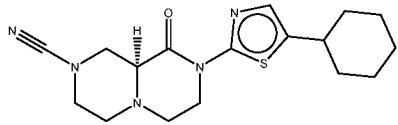
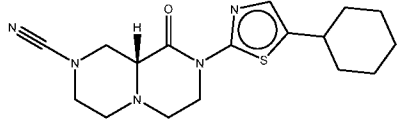
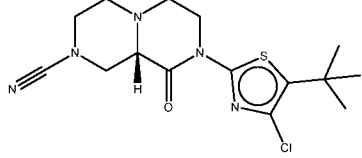
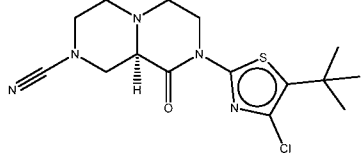
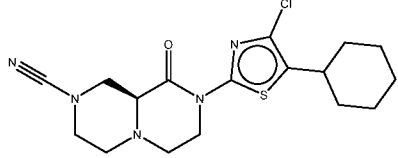
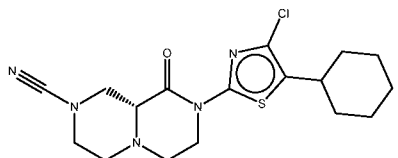
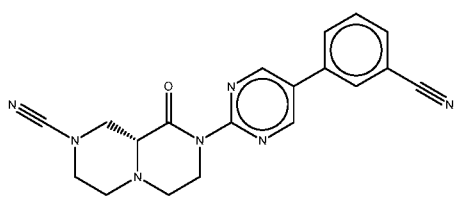
[0124] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), each R is independently selected from hydrogen, C_1-C_6 aliphatic, C_1-C_6 haloaliphatic, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, each R is independently selected from hydrogen, C_1-C_6 alkyl (e.g., methyl, propyl, or isopropyl), C_1-C_6 haloalkyl (e.g., trifluoromethyl), and phenyl. In some embodiments, each R is hydrogen or C_1-C_6 alkyl. In some embodiments, each R is phenyl (i.e., phenyl).

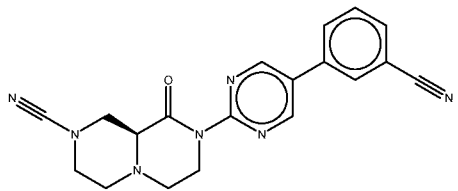
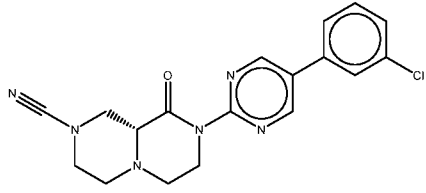
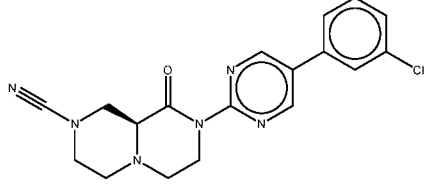
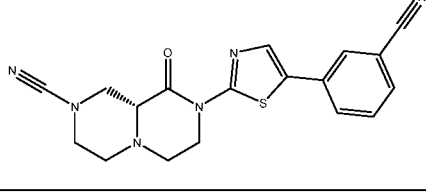
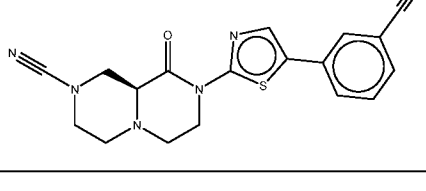
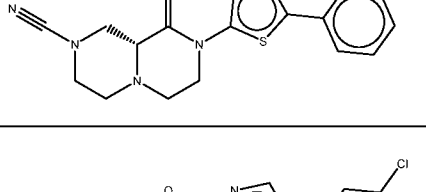
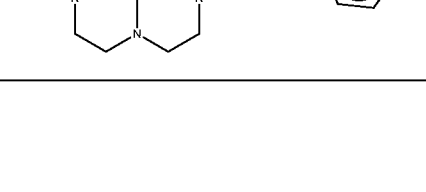
[0125] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), each R' is independently selected from C_1-C_6 aliphatic, C_1-C_6 haloaliphatic, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, each R' is independently C_1-C_6 alkyl.

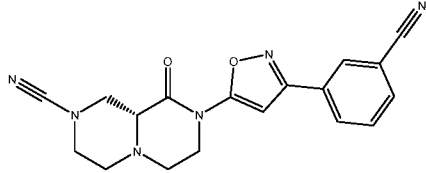
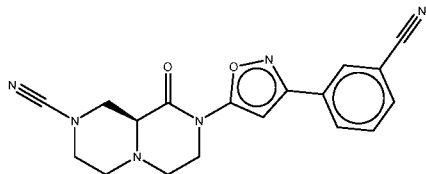
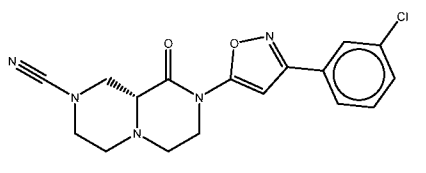
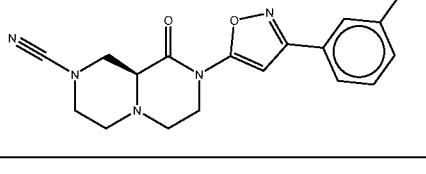
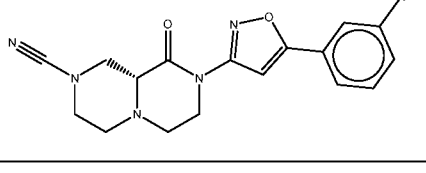
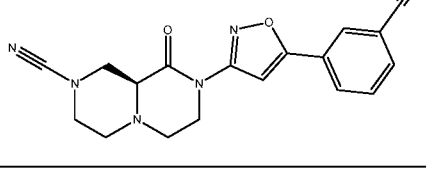
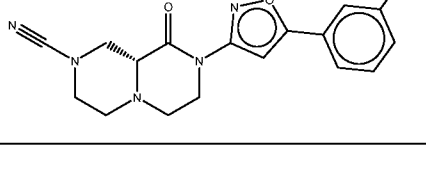
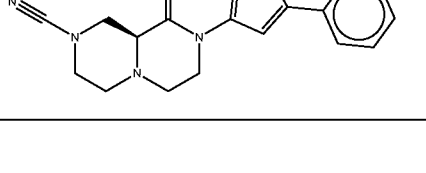
[0126] In some embodiments of Formulas (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), each m is independently 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

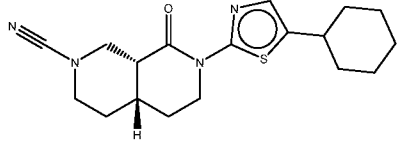
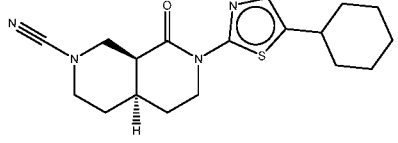
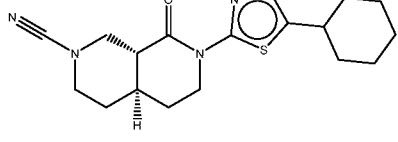
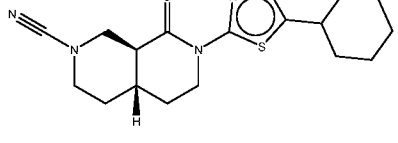
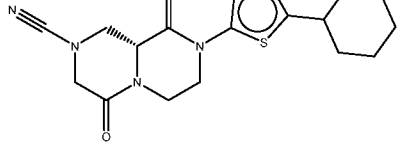
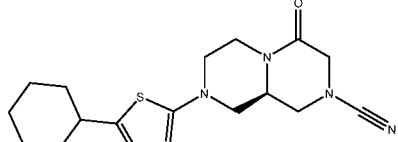
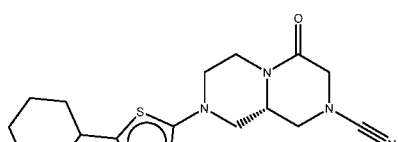
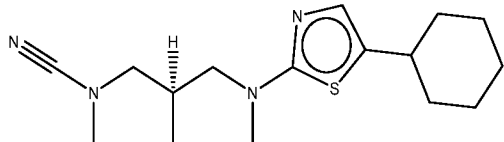
[0127] Examples of the chemical entities (e.g., compounds) disclosed herein can be found in Table B. In some embodiments, the present disclosure provides compounds selected from Table B and enantiomers and/or diastereomers thereof, or a pharmaceutically acceptable salt thereof.

Table B:

Cmpd #	Structure	Chemical Name
1-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-2S		*(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-2R		*(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3S		(S)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3R		(R)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-4R		(R)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-4S		(S)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5R		(R)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5S		(S)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-6R		(R)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-6S		(S)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7R		(R)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7S		(S)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-8R		(R)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-8S		(S)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9R		(R)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9S		(S)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-10R		(R)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-10S		(S)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-11R		(R)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-11S		(S)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-12S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,R		(4aR,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12S,S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
2-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
4-1S,S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile

Cmpd #	Structure	Chemical Name
4-1S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
4-1R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
5-1R,R		(3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-1S,S		(3aS,7aS)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2R,R		(3aR,7aR)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2S,S		(3aS,7aS)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
6-1R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
6-1S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-14S		*(S)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-14R		*(R)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15R		(R)-8-(5-(tert-butyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15S		(S)-8-(5-(tert-butyl)thiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-16		(R)-8-(((1R,2R,5R)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-17		(R)-8-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-18		(R)-8-(4-(4-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-19		(R)-8-(2-cyclohexylthiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-20		(R)-8-(3-cyclohexyl-1-methyl-1H-pyrazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-21		(R)-8-([1,1'-biphenyl]-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-22		(R)-8-(2-cyclohexyl-4-methylthiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-22		(R)-8-(4-isopropylbenzyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-23		(R)-8-((1s,4S)-4-(tert-butyl)cyclohexyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-24		(9aR)-8-(((2S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-25		(R)-9-oxo-8-(3-(trifluoromethyl)phenyl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-26		(R)-8-(2-(2-isopropoxyphenyl)thiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-27		(R)-9-oxo-8-(2-(2-phenoxyphenyl)thiazol-5-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-28		(R)-8-(2-(3,3-difluorocyclobutyl)thiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-29		(R)-9-oxo-8-(4-phenoxyphenyl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-30S		(R)-8-(2-((S)-2,2-dimethylcyclohexyl)thiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-30R		(R)-8-(2-((R)-2,2-dimethylcyclohexyl)thiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-31		(R)-8-(4-chloro-2-cyclohexylthiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-32		(R)-8-(5-cyclohexyl-4-(methoxymethyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-33		(R)-8-(2-cyclohexyl-4-fluorothiazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-34		(R)-8-(4-chloro-3-(trifluoromethyl)phenyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-35SR		(R)-8-(5-((1S,2R)-2-methylcyclohexyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-35RS		(R)-8-(5-((1R,2S)-2-methylcyclohexyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-36SS		(R)-8-(5-((1S,2S)-2-methylcyclohexyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-36RR		(R)-8-(5-((1R,2R)-2-methylcyclohexyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-37		(R)-8-(5-cyclohexyl-4-cyclopropylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-38		(R)-8-(5-cyclohexyl-4-(2-cyclopropyl-3H-2l4-pyrazol-4-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-39		(R)-9-oxo-8-(4-(trifluoromethyl)pyridin-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-40		(R)-8-(5-cyclohexyl-4-methylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-41		(R)-8-(5-cyclohexyl-1-methyl-1H-pyrazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-42		(R)-8-(5-cyclohexyl-4-(trifluoromethyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-43SR		(R)-9-oxo-8-(5-((1S,2R)-2-(trifluoromethyl)cyclohexyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-43RS		(R)-9-oxo-8-(5-((1R,2S)-2-(trifluoromethyl)cyclohexyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-43SS		(R)-9-oxo-8-(5-((1S,2S)-2-(trifluoromethyl)cyclohexyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-43RR		(R)-9-oxo-8-(5-((1R,2R)-2-(trifluoromethyl)cyclohexyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-44		(R)-8-(2-(5-(5-methyl-4H-1,2,4-triazol-3-yl)-[1,1'-biphenyl]-2-yl)ethyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-45		(R)-8-(2-(4'-cyano-5-(5-methyl-4H-1,2,4-triazol-3-yl)-[1,1'-biphenyl]-2-yl)ethyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-46		(R)-8-(2-(3'-cyano-5-(5-methyl-4H-1,2,4-triazol-3-yl)-[1,1'-biphenyl]-2-yl)ethyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-47		(R)-8-((3'-cyano-3-methyl-[1,1'-biphenyl]-4-yl)methyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-48		(R)-8-((3-methyl-3'-nitro-[1,1'-biphenyl]-4-yl)methyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-49		(R)-8-benzyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-50		(9aR)-8-(2-(4-methoxyphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-51		(R)-8-(3-chlorophenyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-52		(R)-8-(6-methoxybenzo[d]thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-53		(R)-8-(6-chlorobenzo[d]thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-54		(R)-9-oxo-8-(3-phenylisoxazol-5-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-55		(R)-9-oxo-8-(5-phenylpyridin-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-56		(R)-8-(5-chlorobenzo[d]oxazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-57		(R)-8-(3,4-dichlorophenyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-58		(9aR)-9-oxo-8-(2-phenoxypropyl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-59		(9aR)-8-(2-(3-methoxyphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-60		(9aR)-8-(2-(3,4-difluorophenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-61		(9aR)-9-oxo-8-(2-phenylpropyl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-62		(R)-8-(3-chloro-4-methylphenyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-63		(R)-9-oxo-8-(quinolin-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-64		(R)-8-(3-(4-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-65		(R)-8-(3-(3-methoxyphenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-66		(9aR)-8-(2-(4-methoxy-3-(1H-pyrazol-5-yl)phenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-67		(9aR)-8-(2-(4-methoxy-3-(1-methyl-1H-pyrazol-5-yl)phenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-68		(R)-9-oxo-8-(5-phenyl-1,3,4-thiadiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

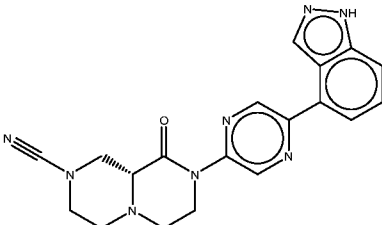
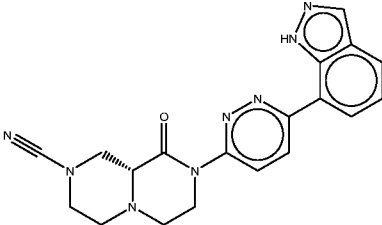
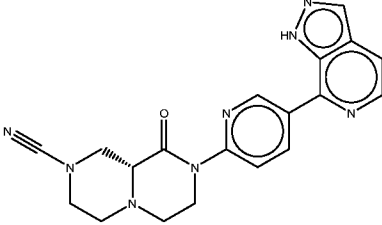
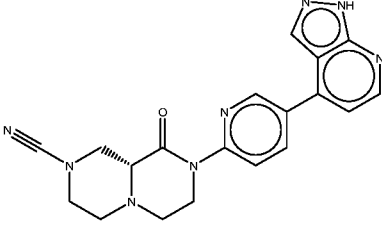
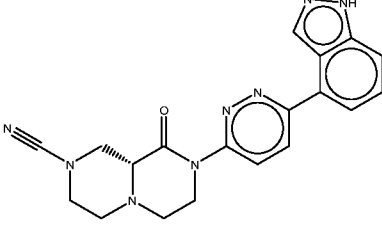
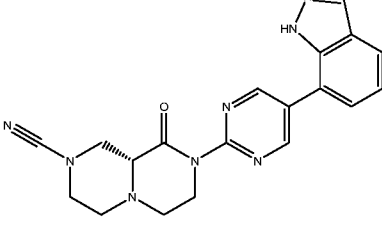
Cmpd #	Structure	Chemical Name
1-69		(R)-9-oxo-8-(1-(pyridin-2-yl)azetidin-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-70		(R)-8-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-71		(R)-8-(5-(3-cyanophenyl)-1,3,4-oxadiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-72		(9aR)-8-(2-(4-cyanophenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-73		(R)-9-oxo-8-(3-(3-(trifluoromethoxy)phenyl)isoxazol-5-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-74		(9aR)-8-(2-(3-cyanophenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-75		(9aR)-8-(2-(5-cyanopyridin-2-yl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-76		(9aR)-8-(2-(4-hydroxyphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

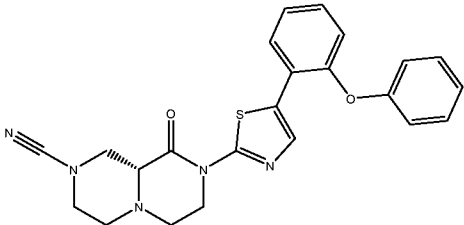
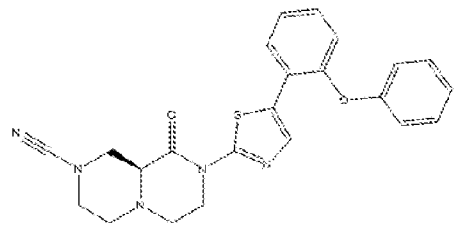
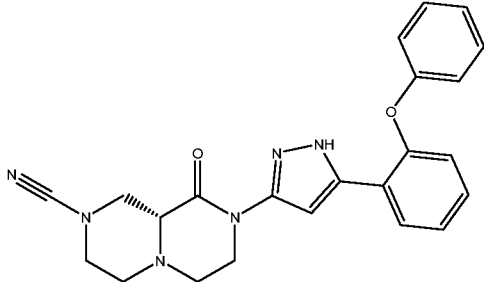
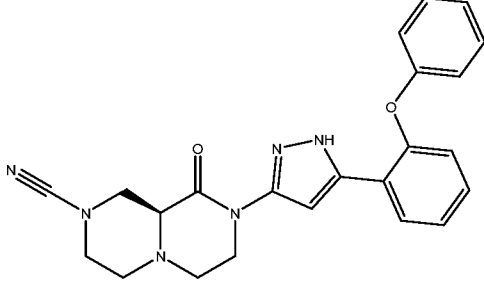
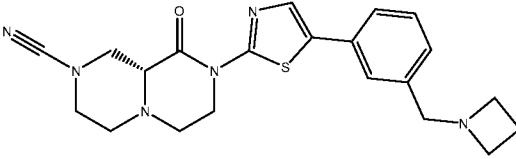
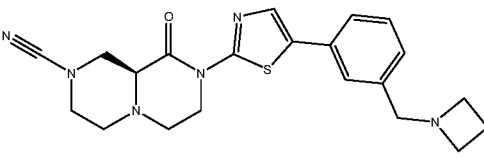
Cmpd #	Structure	Chemical Name
1-77		(9aR)-8-(2-(4-cyano-3-methylphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-78		(9aR)-8-(2-(5-isopropoxyphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-79		(9aR)-8-(2-(4-methoxy-3-(1-methyl-1H-pyrazol-4-yl)phenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-80		(9aR)-8-(2-(2-fluoro-3-methoxyphenyl)propyl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-81		(R)-9-oxo-8-(4-phenylpyridin-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-82		(R)-8-(5-(4-fluorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-83		(R)-9-oxo-8-(3-propoxy-4-(1H-pyrazol-5-yl)phenyl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-84		(R)-8-(6-(3-cyanophenyl)pyrimidin-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-85		(R)-8-(6-(1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-86		(R)-8-(2'-cyano-[4,4'-bipyridin]-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-87		(R)-9-oxo-8-(3-(3-(trifluoromethyl)phenyl)isoxazol-5-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-88		(R)-8-(6-(3-chlorophenyl)pyrimidin-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-89		(R)-8-(6-(3-cyano-5-fluorophenyl)pyrimidin-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-90		(R)-8-(6-(4-chlorophenyl)pyrimidin-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-91		(R)-9-oxo-8-(1-phenyl-1H-imidazol-4-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-92		(R)-9-oxo-8-(5-phenylisoxazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-93		(R)-8-(5-(1H-pyrazol-5-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-94		(R)-8-(4-(3-cyanophenyl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-95		(R)-8-(5-(3-chlorophenyl)pyridazin-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-96		(R)-9-oxo-8-(5-(3-(trifluoromethyl)phenyl)isoxazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-97		(R)-8-(5-(1H-pyrazol-1-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-98		(R)-8-(4-(3-cyanophenyl)oxazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-99		(R)-8-(1-(3-cyanophenyl)-1H-imidazol-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-100		(R)-9-oxo-8-(1-(3-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-101		(R)-9-oxo-8-(1-(3-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-102		(R)-8-(1-(3-cyanophenyl)-1H-1,2,3-triazol-4-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-103		(R)-8-(1-(3-cyanophenyl)-1H-1,2,4-triazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-104		(R)-8-(5-(1H-indazol-7-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-105		(R)-8-(5-(1H-indazol-4-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-106		(R)-8-(5-(1H-indazol-7-yl)pyrazin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-107		(R)-8-(5-(1H-indazol-4-yl)pyrazin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-108		(R)-8-(6-(1H-indazol-7-yl)pyridazin-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-109		(R)-8-(5-(1H-pyrazolo[3,4-c]pyridin-7-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-110		(R)-8-(5-(1H-pyrazolo[3,4-b]pyridin-4-yl)pyridin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-111		(R)-8-(6-(1H-indazol-4-yl)pyridazin-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-112		(R)-8-(5-(1H-indazol-7-yl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-113S		*(S)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-113R		*(R)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115R		(R)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115S		(S)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

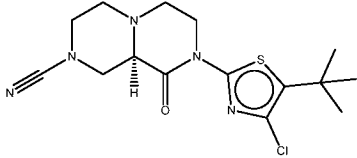
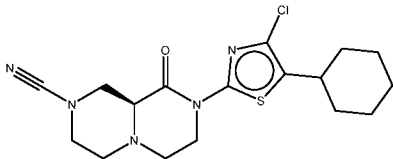
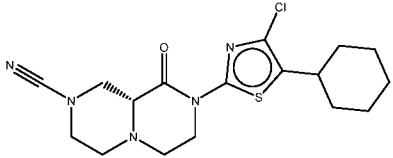
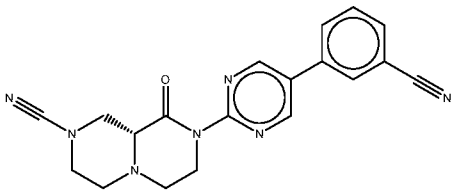
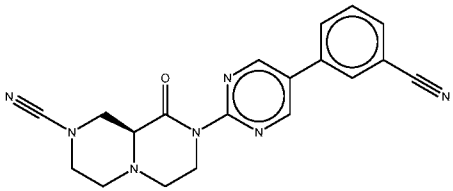
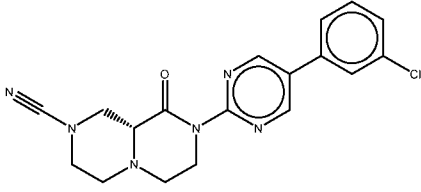
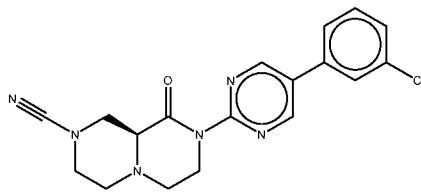
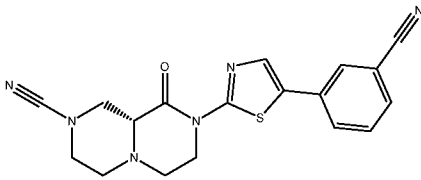
Cmpd #	Structure	Chemical Name
1-116R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-116S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117R		(R)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117S		(S)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,S		(R)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,R		(R)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-118S,S		(S)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118S,R		(S)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-119		2-(5-cyclohexylthiazol-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile

[0128] In some embodiments, chemical entities (e.g., compounds) include those of Table C. In some embodiments, the present disclosure provides compounds selected from Table C, or a pharmaceutically acceptable salt thereof.

Table C:

Cmpd #	Structure	Chemical Name
1-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-2S		*(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-2R		*(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3S		(S)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3R		(R)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-4R		(R)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-4S		(S)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5R		(R)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5S		(S)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-6R		(R)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-6S		(S)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7R		(R)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7S		(S)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-8R		(R)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-8S		(S)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9R		(R)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9S		(S)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-10R		(R)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-10S		(S)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-11R		(R)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-11S		(S)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-12S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,R		(4aR,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12S,S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-14S		*(S)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-14R		*(R)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15R		(R)-8-(5-(tert-butyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15S		(S)-8-(5-(tert-butyl)thiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
2-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
4-1S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
4-1S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile

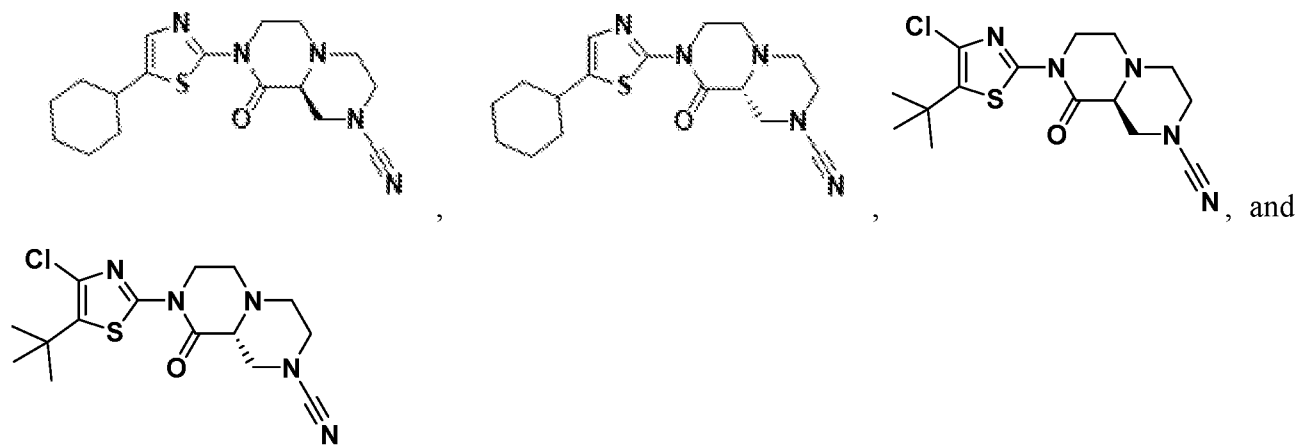
Cmpd #	Structure	Chemical Name
4-1R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
5-1R,R		(3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-1S,S		(3aS,7aS)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2R,R		(3aR,7aR)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2S,S		(3aS,7aS)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
6-1R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
6-1S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-113S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-113R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115R		(R)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115S		(S)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-116R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1-116S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117R		(R)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117S		(S)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,S		(R)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,R		(R)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118S,S		(S)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118S,R		(S)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

[0129]

For example, compounds of the disclosure include:



[0130] 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'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g), (I'-h), (II), (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (III), (III-a), (III-b), (III-c), (IV), (IV-a), (IV-b), and (IV-c), and compound species of such formulas disclosed herein.

[0131] It will be appreciated that throughout the present disclosure, unless otherwise indicated, reference to a “chemical entity” is intended to include, e.g., compounds.

[0132] Unless otherwise stated, it will be appreciated that when “one or more” substituents are recited for a particular variable, it includes one, two, three, four, or more substituents as valency permits.

[0133] As described herein, compounds of the disclosure may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0134] In some embodiments, the present disclosure provided compounds, as disclosed herein, of Formula (I) having an IC_{50} of about 1 micromolar or less in the Ubiquitin-Rhodamine 110

Assay for USP30 as described in Example A herein. In some embodiments, the present disclosure provides compounds of Formula (I) having one or more of the following characteristics when tested in the assay of Example A: (i) an IC_{50} value of $< 10 \mu M$ and $\geq 1 \mu M$; (ii) an IC_{50} value of $< 1 \mu M$ and $\geq 0.1 \mu M$; or (iii) an IC_{50} value of $< 0.1 \mu M$. In some embodiments, compounds of Formula (I) have one or both of the following characteristics when tested in the assay of Example A: (i) an IC_{50} value of $< 1 \mu M$ and $\geq 0.1 \mu M$; or (ii) an IC_{50} value of $< 0.1 \mu M$. In some embodiments, compounds of Formula (I) have an IC_{50} value of $< 0.1 \mu M$ when tested in the assay of Example A.

[0135] The term “aliphatic” or “aliphatic group,” as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic, bicyclic or polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle,” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. In some embodiments, aliphatic groups contain 1-12 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in some embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0136] As used herein, the term “alkyl” is given its ordinary meaning in the art and may include saturated aliphatic groups, including straight-chain alkyl groups and branched-chain alkyl groups.

[0137] The term “heteroalkyl” is given its ordinary meaning in the art and refers to alkyl groups as described herein in which one or more carbon atoms are replaced with a heteroatom (e.g., oxygen, nitrogen, sulfur, and the like). Examples of heteroalkyl groups include, but are not limited to, alkoxy, poly(ethylene glycol)-, and alkyl-substituted amino, etc.

[0138] The term “halogen” means F, Cl, Br, or I.

[0139] As used herein, “cycloalkyl” and “heterocycloalkyl” are understood to mean monocyclic or polycyclic rings. The group can be fused (e.g., decalin) or bridged (e.g., norbornane). Moreover, there are not delocalized π electrons (aromaticity) shared among the entire ring carbons or heteroatoms.

[0140] A “cycloalkyl” ring refers to a saturated aliphatic monocyclic, bicyclic, or polycyclic ring system, having from 3 to 14 ring members. In some embodiments, a cycloalkyl ring has from about 3-10 carbon atoms in their ring structure where such rings are monocyclic or bicyclic, and alternatively about 3, 4, 5, 6 or 7 carbons in the ring structure. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, and adamantyl.

[0141] As used herein, the terms “heterocycle,” “heterocyclyl,” and “heterocyclic ring” are used interchangeably and refer to a stable 3- to 14-membered monocyclic or 7- to 14-membered bicyclic or polycyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to three, heteroatoms. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 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 heterocyclic 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 saturated or partially unsaturated heterocyclyl groups include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” and “heterocyclic ring” also include groups in which a heterocyclyl 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 heterocyclyl ring.

[0142] The term “heterocycloalkyl” as used herein refers to a saturated, heterocyclic, monocyclic, bicyclic or polycyclic ring, having from 3 to 14 ring members. In some embodiments, a heterocycloalkyl ring has from about 3-10 ring members in their ring structure where such rings are monocyclic or bicyclic, and alternatively about 3, 4, 5, 6 or 7 ring members in the ring structure.

[0143] As used herein, “aryl” and “heteroaryl” refer to cyclic, aromatic groups, including monocyclic or bicyclic groups. When containing two aromatic rings (bicyclic), the aromatic rings of the aryl or heteroaryl groups may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl).

[0144] The term “aryl” refers to monocyclic, bicyclic or polycyclic 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 some embodiments of the present disclosure, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, 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.

[0145] The term “heteroaryl” refers to monocyclic, bicyclic, or polycyclic groups having 5 to 14 ring atoms (e.g., 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. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. Also included within the scope of the term “heteroaryl,” as it is used herein, are 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. Non-limiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. 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.

[0146] The term “unsaturated” as used herein, means that a moiety has one or more units of unsaturation. Accordingly, as used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0147] Pharmaceutical forms of the chemical entities disclosed herein can include pharmaceutically acceptable salts, solvates, and the like. Unless indicated otherwise, all pharmaceutical forms, such as all tautomeric forms and stereoisomers, are contemplated herein as

part of the present disclosure. Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each stereocenter. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0148] Unless otherwise indicated with an asterisk (*), stereochemistry indicated herein is arbitrarily assigned. For example, in some cases Table B shows one or more stereoisomers of a compound, and unless otherwise indicated, represents each stereoisomer alone and/or each enantiomer or diastereomer thereof, and/or a mixture thereof. For example, Table B discloses (R)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile, and thus, the present disclosure also encompasses (S)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile, as well as a mixture thereof. In some embodiments, stereochemistry indicated herein refers to the relative stereochemical orientation within each molecule, which is not necessarily the same as the absolute stereochemistry.

[0149] Additionally, 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.

[0150] The compounds of Formula (I) may form salts which are also within the scope of this disclosure. Reference to a compound of the Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. 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).

Compositions of Disclosed Compounds

[0151] Another aspect of the disclosure is directed to pharmaceutical compositions comprising a chemical entity chosen from compounds of Formula (I), and pharmaceutical forms thereof, with a pharmaceutically acceptable carrier. A “pharmaceutically acceptable carrier,” as used herein refers to pharmaceutical excipients, for example, pharmaceutically, physiologically, acceptable organic or inorganic carrier substances suitable for enteral or parenteral application that do not deleteriously

react with the active agent. The pharmaceutical acceptable carrier may further include additional excipients, diluents, and/or surfactants, etc. The compounds disclosed herein for USP30 inhibition can be combined with pharmaceutically acceptable excipients suitable for an intended route of administration to a human or animal. The excipients can be selected to provide a pharmaceutical dosage form suitable for an intended route of administration, including oral or parenteral administration dosage forms.

[0152] In some embodiments, the present disclosure provides pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, provided pharmaceutical compositions can be in a unit dosage form (e.g., a capsule, a tablet, or the like). In some embodiments, pharmaceutical compositions reported herein can be provided in an oral dosage form. In some embodiments, the pharmaceutical composition is orally administered in any orally acceptable dosage form. In some embodiments, an oral dosage form comprises one or more fillers, disintegrants, lubricants, glidants, anti-adherents, and/or anti-statics.

Methods of Using Disclosed Compounds

[0153] The present disclosure also provides uses of compounds of Formula (I). Compounds of Formula (I) are useful in medicine. For example, compounds and compositions described herein are inhibitors of USP30.

[0154] The compounds for inhibiting USP30 provided herein (e.g., compounds of Formula (I)) are useful to inhibit USP30 in a cellular or other living system, including development of pharmaceutical compositions for therapeutically effective treatment of human disease or disease symptomatology associated with activity of USP30. The term "therapeutically effective" as used herein refers to the use of active compound or pharmaceutical agent (e.g., a USP30 inhibitor compound of Formula (I) and/or a USP30 inhibitor compound having an IC₅₀ of less than about 1 micromolar or less in the Ubiquitin-Rhodamine 110 Assay for USP30 as described in Example A herein) that elicits a desired and/or therapeutic biological or medicinal response or effect in a cell, tissue, system, animal, individual or human, including any one or more of the following: (1) preventing the disease (for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease), (2) inhibiting the progression of a disease (for example, slowing or arresting the progression of a disease or symptoms of a disease, condition or

disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder, including arresting further development of the pathology and/or symptomatology), or (3) ameliorating the disease or symptoms thereof (for example, reducing the frequency or intensity of a symptom associated with a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder including reversing the pathology and/or symptomatology). The USP30 inhibitor compounds disclosed herein (e.g., compounds of Formula (I)) can be used in an amount effective to provide an intended effect (e.g., a therapeutically effective amount). In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[0155] While not being bound by any specific theory, the chemical entities of Formula (I) and pharmaceutical forms thereof are useful for inhibition of USP30. This inhibition can result in useful treatment of the symptoms and/or underlying causes of diseases or conditions where USP30 needs inhibition. For example, inhibitors of USP30 can be used to treat neurodegenerative and neurologic diseases or conditions involving mitochondrial dysfunction such as Parkinson's disease.

[0156] Parkinson's disease (PD) is a neurodegenerative disorder that affects more than 10 million people worldwide, including 60,000 new diagnoses a year in the US alone (Parkinson's Disease Foundation, www.pdf.org). PD is characterized by the loss of dopaminergic neurons in the substantia nigra. Although the exact mechanism of neuronal loss is not yet fully elucidated, an increasing body of evidence links mitochondrial dysfunction with dopaminergic neuron vulnerability.

[0157] 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 mitochondrial outer membrane (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).

[0158] 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, the present disclosure encompasses the recognition that inhibition of USP30 with a compound disclosed herein could present a novel treatment paradigm for PD by promoting mitochondrial turnover.

[0159] Accordingly, the present disclosure relates to provided methods of treating a disease or disorder associated with USP30, comprising administering to a patient suffering from at least one of said diseases or disorders a chemical entity of Formula (I) and/or pharmaceutical forms thereof, optionally in a pharmaceutical composition. The disclosed chemical entities can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects. Methods of treating a disease or disorder with a compound known to inhibit USP30 with an IC_{50} of less than about 1 micromolar in the Ubiquitin-Rhodamine 110 Assay for USP30 as described in Example A herein can comprise administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I). In some embodiments, the pharmaceutical composition comprises a USP30 inhibitor compound of Formula (I) and/or a USP30 inhibitor compound having an IC_{50} of less than about 1 micromolar in the Ubiquitin-Rhodamine 110 Assay for USP30 as described in Example A herein.

[0160] In some embodiments, the present disclosure provides a method of inhibiting USP30 in a human, comprising administering a therapeutically effective amount of (i) a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or (ii) a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0161] Methods of treatment (e.g., by inhibiting USP30) can comprise administering to a subject in need thereof a therapeutically effective amount of (i) a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or (ii) a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, a method of treating a disease associated with modulation

(e.g., inhibition) of USP30 comprises administering a therapeutically effective amount of a compound disclosed herein.

[0162] In some embodiments, a method of treating a neurodegenerative or neurologic disease, disorder, or condition comprises administering a therapeutically effective amount of a compound disclosed herein. In some embodiments, a method of treating a disease, disorder, or condition associated with mitochondrial dysfunction comprises administering a therapeutically effective amount of a compound disclosed herein. In some embodiments, a method of treating Parkinson's disease comprises administering a therapeutically effective amount of a compound disclosed herein.

Methods of Synthesizing Disclosed Compounds

[0163] The compounds 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. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

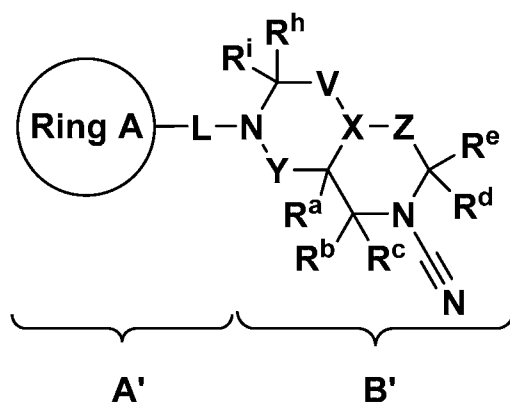
[0164] Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present disclosure includes all possible stereoisomers (unless otherwise specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well.

Preparation of compounds

[0165] The chemical entities of Formula (I) may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

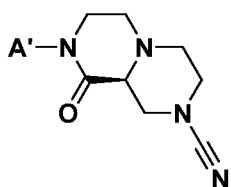
[0166] By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art.

[0167] By way of non-limiting example, the compounds of Formula (I) can be considered according to the following general formula A'—B':

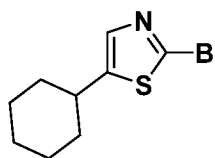


wherein a suitable A' fragment, or precursor thereof, can be coupled using methods provided herein to a suitable B' fragment, or precursor thereof, to form the compounds of Formula (I).

[0168] As set forth below, in some embodiments, compounds of the formula A'—B' are of formula I-i and/or I-ii:

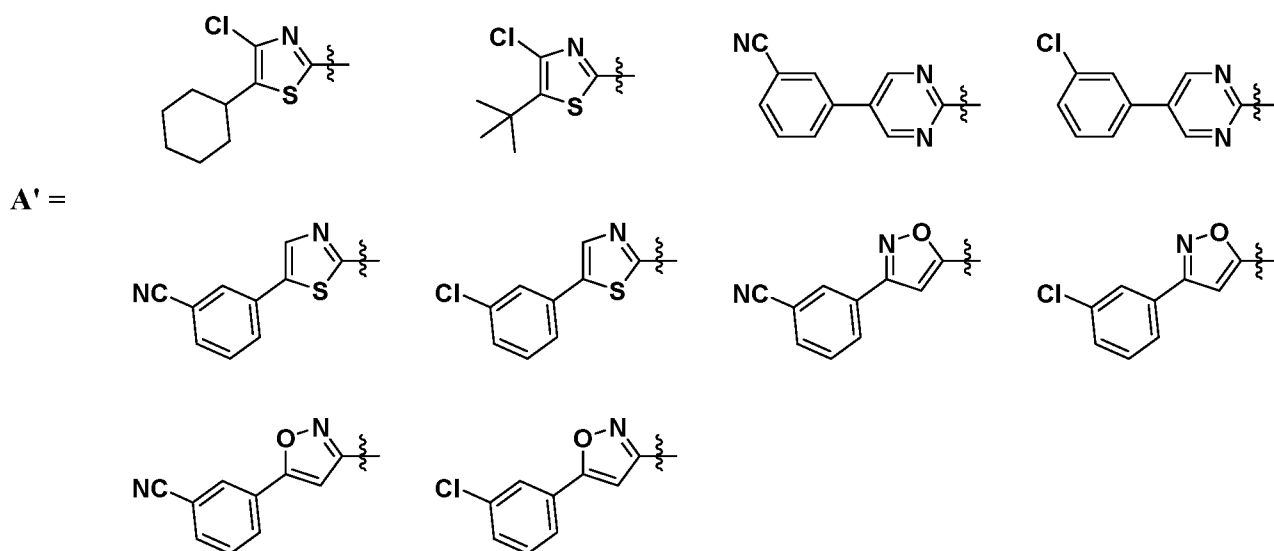


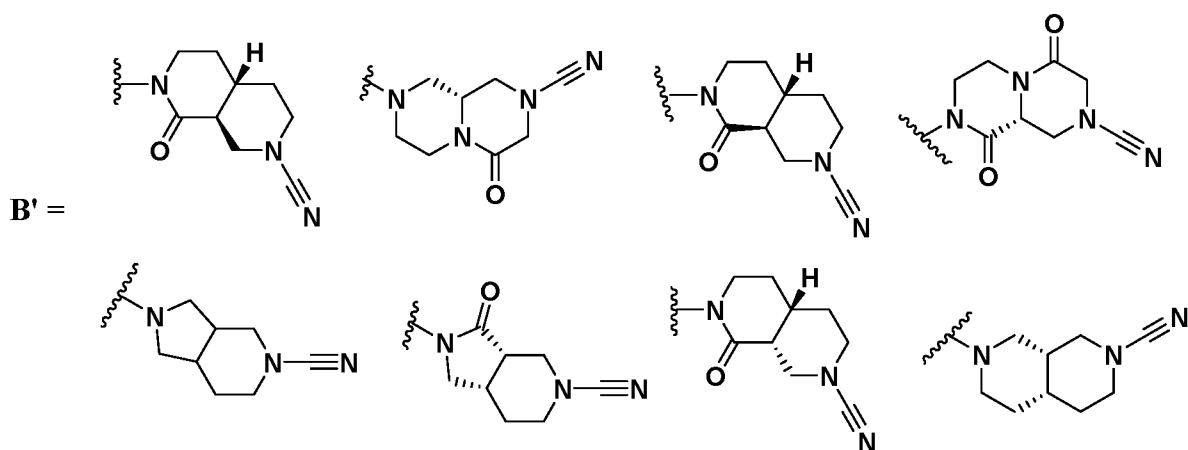
I-i



I-ii

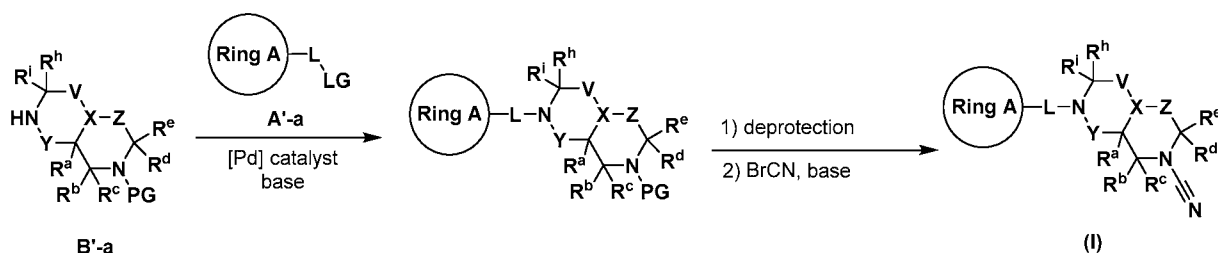
wherein all options for A' and B' are interchangeable:





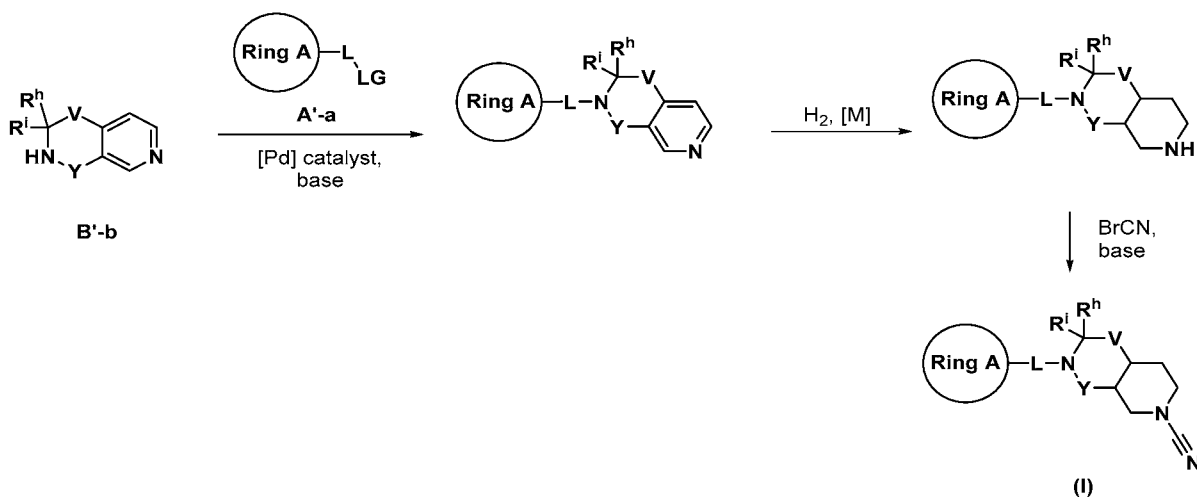
[0169] The compounds described herein may be made from commercially available starting materials or they may be synthesized using known organic, inorganic, and/or enzymatic processes. For example, starting materials B' can be purchased, or made using methods provided herein. In some embodiments, B' can then be coupled to A' according to several routes, such as these non-limiting examples:

General Scheme 1:

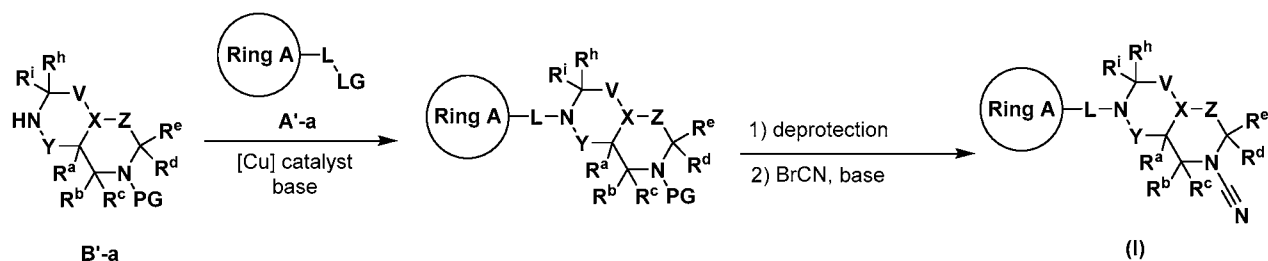


[0170] A protected **B'-a** group (such as Intermediate B'-1), wherein PG is a suitable nitrogen protecting group (e.g., a Boc group), can be coupled to an **A'-a** group (such as 2-bromo-5-cyclohexylthiazole), wherein LG is a suitable leaving group (e.g., halogen, -OTf, etc.) via cross-coupling using a suitable metal catalyst (e.g., a palladium catalyst) and a base (e.g., Cs₂CO₃). Lastly, the protecting group can be removed under suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid), and the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., NaHCO₃) and a cyanating reagent (e.g., BrCN).

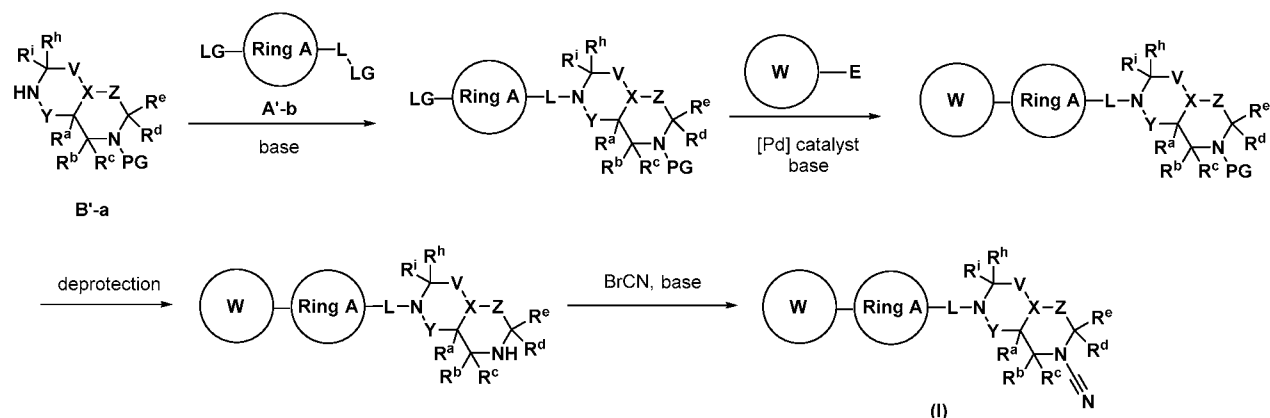
[0171] Additional coupling techniques are outlined below:

General Scheme 2:

[0172] **B'-b** can be coupled to an **A'-a** group, wherein LG is a suitable leaving group (e.g., halogen, $-OTf$, etc.) via cross-coupling using a suitable metal catalyst (e.g., a palladium catalyst). The resulting compound can then be reduced in the presence of H_2 , or another suitable hydride source, and a suitable metal catalyst (e.g., $Pd(OH)_2$). Lastly, the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., $NaHCO_3$) and a cyanating reagent (e.g., $BrCN$).

General Scheme 3:

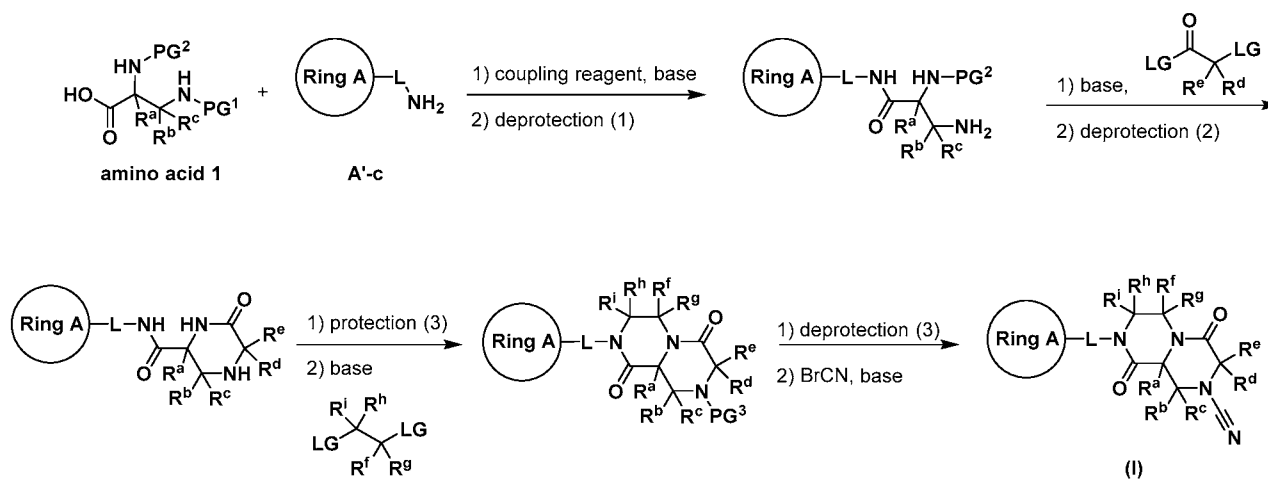
[0173] A protected **B'-a** group, wherein PG is a suitable nitrogen protecting group (e.g., a Boc group), can be coupled to an **A'-a** group, wherein LG is a suitable leaving group (e.g., halogen, $-OTf$, etc.) via cross-coupling using a suitable metal catalyst (e.g., a copper catalyst) and a base (e.g., K_3PO_4). Lastly, the protecting group can be removed under suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid), and the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., $NaHCO_3$) and a cyanating reagent (e.g., $BrCN$).

General Scheme 4:

[0174] A protected **B'-a** group, wherein PG is a suitable nitrogen protecting group (e.g., a Boc group), can be coupled to an **A'-b** group, wherein each LG is independently a suitable leaving group (e.g., halogen, -OTf, etc.) via a substitution reaction in the presence of a base (e.g., DIPEA). The resulting product can be coupled with a **W** group (particularly when **W** is an aryl or heteroaryl ring as defined herein), wherein **E** is a suitable electrophilic group (e.g., -B(OH)₂) via cross-coupling in the presence of a suitable metal catalyst (e.g., a palladium catalyst) and a base (e.g., K₃PO₄). Then, the protecting group can be removed under suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid), and the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., NaHCO₃) and a cyanating reagent (e.g., BrCN).

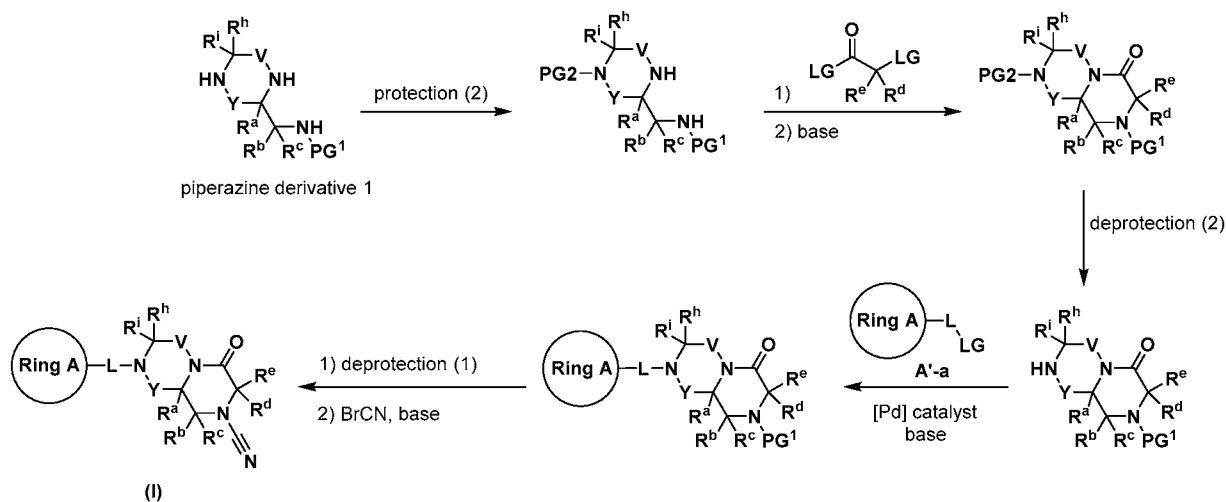
[0175] In some embodiments, **B'** is prepared after coupling with **A'** along the same route. Non-limiting examples include:

General Scheme 5:



[0176] Amino acid 1 (e.g., (R)-2-(((benzyloxy)carbonyl)amino)-3-((tert-butoxycarbonyl)amino)propanoic acid) can be coupled to an amine (e.g., the A'-c group above) using a standard coupling reagent (e.g., HATU) and base (e.g., DIEA) in a suitable solvent and protecting group 1 (i.e., PG^1), such as a Boc group, can then be removed using suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid or hydrochloric acid) in a suitable solvent. The resulting amine can be reacted with a suitable carboxylic acid derivative (e.g., methyl 2-bromoacetate), wherein each LG is independently a leaving group (e.g., halogen, -OTf, -OCH₃, etc.). Protecting group 2 (i.e., PG^2), such as a Cbz group, is removed under suitable deprotection conditions (e.g., a Cbz group can be removed in the presence of H₂ and a suitable metal catalyst, such as Pd/C), followed by *in situ* cyclization to a piperazinone ring. The piperazinone ring can be protected under suitable conditions with protecting group 3 (i.e., PG^3), such as a Boc group, followed by bis-alkylation with an appropriate electrophile (e.g., ethane-1,2-diyl bis(trifluoromethanesulfonate)), wherein each LG is independently a leaving group (e.g., halogen, -OTf, etc.) forms the bicyclic ring architecture. Lastly, protecting group 3 can be removed under suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid), and the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., NaHCO₃) and a cyanating reagent (e.g., BrCN).

[0177] An additional technique for preparing B' after coupling to A' is outlined below:

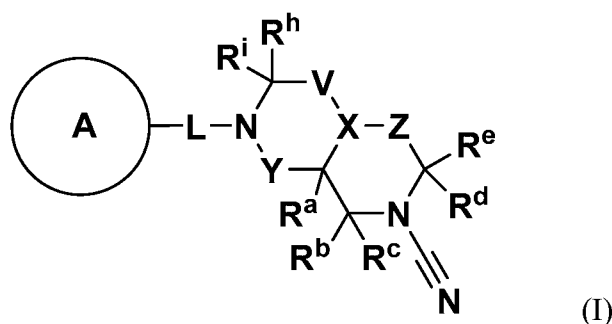
General Scheme 6:

[0178] Piperazine derivative 1 can be protected with a suitable nitrogen protecting group (i.e., PG²) under suitable conditions (e.g., a Cbz protecting group can be installed with CbzCl). Then, the bicycle is formed in the presence of a suitable electrophile (e.g., 2-chloroacetyl chloride), wherein each LG is independently a leaving group (e.g., halogen, -OTf, -OCH₃, etc.), followed by base (e.g., NaH). Protecting group 2 (i.e., PG²) is removed under suitable deprotection conditions (e.g., a Cbz group can be removed in the presence of H₂ and a suitable metal catalyst, such as Pd/C), followed by coupling to an A'-a group, wherein LG is a suitable leaving group (e.g., halogen, -OTf, etc.) via cross-coupling using a suitable metal catalyst (e.g., a palladium catalyst) and a base (e.g., Cs₂CO₃). Lastly, protecting group 1 (i.e., PG¹) can be removed under suitable deprotection conditions (e.g., a Boc protecting group can be removed in the presence of an acid, such as trifluoroacetic acid), and the resulting amine can be functionalized with a nitrile group in the presence of a base (e.g., NaHCO₃) and a cyanating reagent (e.g., BrCN).

Exemplary Embodiments

[0179] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the present disclosure:

1. At least one chemical entity chosen from compounds of Formula (I):



and pharmaceutically acceptable forms thereof, wherein:

V is selected from a bond and CR^fR^g ;

X is selected from N and CR^x ;

Y is selected from a bond, carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

Z is selected from a carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

L is $-(\text{CH}_2)_n-$, $n = 0, 1, 2, 3$, where if n is 2 or 3, then L can optionally be substituted or interrupted with one or two alkyls and/or heteroatoms;

R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x are each independently selected from small lipophilic and/or electron withdrawing groups that exhibit activity in a USP30 biochemical assay;

R^f and R^g can also be combined to form a carbonyl;

R^j and R^k can also cyclize;

Ring A is selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group;

W is chosen from hydrogen, halogen, cyano groups, alkyl groups, alkyl ester groups, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R^l group, which can be the same or different;

R^l is independently selected from small lipophilic or electron withdrawing groups that exhibit activity in a USP30 biochemical assay.

2. The chemical entity of embodiment 1, wherein:

R^a , R^b , R^c , R^d , R^e , R^h , R^i , R^j , R^k , and R^x are each independently selected from hydrogen, halogens, hydroxy groups, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and branched alkyl groups optionally interrupted with heteroatoms, and/or optionally substituted with R^l ;

R^f and R^g are each independently selected from hydrogen, halogens, hydroxy groups, cyano groups, amides, amines, alkyl amines, alkyl esters, alkyl alcohols, cyclopropyl groups, linear and

branched alkyl groups optionally interrupted with heteroatoms, and/or optionally substituted with R^1 , or can be combined to form a carbonyl;

Ring A is selected from 4- to 13-membered cycloalkyl and heterocycloalkyl groups, and 5 to 10 membered aryl and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group;

W is chosen from hydrogen, halogen, cyano groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl ester groups, 3- to 10-membered cycloalkyl and heterocycloalkyl groups, and 5- to 10-membered aryl and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R^1 group, which can be the same or different; and

R^1 is independently selected from hydrogen, halogen, hydroxy groups, cyano groups, amides, amines, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl esters, C_1 - C_6 alkyl amines, C_1 - C_6 alkyl alcohols, C_3 - C_6 cycloalkyl groups, $S(O)_2$ groups, and trifluoromethyl and trifluoromethylester groups.

3. The chemical entity according to embodiment 1 or 2, wherein:

R^a and R^x are hydrogen;

one of R^b and R^c is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^1 ;

one of R^d and R^e is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^1 ;

one of R^f and R^g is hydrogen, and the other is selected from hydrogen, alkyl and heteroalkyl groups optionally substituted with R^1 , or alternatively, R^f and R^g combine to form a carbonyl;

one of R^h and R^i is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^1 ; and

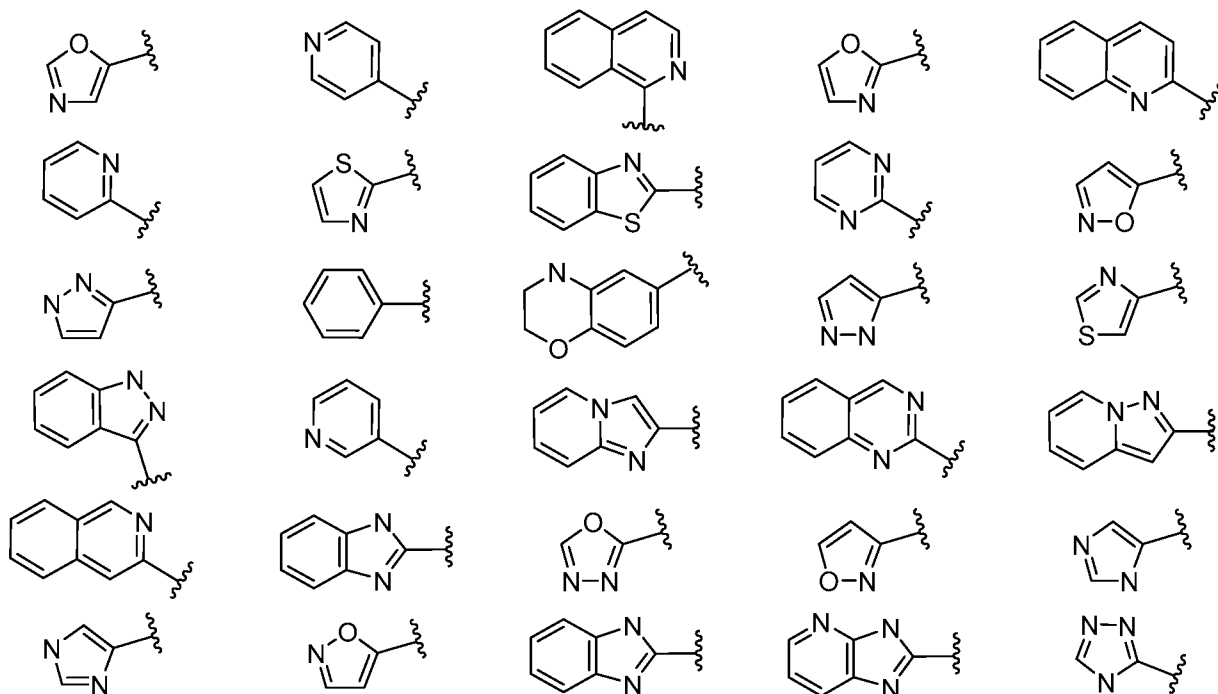
one of R^j and R^k is hydrogen, and the other is selected from hydrogen, alkyl and heteroalkyl groups optionally substituted with R^1 .

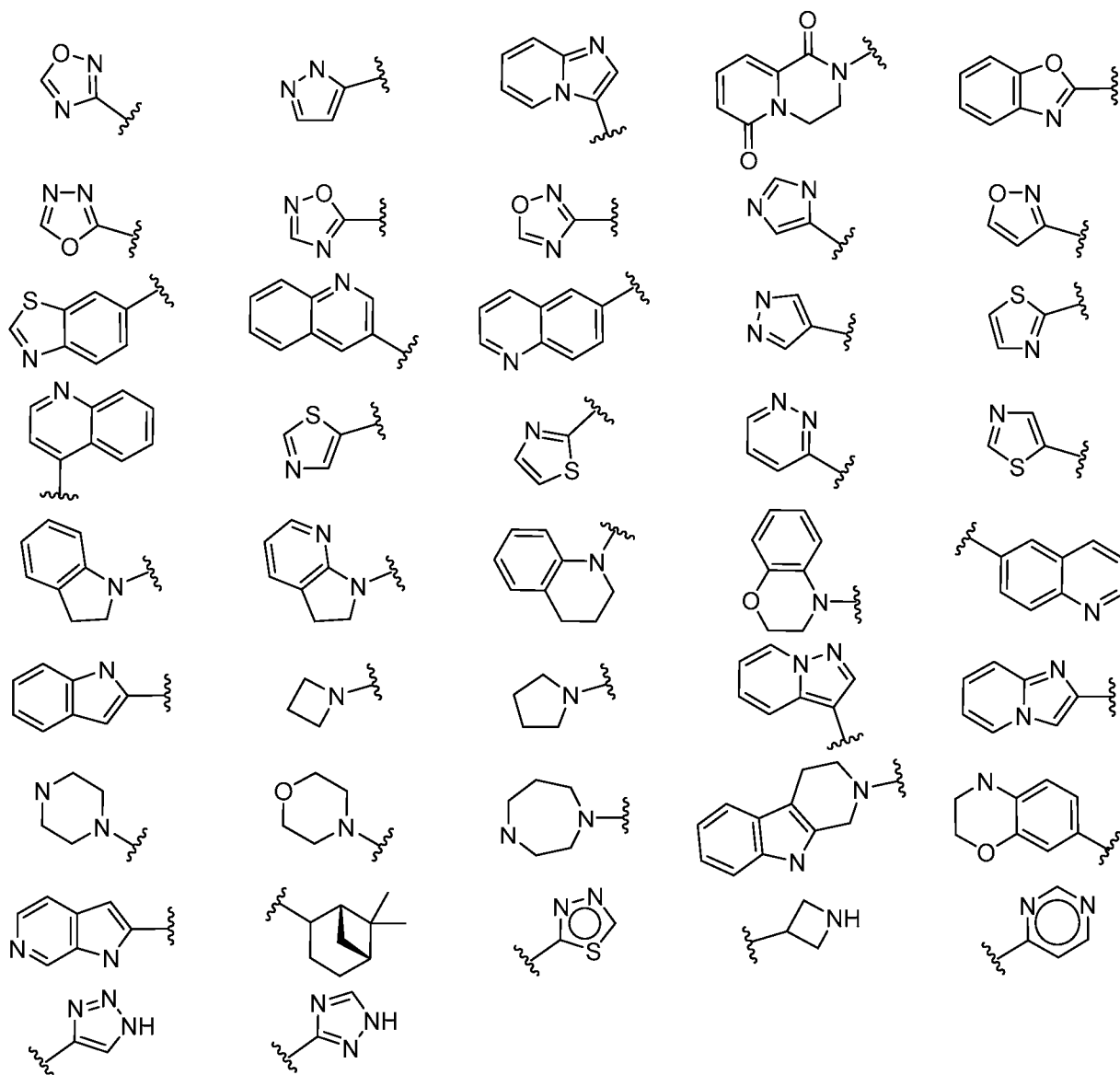
4. The chemical entity of any one of embodiments 1 to 3, wherein Ring A is selected from 5- to 10-membered cycloalkyl and heterocycloalkyl groups, and 5- to 10-membered heteroaryl groups, the groups being unsubstituted or substituted with at least one W group.

5. The chemical entity of any one of embodiments 1 to 4, wherein

- one of R^b and R^c is hydrogen, and the other is selected from hydrogen, C₁-C₆ linear or branched alkyl groups, and C₁-C₆ linear or branched heteroalkyl groups, the groups optionally substituted with R¹;
- one of R^d and R^e is hydrogen, and the other is selected from hydrogen, C₁-C₆ linear or branched alkyl groups, and C₁-C₆ linear or branched heteroalkyl groups, the groups optionally substituted with R¹;
- one of R^f and R^g is hydrogen, and the other is selected from hydrogen, C₁-C₆ linear or branched alkyl groups, and C₁-C₆ linear or branched heteroalkyl groups, the groups optionally substituted with R¹, or alternatively, they form a carbonyl;
- one of R^h and Rⁱ is hydrogen, and the other is selected from hydrogen, C₁-C₆ linear or branched alkyl groups, and C₁-C₆ linear or branched heteroalkyl groups, the groups optionally substituted with R¹; and
- one of R^j and R^k is hydrogen, and the other is selected from hydrogen, C₁-C₆ linear or branched alkyl groups and C₁-C₆ linear or branched heteroalkyl groups, the groups optionally substituted with R¹.

6. The chemical entity of any one of embodiments 1 to 3 and 5, wherein Ring A is selected from:



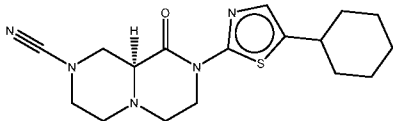
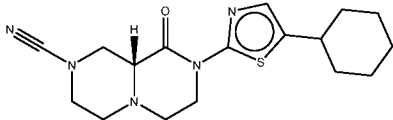
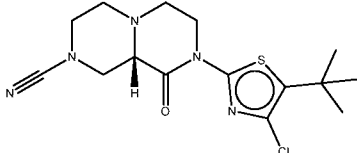
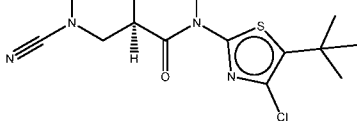
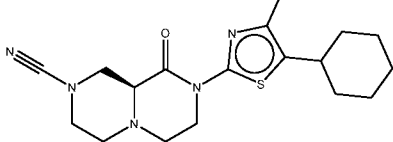
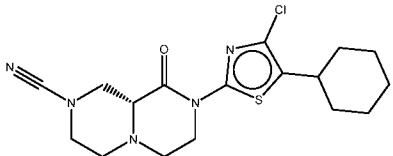
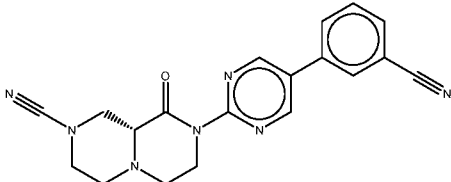


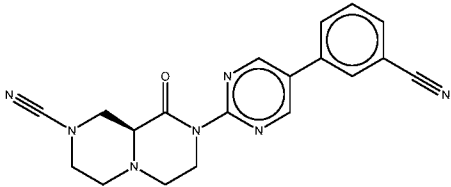
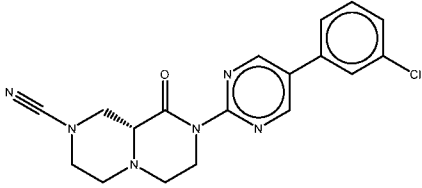
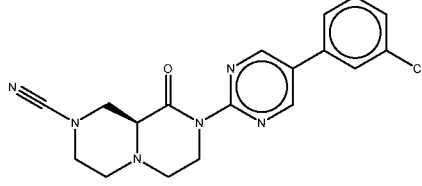
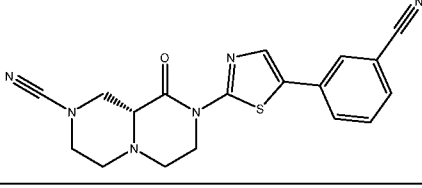
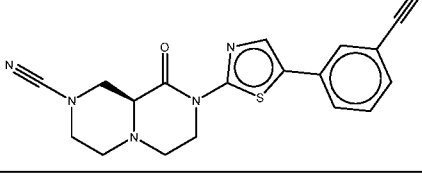
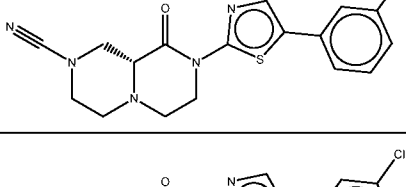
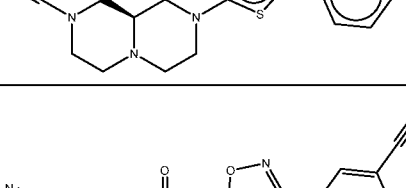
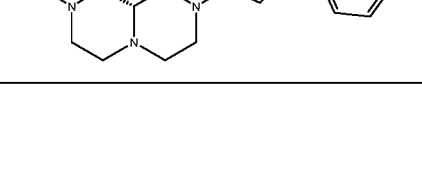
the groups being optionally substituted with at least one W group.

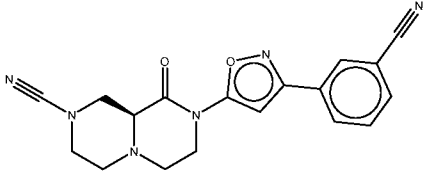
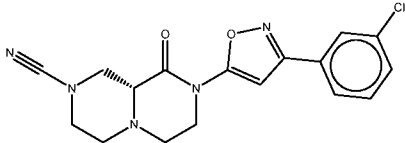
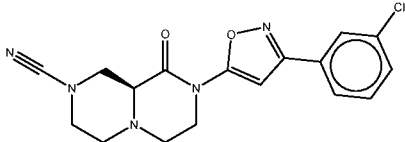
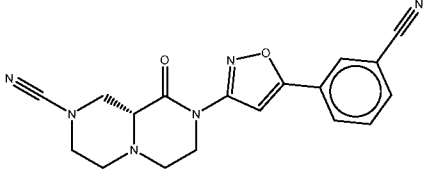
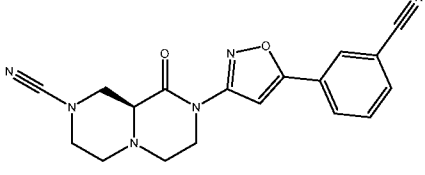
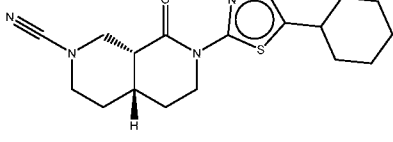
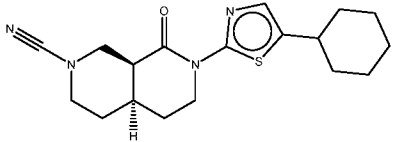
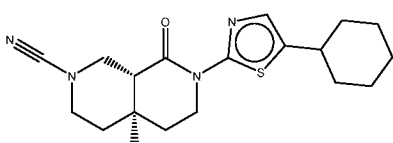
7. The chemical entity of any one of embodiments 1 to 6, wherein W is selected from hydrogen, halogen, cyano groups, alkyl groups, alkyl ester groups, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R¹ group, which can be the same or different.
8. The chemical entity of any one of embodiments 1 to 7, wherein R¹ is independently selected from hydrogen, halogen, cyano, amides, C₁-C₆ alkyl groups, C₁-C₆ alkyl esters, and trifluoromethyl and trifluoromethylester groups.

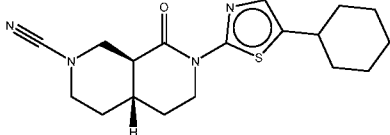
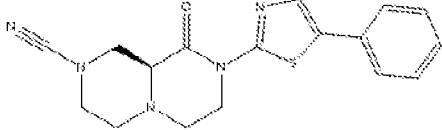
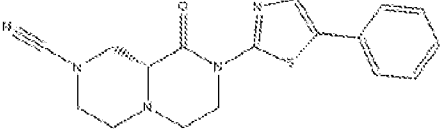
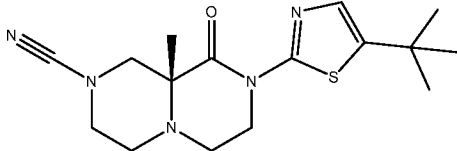
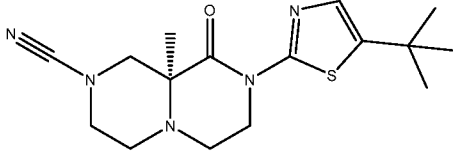
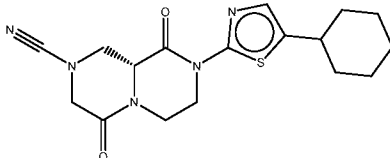
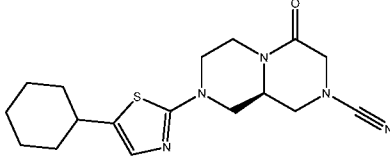
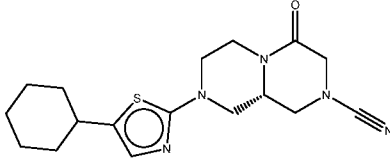
9. The chemical entity of embodiment 1 selected from the compounds of Table B.

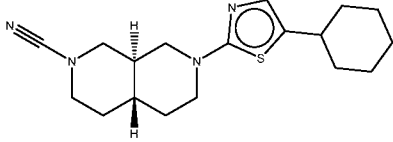
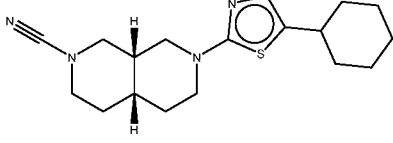
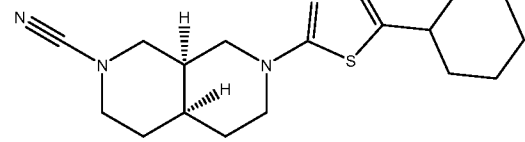
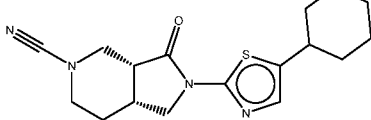
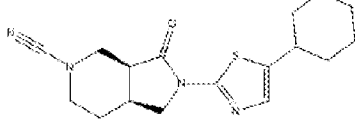
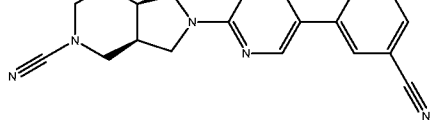
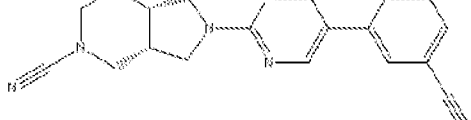
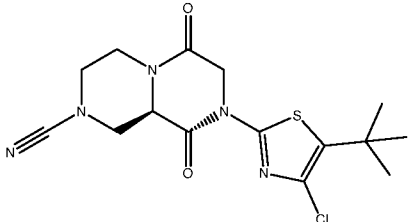
10. The chemical entity of embodiment 1 selected from the compounds:

Cmpd #	Structure	Chemical Name
1-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-2S		*(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-2R		*(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3S		(S)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-3R		(R)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-4R		(R)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

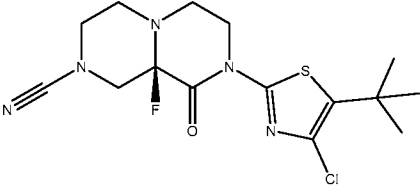
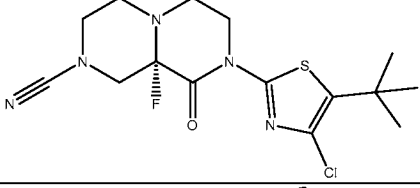
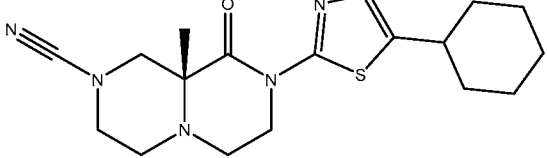
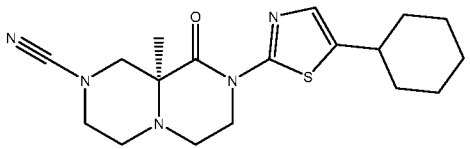
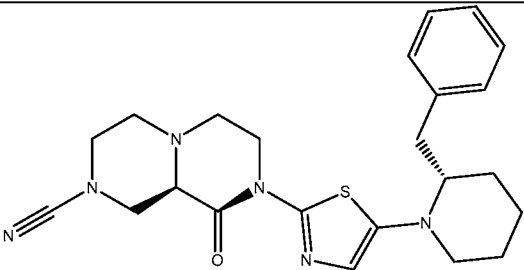
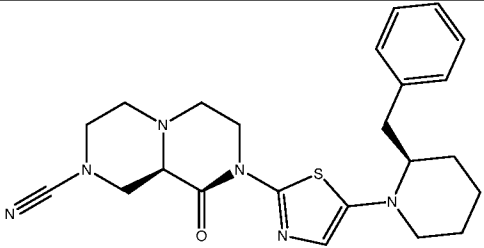
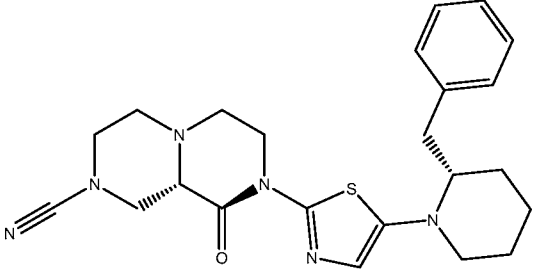
Cmpd #	Structure	Chemical Name
1-4S		(S)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5R		(R)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-5S		(S)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-6R		(R)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-6S		(S)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7R		(R)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-7S		(S)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-8R		(R)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

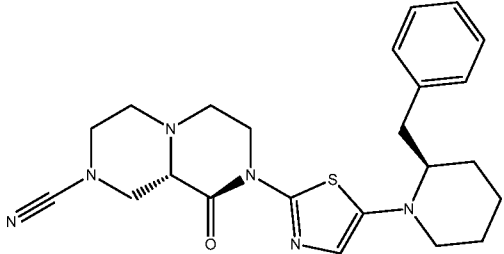
Cmpd #	Structure	Chemical Name
1-8S		(S)-8-(3-(3-cyanophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9R		(R)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-9S		(S)-8-(3-(3-chlorophenyl)isoxazol-5-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-10R		(R)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-10S		(S)-8-(5-(3-cyanophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-12S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-12R,R		(4aR,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile

Cmpd #	Structure	Chemical Name
1-12S,S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile
1-14S		*(S)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-14R		*(R)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15R		(R)-8-(5-(tert-butyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-15S		(S)-8-(5-(tert-butyl)thiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
2-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
3-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

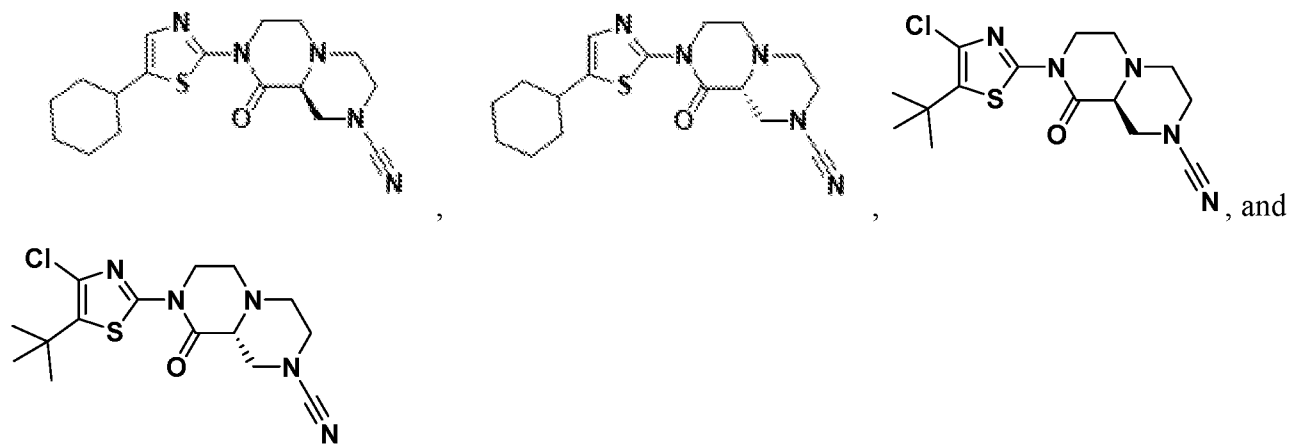
Cmpd #	Structure	Chemical Name
4-1S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
4-1S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
4-1R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile
5-1R,R		(3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-1S,S		(3aS,7aS)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2R,R		(3aR,7aR)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
5-2S,S		(3aS,7aS)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile
6-1R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
6-1S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-113S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-113R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-114S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115R		(R)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-115S		(S)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

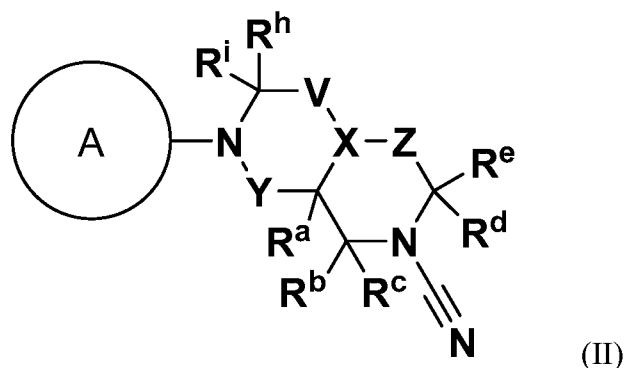
Cmpd #	Structure	Chemical Name
1-116R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-116S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117R		(R)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-117S		(S)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,S		(R)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118R,R		(R)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile
1-118S,S		(S)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

Cmpd #	Structure	Chemical Name
1- 118S,R		(S)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile

11. The chemical entity of embodiment 1 selected from



12. At least one chemical entity selected from compounds of Formula (II):



and pharmaceutically acceptable forms thereof, wherein:

V is selected from a bond and CR^fR^g ;

X is selected from N and CH;

Y is selected from a bond, carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

Z is selected from a carbonyl ($\text{C}=\text{O}$), and CR^jR^k ;

R^a is selected from hydrogen;

one of R^b and R^c is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^l;

one of R^d and R^e is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^l;

one of R^f and R^g is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^l, or alternatively, they form a carbonyl;

one of R^h and Rⁱ is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^l;

one of R^j and R^k is hydrogen, and the other is selected from hydrogen, alkyl, and heteroalkyl groups optionally substituted with R^l;

Ring A is selected from 5- to 10-membered cycloalkyl, heterocycloalkyl, and heteroaryl groups, the groups being unsubstituted or substituted with at least one W group;

W is selected from hydrogen, halogen, cyano groups, alkyl groups, alkyl ester groups, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl groups, the groups being unsubstituted, or substituted with at least one R^l group, which can be the same or different; and

R^l is independently selected from hydrogen, halogen, cyano, amides, C₁-C₆ alkyl groups, C₁-C₆ alkyl esters, and trifluoromethyl and trifluoromethylester groups.

13. The chemical entity of embodiment 12, wherein:

V is CR^fR^g

X is N;

R^a is hydrogen;

one of R^b and R^c is hydrogen, and the other is selected from hydrogen, cyano, and alkyl groups;

one of R^d and R^e is hydrogen, and the other is selected from hydrogen, cyano, and alkyl groups;

one of R^f and R^g is hydrogen, and the other is selected from hydrogen, cyano, and alkyl groups, or alternatively, they form a carbonyl;

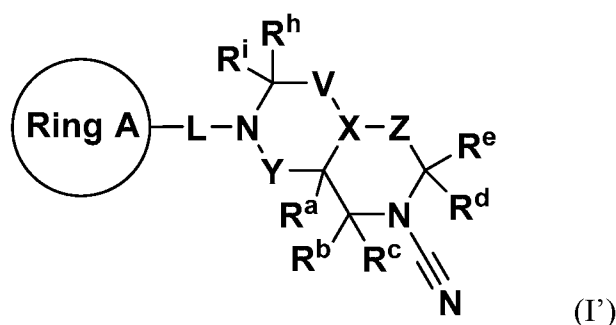
one of R^h and Rⁱ is hydrogen, and the other is selected from hydrogen, cyano, and alkyl groups; and

one of R^j and R^k is hydrogen, and the other is selected from hydrogen, cyano, and alkyl groups.

14. A composition comprising at least one chemical entity of any one of embodiments 1 to 13, and at least one excipient.

15. A method for inhibiting USP30 activity in a mammal in need thereof comprising administering an effective amount of at least one chemical entity according to any one of embodiments 1 to 13, or a composition of embodiment 14, to the mammal in need thereof.

16. A compound of Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from a bond, C(O), and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is $-(CH_2)_n-$;

n is 0, 1, 2, or 3,

wherein each methylene unit of L is optionally substituted with one or two C₁-C₆ alkyl, and

wherein if n is 2 or 3, then one methylene unit of L is optionally replaced with a heteroatom selected from nitrogen, oxygen, and sulfur;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

or R^b and R^c, or R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

wherein an optionally substituted R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x group may be substituted with one or more R¹;

Ring A is selected from C₃-C₁₃ cycloalkyl, 3- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C₁₀ aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, optionally substituted C₁₀ aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R¹;

each R¹ is independently selected from oxo, halogen, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, -(CH₂)_m(C₃-C₁₀cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), -(CH₂)_m(phenyl), -(CH₂)_m(C₁₀aryl), and -(CH₂)_m(5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur);

each R is independently selected from hydrogen, C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

each R' is independently selected from C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur; and

each m is independently 0, 1, or 2.

17. The compound of embodiment 16, wherein: Y is selected from C(O) and CR^jR^k;
n is 0, 1, or 2,

wherein each methylene unit of L is optionally substituted with one C₁-C₆ alkyl, and
wherein if n is 2, then one methylene unit of L is optionally replaced with an oxygen;

each occurrence of R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x is independently selected from hydrogen, halogen, and C_1 - C_6 alkyl;

Ring A is selected from C_3 - C_{10} cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, -OR, -CN, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l ;

each R^l is independently selected from halogen, -OR, -CN, -NO₂, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-(CH_2)_m(C_3-C_{10} \text{ cycloalkyl})$, $-(CH_2)_m(3\text{- to } 10\text{-membered heterocyclyl containing } 1 \text{ to } 3 \text{ heteroatoms selected from nitrogen, oxygen, and sulfur})$, and $-(CH_2)_m(C_6\text{aryl})$;

each R is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, and phenyl; and

each m is independently 0 or 1.

18. The compound of embodiment 16 or 17, wherein:

Y is selected from C(O) and CR^jR^k ;

n is 0;

R^a is selected from hydrogen, halogen, and C_1 - C_6 alkyl;

R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x are each hydrogen;

Ring A is 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R^l ;

each R^l is independently selected from halogen, -OR, -CN, $-(CH_2)_m(3\text{- to } 10\text{-membered heterocyclyl containing } 1 \text{ to } 3 \text{ heteroatoms selected from nitrogen, oxygen, and sulfur})$, and $-(CH_2)_m(C_6\text{aryl})$;

each R is phenyl; and
each m is 1.

19. The compound of any one of embodiments 16-18, wherein:

V is selected from C(O) and CR^fR^g;

X is N;

Y is C(O);

n is 0;

R^a is hydrogen;

R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen;

Ring A is 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

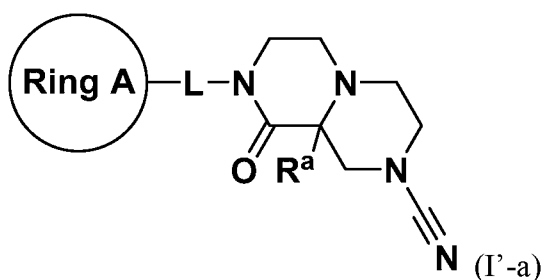
each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclcyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, and -(CH₂)_m(phenyl);

each R is phenyl; and

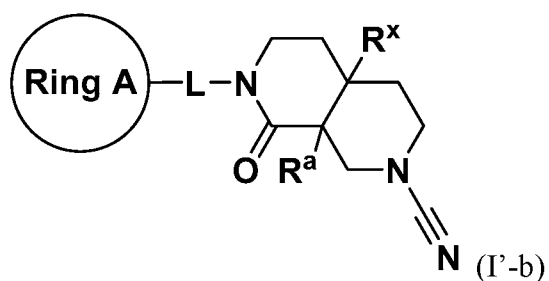
each m is 1.

20. The compound of any one of embodiments 16-19, wherein the compound is of formula (I'-a):



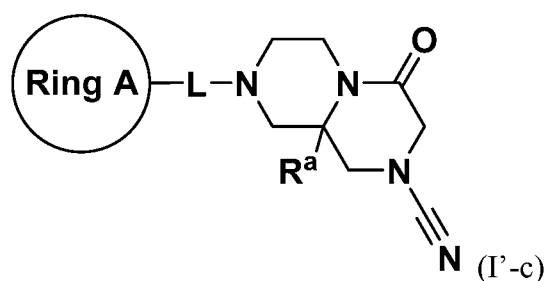
or a pharmaceutically acceptable salt thereof.

21. The compound of any one of embodiments 16-18, wherein the compound is of formula (I'-b):



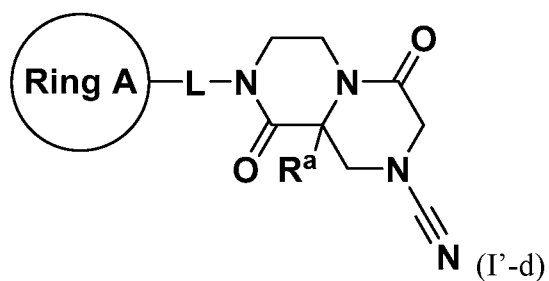
or a pharmaceutically acceptable salt thereof.

22. The compound of any one of embodiments 16-19, wherein the compound is of formula (I'-c):



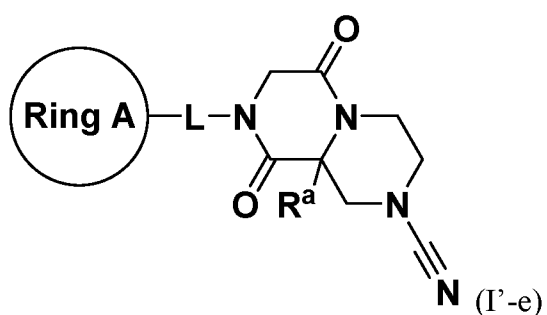
or a pharmaceutically acceptable salt thereof.

23. The compound of any one of embodiments 16-19, wherein the compound is of formula (I'-d):



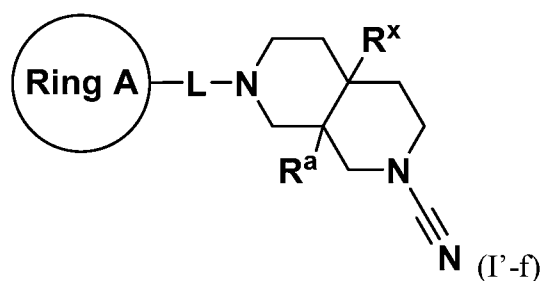
or a pharmaceutically acceptable salt thereof.

24. The compound of any one of embodiments 16-19, wherein the compound is of formula (I'-e):



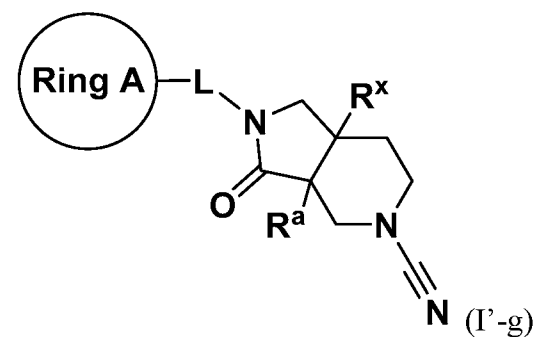
or a pharmaceutically acceptable salt thereof.

25. The compound of any one of embodiments 16-18, wherein the compound is of formula (I'-f):



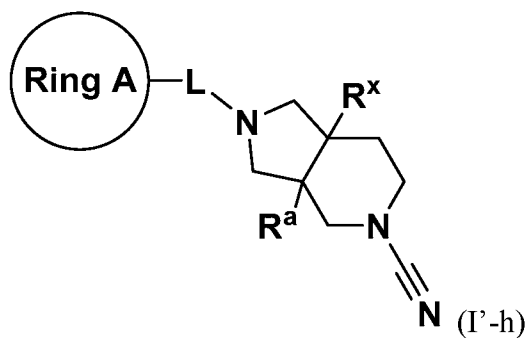
or a pharmaceutically acceptable salt thereof.

26. The compound of any one of embodiments 16-18, wherein the compound is of formula (I'-g):



or a pharmaceutically acceptable salt thereof.

27. The compound of any one of embodiments 16-18, wherein the compound is of formula (I'-h):

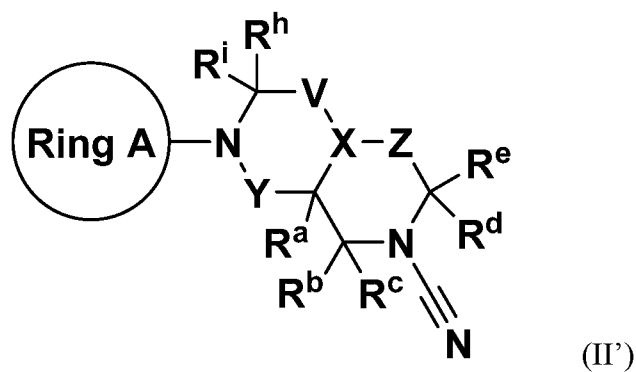


or a pharmaceutically acceptable salt thereof.

28. The compound of any one of embodiments 16-27, wherein **L** is selected from $-(CH_2)_0-$, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, and $-CH_2CH(CH_3)O-$.

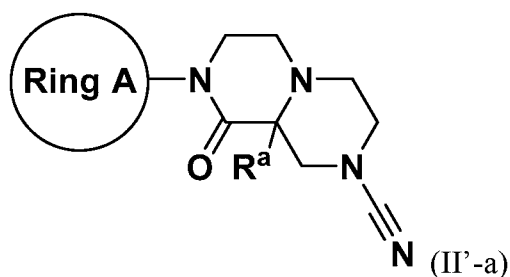
29. The compound of any one of embodiments 16-28, wherein **n** is 0.

30. The compound of any one of embodiments 16-29, wherein the compound is of formula (II'):



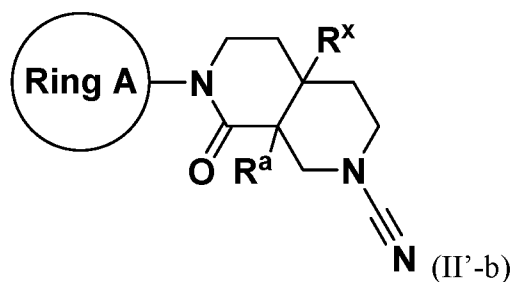
or a pharmaceutically acceptable salt thereof.

31. The compound of any one of embodiments 16-19 and 28-30, wherein the compound is of formula (II'-a):



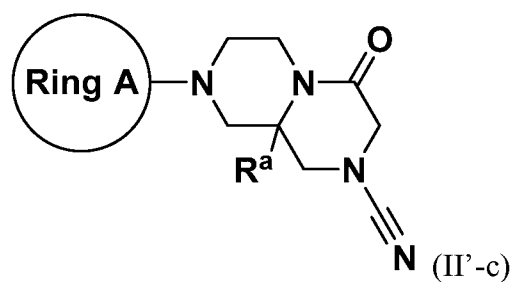
or a pharmaceutically acceptable salt thereof.

32. The compound of any one of embodiments 16-18 and 28-30, wherein the compound is of formula (II'-b):



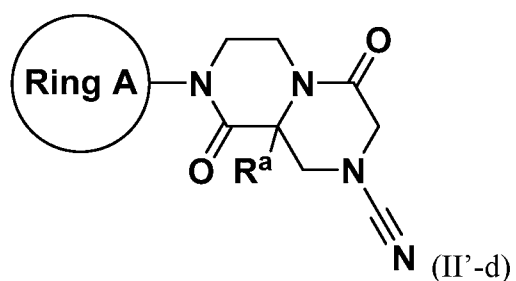
or a pharmaceutically acceptable salt thereof.

33. The compound of any one of embodiments 16-18 and 28-30, wherein the compound is of formula (II'-c):



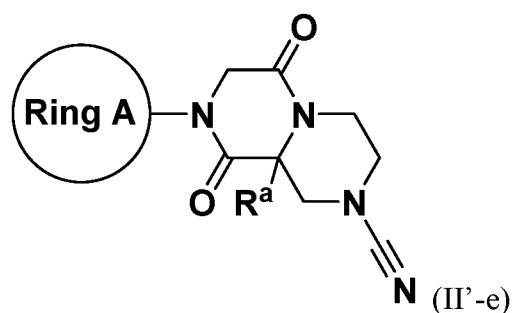
or a pharmaceutically acceptable salt thereof.

34. The compound of any one of embodiments 16-19 and 28-30, wherein the compound is of formula (II'-d):



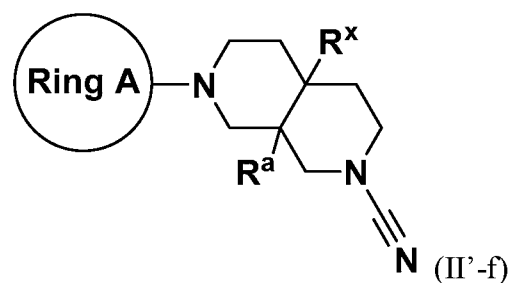
or a pharmaceutically acceptable salt thereof.

35. The compound of any one of embodiments 16-19 and 28-30, wherein the compound is of formula (II'-e):



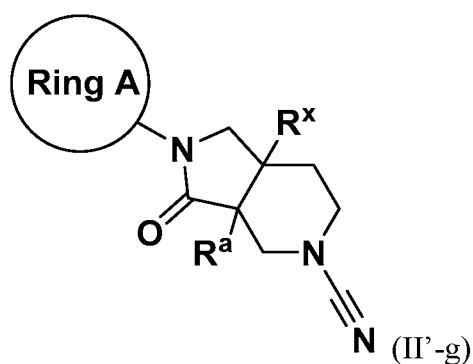
or a pharmaceutically acceptable salt thereof.

36. The compound of any one of embodiments 16-18 and 28-30, wherein the compound is of formula (II'-f):



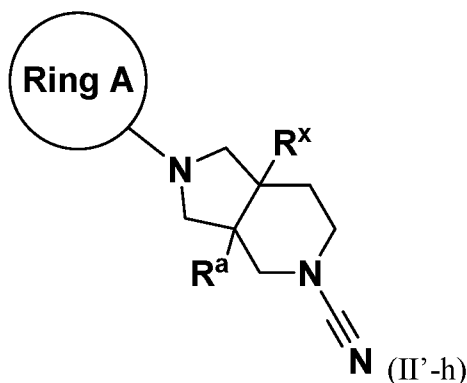
or a pharmaceutically acceptable salt thereof.

37. The compound of any one of embodiments 16-18 and 28-30, wherein the compound is of formula (II'-g):



or a pharmaceutically acceptable salt thereof.

38. The compound of any one of claims 16-18 and 28-30, wherein the compound is of formula (II'-h):



or a pharmaceutically acceptable salt thereof.

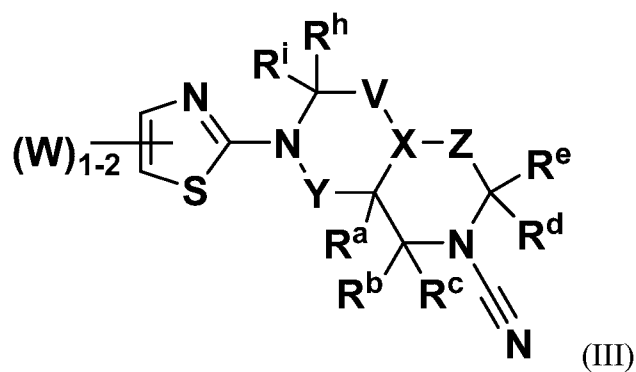
39. The compound of any one of embodiments 16, 17, and 20-38, wherein Ring A is selected from C₃-C₁₀ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W.

40. The compound of any one of embodiments 16-18 and 20-39, wherein Ring A is optionally substituted 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

41. The compound of any one of embodiments 16-40, wherein Ring A is optionally substituted 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

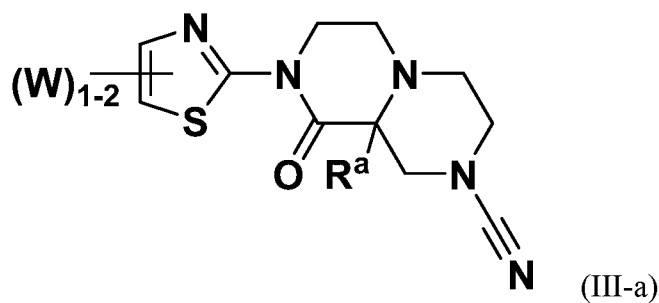
42. The compound of any one of embodiments 16-41, wherein Ring A is optionally substituted thiazolyl or pyrazolyl.

43. The compound of any one of embodiments 16-42, wherein the compound is of formula (III):



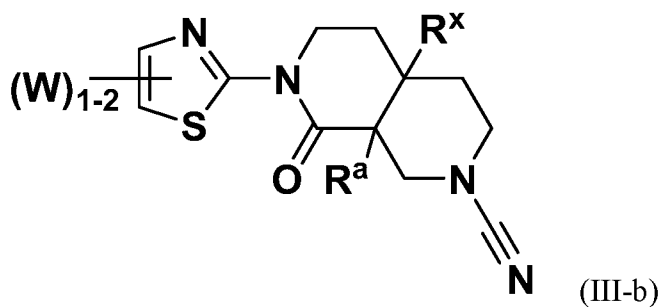
or a pharmaceutically acceptable salt thereof.

44. The compound of any one of embodiments 16-19, 28-31, and 39-43, wherein the compound is of formula (III-a):



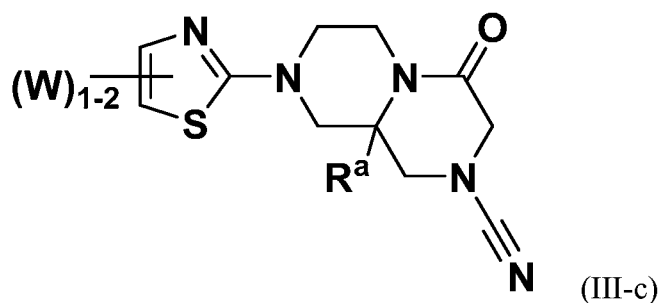
or a pharmaceutically acceptable salt thereof.

45. The compound of any one of embodiments 16-19, 21, 28-31, 32, and 39-43, wherein the compound is of formula (III-b):



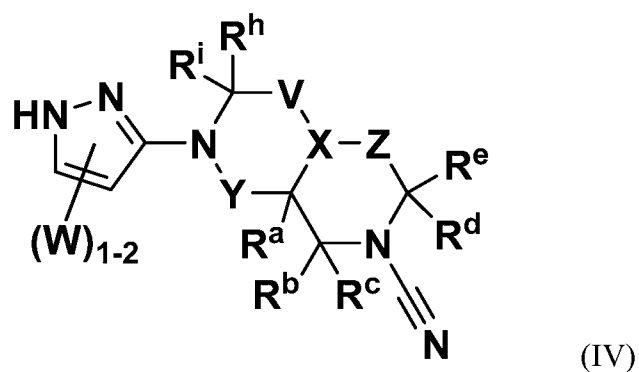
or a pharmaceutically acceptable salt thereof.

46. The compound of any one of embodiments 16-18, 22, 28-31, 33, and 39-43, wherein the compound is of formula (III-c):



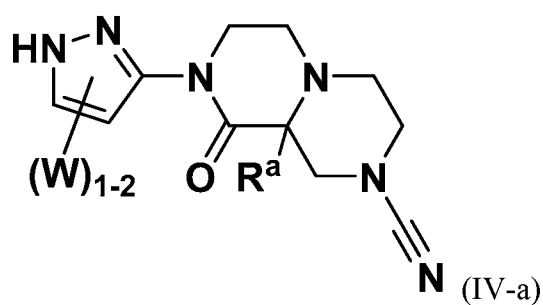
or a pharmaceutically acceptable salt thereof.

47. The compound of any one of embodiments 16-42, wherein the compound is of formula (IV):



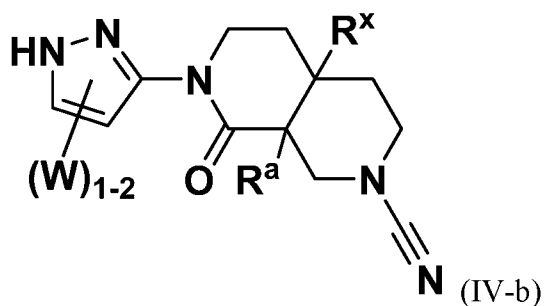
or a pharmaceutically acceptable salt thereof.

48. The compound of any one of embodiments 16-20, 28-31, 39-42 and 47, wherein the compound is of formula (IV-a):



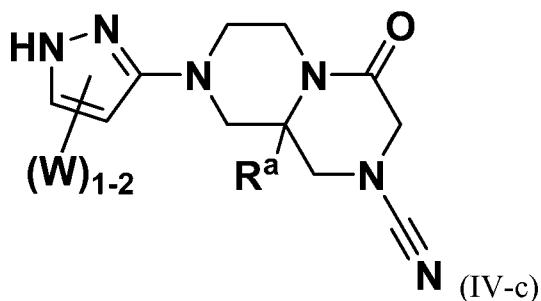
or a pharmaceutically acceptable salt thereof.

49. The compound of any one of embodiments 16-19, 21, 28-30, 32, 39-42, and 47, wherein the compound is of formula (IV-b):



or a pharmaceutically acceptable salt thereof.

50. The compound of any one of embodiments 16-18, 22, 28-30, 33, 39-42, and 47, wherein the compound is of formula (IV-c):



or a pharmaceutically acceptable salt thereof.

51. The compound of any one of embodiments 16-18, 30, 43, and 47, wherein V is a bond.

52. The compound of any one of embodiments 16-19, 30, 43, and 47, wherein V is C(O).

53. The compound of any one of embodiments 16-19, 30, 43, and 47, wherein V is CR^fR^g.

54. The compound of any one of embodiments 16-19, 30, 43, and 47, wherein X is N.

55. The compound of any one of embodiments 16-19, 30, 43, and 47, wherein X is R^x.

56. The compound of any one of embodiments 16, 30, 43, and 47, wherein Y is a bond.

57. The compound of any one of embodiments 16-19, 30, 43, and 47, wherein Y is C(O).

58. The compound of any one of embodiments 16-18, 30, 43, and 47, wherein Y is CR^jR^k.

59. The compound of any one of embodiments 16-18, 30, 43, and 47, wherein Z is C(O).
60. The compound of any one of embodiments 16-18, 30, 43, and 47, wherein Z is CR^jR^k.
61. The compound of any one of embodiments 16, 17, 28-30, 39-43, 47, and 51-60, wherein each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, and C₁-C₆ alkyl.
62. The compound of any one of embodiments 16-18 and 20-61, wherein R^a is selected from hydrogen, halogen, and C₁-C₆ alkyl.
63. The compound of any one of embodiments 16-62, wherein each occurrence of R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen.
64. The compound of any one of embodiments 1-63, wherein R^a is hydrogen.
65. The compound of any one of embodiments 16, 17, and 20-64, wherein each W is independently selected from halogen, -OR, -CN, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.
66. The compound of any one of embodiments 16-65, wherein each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl.
67. The compound of any one of embodiments 16-66, wherein each W is independently selected from halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, optionally substituted 5- to 6-membered heterocyclyl

containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl.

68. The compound of any one of embodiments 16-67, wherein each W is independently selected from chloro, tert-butyl, cyclohexyl, 2-benzylpiperidinyl, phenyl, 3-cyanophenyl, 3-chlorophenyl, 2-phenoxyphenyl, and 3-(azetidin-1-ylmethyl)phenyl.

69. The compound of any one of embodiments 16, 17, and 20-68, wherein each R¹ is independently selected from halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_m(C₃-C₁₀ cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl).

70. The compound of any one of embodiments 16-18 and 20-69, wherein each R¹ is independently selected from halogen, -OR, -CN, -(CH₂)_m(3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl).

71. The compound of any one of embodiments 16-70, wherein each R¹ is independently halogen, -OR, -CN, and -(CH₂)_m(phenyl).

72. The compound of any one of embodiments 16, 17, and 20-71, wherein each R is independently selected from hydrogen, C₁-C₆ alkyl, and phenyl.

73. The compound of any one of embodiments 16-72, wherein each R is phenyl.

74. The compound of any one of embodiments 16 and 20-73, wherein each R' is C₁-C₆ alkyl.

75. The compound of any one of embodiments 16, 17, and 20-74, wherein each m is 0 or 1.

76. The compound of any one of embodiments 16-75, wherein each m is 1.

77. A compound selected from Table B, or a pharmaceutically acceptable salt thereof.

78. A compound selected from Table C, or a pharmaceutically acceptable salt thereof.
79. A pharmaceutical composition comprising the compound of any one of embodiments 16-78, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
80. A method of inhibiting USP30 in a human, comprising administering the compound of any one of embodiments 16-78, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 79.
81. A method of treating a disease, disorder, or condition associated with USP30, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of embodiments 16-78, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 79.
82. A method of treating a neurodegenerative or neurologic disease, disorder, or condition, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of embodiments 16-78, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 79.
83. A method of treating a disease, disorder, or condition associated with mitochondrial dysfunction, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of embodiments 16-78, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of embodiment 79.
84. The method of any one of embodiments 81-83, wherein the disease, disorder, or condition is Parkinson's disease.

[0180] The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and

equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

EXAMPLES

Abbreviations

AMphos-Pd G3	[4-(Di- <i>tert</i> -butylphosphino)- <i>N,N</i> -dimethylaniline-2-(2'-aminobiphenyl)]palladium(II) methanesulfonate
BGG	Bovine γ -globulin
Boc	<i>tert</i> -butyloxycarbonyl
CbzCl	Benzyl chloroformate
δ	chemical shift
DCM	dichloromethane
DIEA	<i>N,N</i> -Diisopropylethylamine
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
^1H 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
NMP	<i>N</i> -methyl-2-pyrrolidone
r.t	Room temperature
RT	Retention time
TFA	Trifluoroacetic acid
XPhos-Pd 3G	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Assay Example A: Description of Biochemical Assay: Ubiquitin-Rhodamine 110 Assay for USP30 Activity

[0181] The assay was performed in a final volume of 6 μL in assay buffer containing 20 mM Tris-HCl (pH 8.0, (1M Tris-HCl, pH 8.0 solution; Corning 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

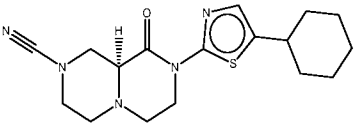
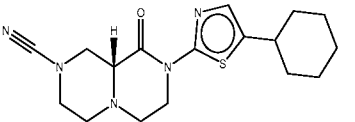
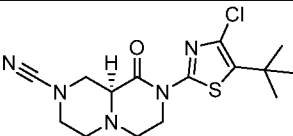
fixed substrate concentration ($\ll K_m$). The final concentration of enzyme (human recombinant USP30, Boston Biochem, cat. # E-582) in the assay was 0.4 nM. Final substrate (Ub-Rh110; Ubiquitin-Rhodamine 110, UbiQ-126) concentration was 25 nM. 3 μ L of 2x enzyme was added to assay plates (pre-stamped with compound), preincubated for 30 minutes and then treated with 3 μ L of 2x substrate. Plates were read for fluorescence on the Envision (Perkin Elmer) or PheraSTAR (BMG) (excitation at 485 nm and emission at 535 nm) 5 times over the course of 11 minutes and the slope of this kinetic read used to normalize the raw data.

[0182] 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=32), and AveHigh = average Fluorescence of DMSO control (n=32). IC₅₀ 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 are fitted using the Levenburg Marquardt algorithm.

[0183] Compounds in the USP30 biochemical assay were identified having an IC₅₀ of < 10 μ M (In some embodiments, compounds were identified having an IC₅₀ of < 5 micromolar, and in some embodiments, compounds were identified having an IC₅₀ < 1 micromolar, using the assay of Example A).

[0184] The activity of compounds in the USP30 biochemical IC₅₀ assay (IC₅₀ ranges) according to the present disclosure are reported in Table D below according to the following: “-”: inactive, “+”: ≥ 10 μ M and < 25 μ M, “++”: ≥ 1 μ M and < 10 μ M, “+++”: ≥ 0.1 μ M and < 1 μ M, “++++”: < 0.1 μ M.

Table D.

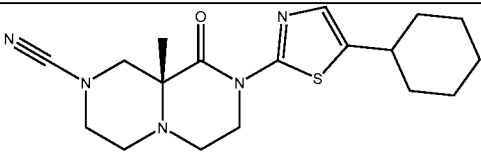
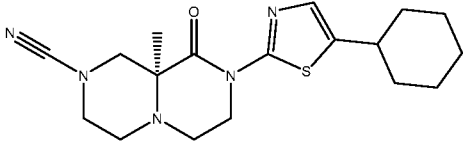
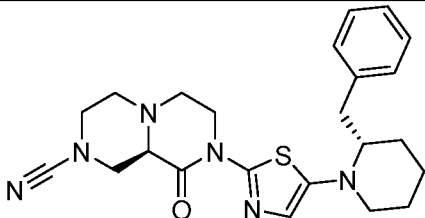
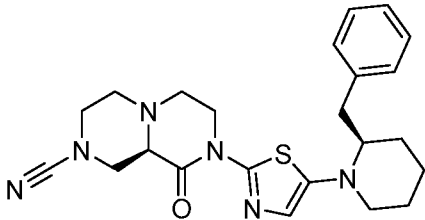
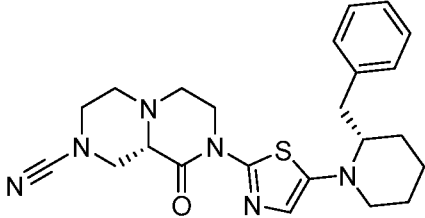
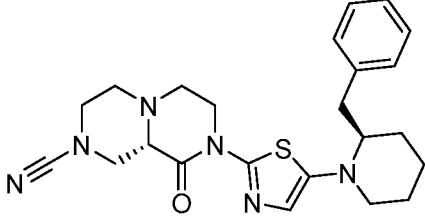
Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
1-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-2S		*(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++

Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
1-2R		*(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-3S		(S)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-3R		(R)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-4R		(R)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-4S		(S)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-5R		(R)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-5S		(S)-8-(5-(3-chlorophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-6R		(R)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-6S		(S)-8-(5-(3-cyanophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-7R		(R)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-7S		(S)-8-(5-(3-chlorophenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++

Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
1-11R		(R)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	-
1-11S		(S)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	-
1-12S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile	++
1-12S,S		(4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile	++
1-12R,R		(4aR,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile	+++
1-14S		*(S)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-14R		*(R)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
3-1S		(S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
3-1R		(R)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-15R		(R)-8-(5-(tert-butyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++

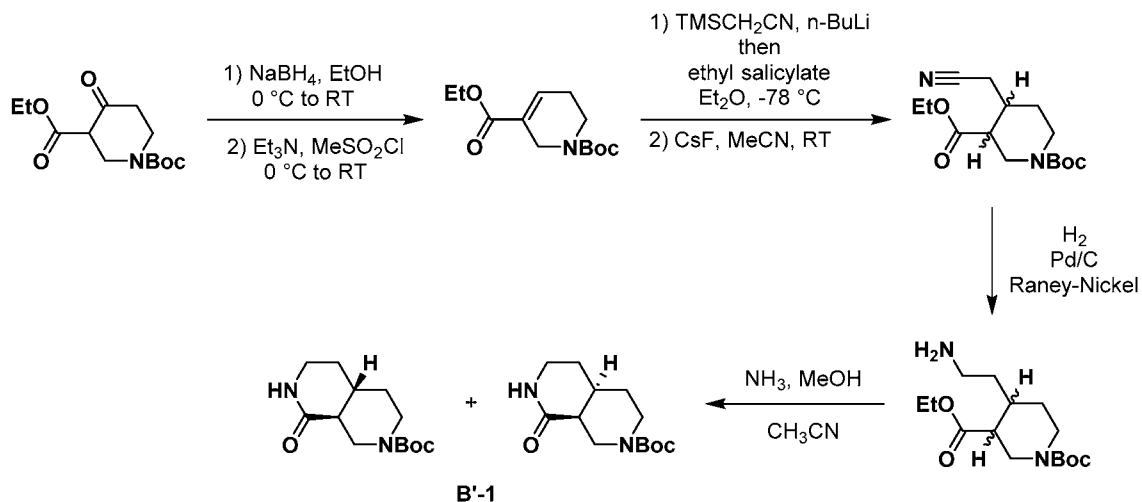
Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
4-1S,R		(4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile	++
4-1R,S		(4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile	++
5-1R,R		(3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile	+
5-1S,S		(3aS,7aS)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile	++
5-2R,R		(3aR,7aR)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile	—
5-2S,S		(3aS,7aS)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile	+
6-1R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
6-1S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-113S		*(S)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++

Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
1-113R		*(R)-9-oxo-8-(5-(2-phenoxyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-114R		(R)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-114S		(S)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-115R		(R)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-115S		(S)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-116R		(R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-116S		(S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++

Cmpd #	Structure	Chemical Name	USP30 IC ₅₀
1-117R		(R)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-117S		(S)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++
1-118R,S		(R)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	++++
1-118R,R		(R)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-118S,S		(S)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++
1-118S,R		(S)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile	+++

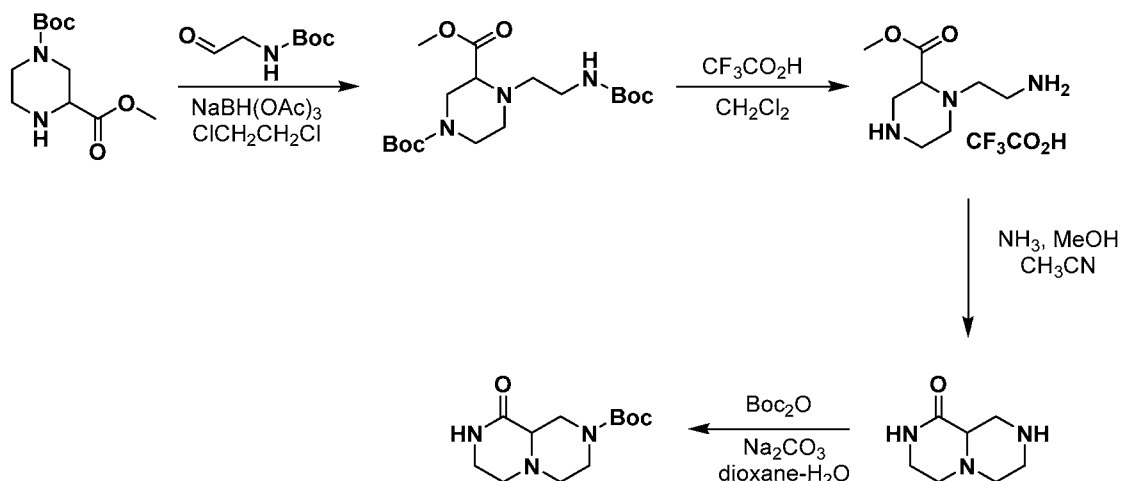
Compound Synthesis

Intermediate B'-1: Synthesis of *tert*-butyl 8-oxooctahydro-2,7-naphthyridine-2(1H)-carboxylate



[0185] A protected heterocyclic carbamate (such as a Boc-protected piperidine carbamate derivative) was reacted to reduce a carbonyl group to a ring double bond via a metal hydride reaction, followed by adding a base, such as triethylamine, and methanesulfonyl chloride. The ring double bond was then functionalized using a regioselective reagent, such as trimethylsilylacetonitrile, with a metal reagent, such as *n*-butyl lithium, followed by desilylation in the presence of CsF. The nitrile group was reduced to an amine, for instance via hydrogenation in the presence of palladium on carbon and Raney-Nickel. The ring was closed using ammonia and methanol in acetonitrile to form the Boc-protected oxooctahydro-2,7-naphthyridine (Intermediate B'-1) as a mixture of diastereomers.

Intermediate B'-2: Synthesis of *tert*-butyl 9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate



Step 1. 1-*tert*-butyl 3-methyl 4-(2-(*tert*-butoxycarbonylamino)ethyl)piperazine-1,3-dicarboxylate

[0186] A solution of *tert*-butyl (2-oxoethyl)carbamate (4.89 g, 30.7 mmol) in 1,2-dichloroethane (50 mL) was added to a solution of 1-(*tert*-butyl) 3-methyl piperazine-1,3-dicarboxylate (5 g, 20.5 mmol) in 1,2-dichloroethane (25 mL). The solution stirred at 25 °C under nitrogen atmosphere for 30 min. Sodium triacetoxyborohydride (8.69 g, 41.0 mmol) was added, and the resulting mixture stirred at 25 °C for 15 h. The reaction was quenched by the addition of water (50 mL) at 25 °C. The resulting mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and the solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 1:1 ethyl acetate/petroleum ether) to afford 1-*tert*-butyl 3-methyl 4-(2-(*tert*-butoxycarbonylamino)ethyl)piperazine-1,3-dicarboxylate as yellow oil (5.1 g, 64%). LCMS (ES, *m/z*): 388 [M+H]⁺.

Step 2. methyl 1-(2-aminoethyl)piperazine-2-carboxylate 2,2,2-trifluoroacetate

[0187] Trifluoroacetic acid (10 mL) was added dropwise to a 0 °C solution of 1-*tert*-butyl 3-methyl 4-(2-(*tert*-butoxycarbonylamino)ethyl)piperazine-1,3-dicarboxylate (5.1 g, 13.1 mmol) in dichloromethane (30 mL). The reaction solution stirred at 25 °C for 6 h. The reaction mixture was concentrated under vacuum to afford methyl 1-(2-aminoethyl)piperazine-2-carboxylate 2,2,2-trifluoroacetate (4.5 g). LCMS (ES, *m/z*): 188 [M+H]⁺.

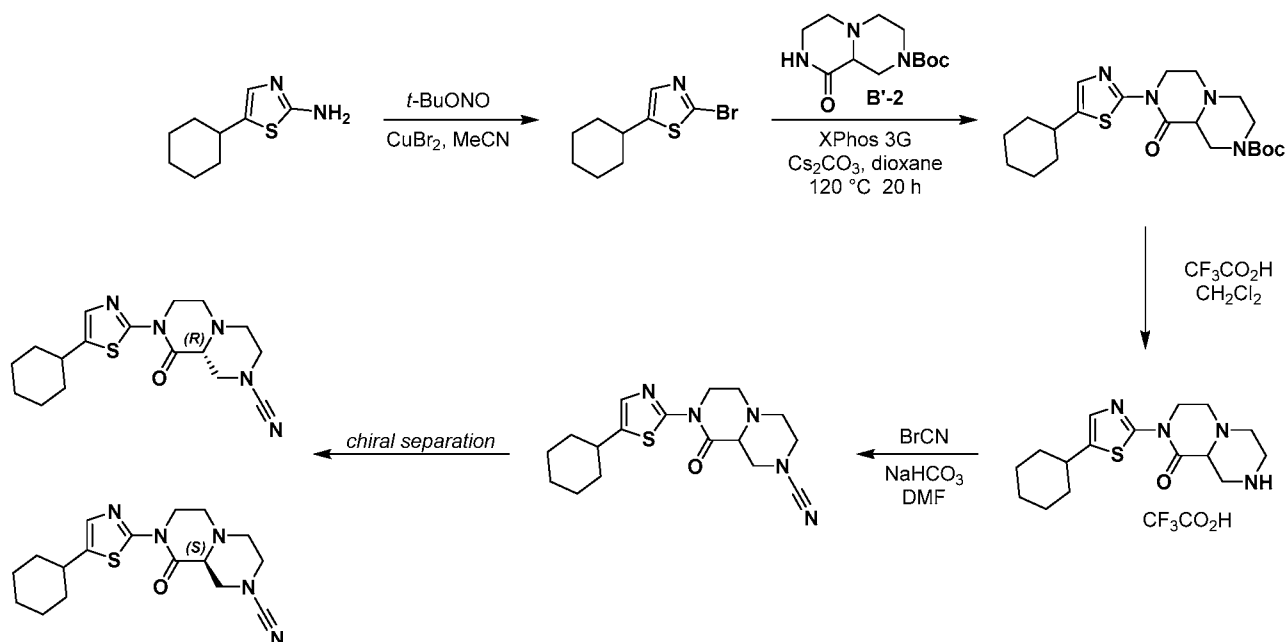
Step 3. Hexahydro-2H-pyrazino[1,2-a]pyrazin-1(6H)-one

[0188] Ammonia in methanol (7 N, 20 mL) was added to a solution of methyl 1-(2-aminoethyl)piperazine-2-carboxylate 2,2,2-trifluoroacetate (4.5 g) in acetonitrile (20 mL), and the solution stirred at 25 °C for 1 h. The resulting reaction mixture was concentrated under vacuum to afford hexahydro-2H-pyrazino[1,2-a]pyrazin-1(6H)-one (3.7 g). LCMS (ES, m/z): 156 [M+H]⁺.

Step 4. *tert*-butyl 9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate

[0189] Di-*tert*-butyl dicarbonate (6.25 g, 28.7 mmol) was added to a mixture of hexahydro-2H-pyrazino[1,2-a]pyrazin-1(6H)-one (3.7 g, 23.9 mmol) and saturated aqueous sodium carbonate solution (40 mL) in dioxane (60 mL). The reaction mixture stirred at 25 °C for 14 h. The resulting mixture was diluted with water (30 mL) and the resulting mixture was extracted with dichloromethane (3 x 60 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, and the solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 1:15 methanol/dichloromethane) to afford *tert*-butyl 9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate as a yellow solid (1.9 g, 30%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 7.78 (brs, 1H), 4.28-4.22 (m, 1H), 3.87-3.81 (m, 1H), 3.28-3.24 (m, 1H), 3.08-3.06 (m, 1H), 2.87-2.80 (m, 3H), 2.60-2.56 (m, 1H), 2.44-2.33 (m, 2H), 2.11-2.07 (m, 1H), 1.41 (s, 9H). LCMS (ESI, m/z): 256 [M+H]⁺.

Example 1-1. Synthesis of (S)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile and (R)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile



Step 1. 2-bromo-5-cyclohexyl-1, 3-thiazole

[0190] A mixture of 5-cyclohexyl-1,3-thiazol-2-amine (600 mg, 3.29 mmol), tert-butyl nitrite (0.390 mL, 3.83 mmol) and copper (II) bromide (1.47 g, 6.58 mmol) in acetonitrile (4 mL) was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (6 mL). The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting with 10/1 petroleum ether/ethyl acetate) to afford 2-bromo-5-cyclohexyl-1,3-thiazole (200 mg, 22%) as a light yellow oil. LCMS (ES, m/z): 246, 248 [M+H]⁺.

Step 2. tert-butyl 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carboxylate

[0191] A mixture of 2-bromo-5-cyclohexyl-1,3-thiazole (200 mg, 0.816 mmol), tert-butyl 9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carboxylate (**B'-2**, 250 mg, 0.979 mmol), cesium carbonate (532 mg, 1.63 mmol) and methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct (68.7 mg, 0.082 mmol) in dioxane (6 mL) was stirred for 36 h at 120 °C and then cooled to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (eluting with 1/1 petroleum ether/ethyl acetate) to afford tert-butyl 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carboxylate (70.0 mg, 20%) as a yellow solid. LCMS (ES, m/z): 421 [M+H]⁺.

[0192] Tert-butyl 9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carboxylate can be purchased, or can be made, for example according to the procedure in Example 1-1B' below.

Step 3. 2-(5-cyclohexyl-1,3-thiazol-2-yl)-octahydro-1H-[1,4]diazino[1,2-a]pyrazin-1-one trifluoroacetate

[0193] A solution of tert-butyl 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carboxylate (70.0 mg, 0.167 mmol) and trifluoroacetic acid (0.8 mL, 10.1 mmol) in dichloromethane (4 mL) was stirred for 2 h at room temperature. The resulting solution was concentrated under reduced pressure to afford 2-(5-cyclohexyl-1,3-thiazol-2-yl)-octahydro-1H-[1,4]diazino[1,2-a]pyrazin-1-one trifluoroacetate (71.0 mg, crude) as a light yellow oil. LCMS (ES, m/z): 321 [M+H]⁺.

Step 4. 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile

[0194] A mixture of 2-(5-cyclohexyl-1,3-thiazol-2-yl)-octahydro-1H-[1,4]diazino[1,2-a]pyrazin-1-one trifluoroacetate (40.0 mg, 0.096 mmol), sodium bicarbonate (105 mg, 1.25 mmol) and cyanogen bromide (13.2 mg, 0.125 mmol) in N,N-dimethylformamide (2 mL) was stirred for 1 h at room temperature. The reaction was quenched by the addition of water/ice at 0 °C. The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product (35.0 mg) was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 mm, 19 x 150 mm; Mobile Phase, A: water (containing 0.05% ammonium bicarbonate) and B: acetonitrile (46% to 60% in 7 min); Flow rate: 20 mL/min; Detector: 220/254 nm) to afford 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile (12.0 mg, 4%) as a white solid. LCMS (ES, m/z): 346 [M+H]⁺.

Step 5. (S)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile and (R)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile

[0195] 8-(5-cyclohexyl-1,3-thiazol-2-yl)-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile (12.0 mg, 0.034 mmol) was separated by chiral-HPLC (Column: Chiralpak IA, 2*25 cm, 5 mm; Mobile Phase, A: methanol (containing 0.1% diethylamine) and B: dichloromethane (hold 70% in 20 min); Flow rate: 18 mL/min; Detector: 220/254 nm; RT1: 7.121 min and RT2: 12.341 min) to afford:

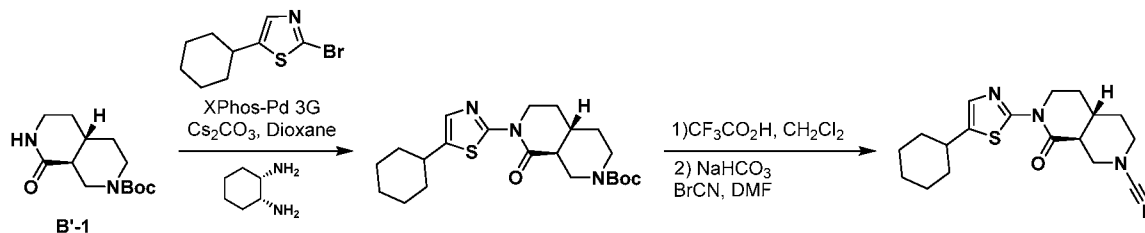
(S)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile (RT1: 7.121 min) (3.60 mg, 30%) as a white solid. ¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm) 7.29 (s, 1H), 4.22-4.19 (m, 1H), 3.84-3.80 (m, 1H), 3.78-3.73 (m, 1H), 3.40-3.32 (m, 1H), 3.18-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.84-2.71 (m, 2H), 2.43-2.38 (m, 1H), 1.98-1.92 (m, 2H), 1.78-1.74 (m, 2H), 1.69-1.66 (m, 1H), 1.43-1.34 (m, 4H), 1.27-1.98 (m, 1H). Absolute stereochemistry arbitrarily assigned.

and

(R)-8-(5-cyclohexylthiazol-2-yl)-9-oxo-hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carbonitrile (RT2: 12.341 min) (3.10 mg, 26%) as a white solid. LCMS (ES, m/z): 346 [M+H]⁺. ¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm) 7.29 (s, 1H), 4.22-4.19 (m, 1H), 3.84-3.80 (m, 1H), 3.78-3.73 (m, 1H), 3.40-3.32 (m, 1H), 3.18-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.83-2.68 (m, 2H), 2.43-2.38 (m,

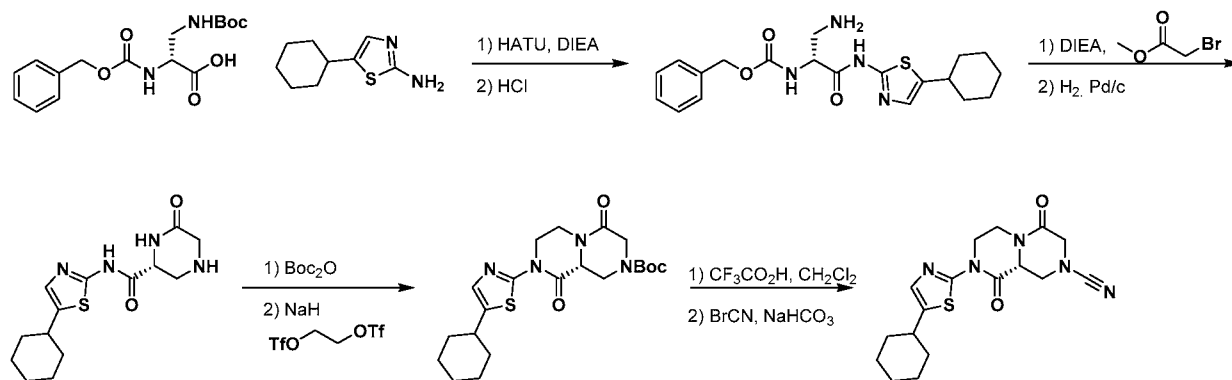
1H), 1.98-1.91 (m, 1H), 1.81-1.76 (m, 2H), 1.72-1.67 (m, 1H), 1.45-1.28 (m, 4H), 1.27-1.97 (m, 1H). Absolute stereochemistry arbitrarily assigned.

Example 1-12. Synthesis of (4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile.



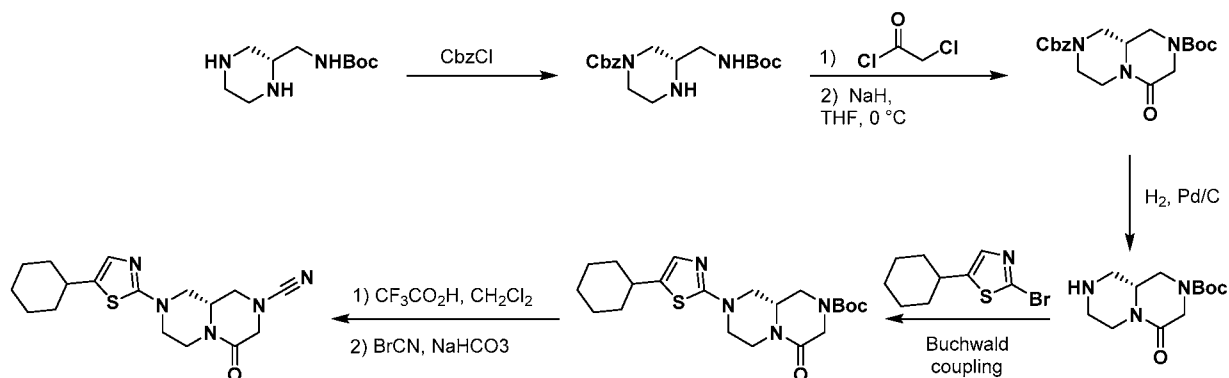
[0196] Boc-protected oxooctahydro-2,7-naphthyridine (**B'-1**) was coupled to a 2-bromo-5-cyclohexylthiazole via cross-coupling using a metal catalyst (e.g., XPhos-Pd 3G). Lastly, the Boc protecting group was removed in the presence of trifluoroacetic acid and replaced with a nitrile group in the presence of BrCN and base (e.g., NaHCO₃).

Example 2-1. Synthesis of (R)-8-(5-cyclohexylthiazol-2-yl)-4,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile.



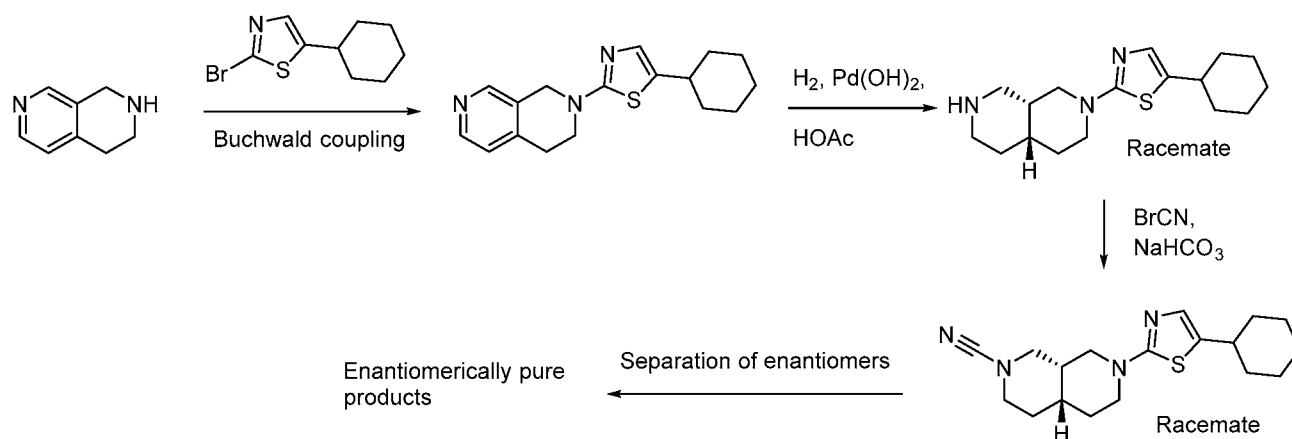
[0197] (R)-2-(((benzyloxy)carbonyl)amino)-3-((tert-butoxycarbonyl)amino)propanoic acid can be coupled to 5-cyclohexylthiazol-2-amine using a standard coupling reagent (i.e., HATU) and base (i.e., DIEA) in a suitable solvent and the Boc group can then be removed using either TFA or HCl in a suitable solvent. The resulting amine can be reacted with methyl 2-bromoacetate, which cyclizes to the piperazinone ring upon removal of the Cbz group under hydrogenation conditions. The piperazinone can be protected with a Boc group and bis-alkylation with an appropriate electrophile (i.e., ethane-1,2-diyl bis(trifluoromethanesulfonate)) can form the bicyclic ring architecture. Lastly, the Boc protecting group can be removed and replaced with a nitrile group.

Example 3-1. Synthesis of (S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile.



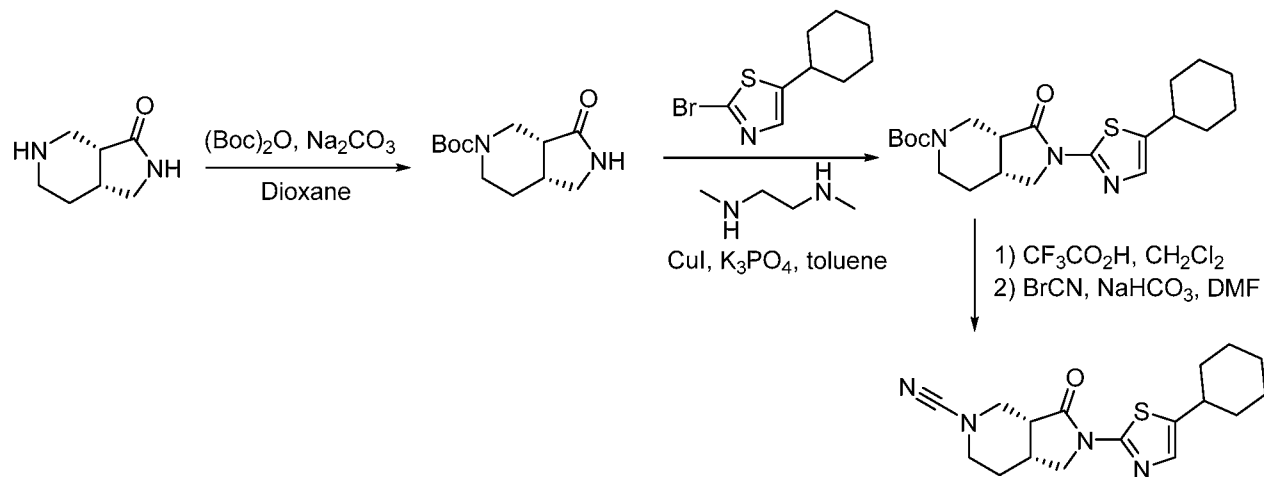
[0198] tert-butyl (R)-(piperazin-2-ylmethyl)carbamate was protected with a Cbz group in the presence of CbzCl. Then, the bicycle was formed in the presence of 2-chloroacetyl chloride, followed by NaH. The Cbz group was removed in the presence of H₂ and Pd/C, followed by coupling to 2-bromo-5-cyclohexylthiazole via Buchwald coupling. Lastly, the Boc protecting group was removed in the presence of trifluoroacetic acid, and the resulting amine was functionalized with a nitrile group in the presence of NaHCO₃ and BrCN.

Example 4-1. Synthesis of (4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile and (4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile.



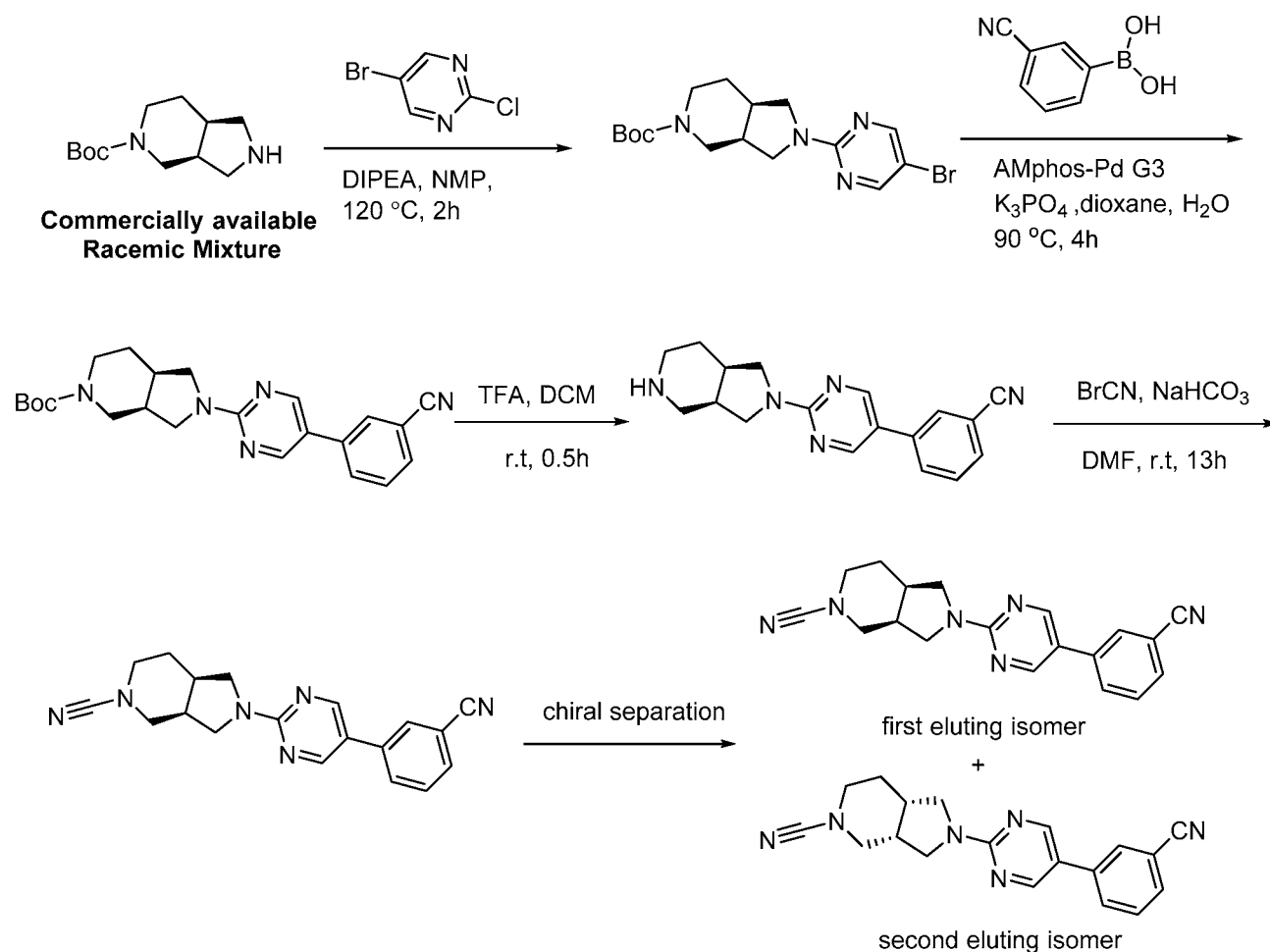
[0199] 1,2,3,4-tetrahydro-2,7-naphthyridine was coupled to 2-bromo-5-cyclohexylthiazole via Buchwald coupling. The resulting compound was then reduced in the presence of H₂ and Pd(OH)₂. The resulting amine was then functionalized with a nitrile group in the presence of NaHCO₃ and BrCN to give a racemic mixture, which was separated to give enantiomerically pure products.

Example 5-1. Synthesis of (3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile.



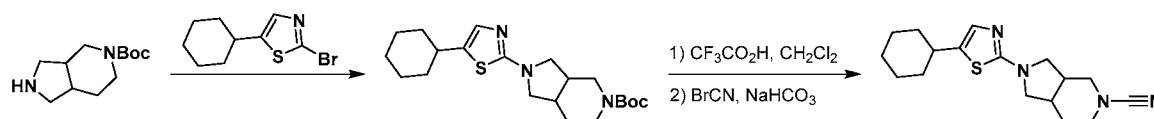
[0200] (3aR,7aR)-octahydro-3H-pyrrolo[3,4-c]pyridin-3-one was protected with a Boc group in the presence of $(\text{Boc})_2\text{O}$ and Na_2CO_3 . The Boc-protected product was coupled to 2-bromo-5-cyclohexylthiazole via cross-coupling in the presence of a copper catalyst and K_3PO_4 . Lastly, the protecting group was removed in the presence of trifluoroacetic acid, and the resulting amine was functionalized with a nitrile group in the presence of NaHCO_3 and BrCN .

Example 5-2. Synthesis of (3a,7a)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile



[0201] tert-butyl octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate was coupled to 5-bromo-2-chloropyrimidine via a substitution reaction in the presence of DIPEA. The resulting product was coupled with (3-cyanophenyl)boronic acid via cross-coupling in the presence of AMphos-Pd G3 and K₃PO₄. Then, the Boc group was removed in the presence of trifluoroacetic acid, and the resulting amine was functionalized with a nitrile group in the presence of NaHCO₃ and BrCN to give (3a,7a)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile as a racemic mixture. The enantiomers were separated by chiral separation.

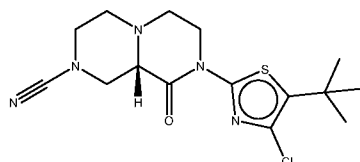
Example 1-119. Synthesis of 2-(5-cyclohexylthiazol-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile.



[0202] tert-butyl octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate can be coupled to 2-bromo-5-cyclohexylthiazole via cross-coupling. Then, the Boc group can be removed in the presence of trifluoroacetic acid, and the resulting amine can be functionalized with a nitrile group in the presence of NaHCO₃ and BrCN.

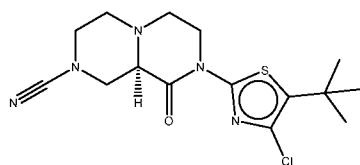
[0203] The following compounds were prepared according to the methods described herein:

[0204] **Compound 1-2S. (S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



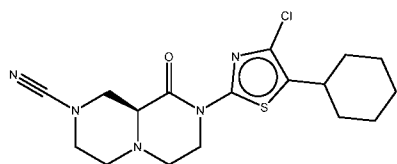
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 4.14-4.10 (m, 1H), 3.80-3.75 (m, 1H), 3.71-3.68 (m, 1H), 3.40-3.37 (m, 1H), 3.28-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.79-2.73 (m, 1H), 2.47-2.41 (m, 1H), 1.43 (s, 9H). LCMS (ES, m/z): 354, 356 [M+H]⁺.

[0205] **Compound 1-2R. (9aR)-8-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-9-oxooctahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile**



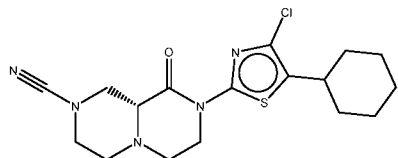
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 4.14-4.10 (m, 1H), 3.81-3.75 (m, 1H), 3.71-3.68 (m, 1H), 3.40-3.37 (m, 1H), 3.28-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.79-2.75 (m, 1H), 2.46-2.40 (m, 1H), 1.43 (s, 9H). LCMS (ES, m/z): 354, 356 [M+H]⁺.

[0206] **Compound 1-3S. (S)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



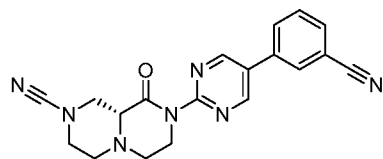
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 4.16-4.12 (m, 1H), 3.82-3.79 (m, 1H), 3.72-3.68 (m, 1H), 3.41-3.32 (m, 1H), 3.29-3.25 (m, 1H), 3.21-3.11 (m, 3H), 2.95-2.92 (m, 1H), 2.85-2.75 (m, 2H), 2.44-2.34 (m, 1H), 1.91-1.87 (m, 2H), 1.78-1.77 (m, 2H), 1.69-1.67 (m, 1H), 1.39-1.24 (m, 5H).
LCMS (ES, m/z): 380, 382 $[\text{M}+\text{H}]^+$.

[0207] Compound 1-3R. (R)-8-(4-chloro-5-cyclohexylthiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



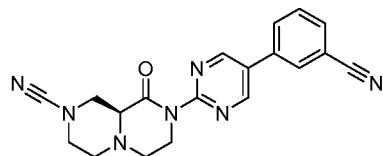
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 4.16-4.12 (m, 1H), 3.80-3.79 (m, 1H), 3.72-3.68 (m, 1H), 3.41-3.32 (m, 1H), 3.28-3.25 (m, 1H), 3.21-3.11 (m, 3H), 2.95-2.92 (m, 1H), 2.84-2.75 (m, 2H), 2.50-2.42 (m, 1H), 1.93-1.90 (m, 2H), 1.84-1.75 (m, 2H), 1.74-1.68 (m, 1H), 1.39-1.22 (m, 5H).
LCMS (ES, m/z): 380, 382 $[\text{M}+\text{H}]^+$.

[0208] Compound 1-4R. (R)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



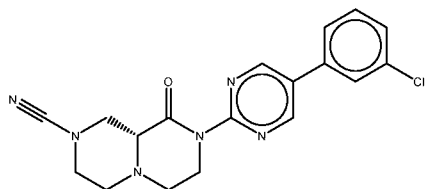
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 9.23 (s, 1H), 8.39 (s, 1H), 8.20 (d, $J = 8.0\text{Hz}$, 1H), 7.95 (d, $J = 7.6\text{Hz}$, 1H), 7.76 (t, $J = 8.0\text{Hz}$, 1H), 3.96-3.83 (m, 2H), 3.71-3.64 (m, 1H), 3.42-3.30 (m, 2H), 3.25-3.09 (m, 4H), 2.97-2.94 (m, 1H), 2.82-2.75 (m, 1H), 2.48-2.42 (m, 1H). LCMS (ES, m/z): 360 $[\text{M}+\text{H}]^+$.

[0209] Compound 1-4S. (S)-8-(5-(3-cyanophenyl)pyrimidin-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



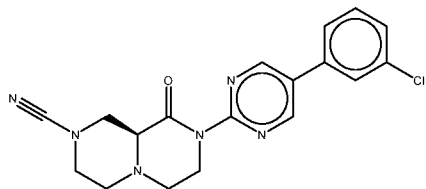
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 9.23 (s, 1H), 8.39 (s, 1H), 8.19 (d, $J = 8.0\text{Hz}$, 1H), 7.95 (d, $J = 7.6\text{Hz}$, 1H), 7.76 (t, $J = 8.0\text{Hz}$, 1H), 3.96-3.84 (m, 2H), 3.71-3.64 (m, 1H), 3.42-3.35 (m, 1H), 3.24-3.21 (m, 1H), 3.19-3.17 (m, 3H), 2.97-2.90 (m, 1H), 2.82-2.75 (m, 1H), 2.48-2.42 (m, 1H). LCMS (ES, m/z): 360 $[\text{M}+\text{H}]^+$.

[0210] Compound 1-5R. (9aR)-8-[5-(3-chlorophenyl)pyrimidin-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



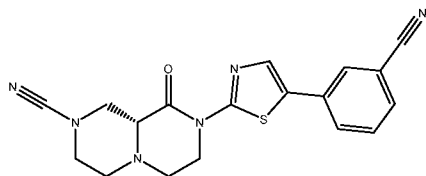
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 9.19 (s, 1H), 7.96 (s, 1H), 7.81 (d, $J = 7.2\text{Hz}$, 1H), 7.59 (d, $J = 8.0\text{Hz}$, 1H), 7.56-7.53 (m, 2H), 3.96-3.82 (m, 2H), 3.71-3.64 (m, 1H), 3.41-3.38 (m, 1H), 3.25-3.11 (m, 4H), 2.96-2.93 (m, 1H), 2.82-2.75 (m, 1H), 2.48-2.42 (m, 1H). LCMS (ES, m/z): 369 $[\text{M}+\text{H}]^+$.

[0211] Compound 1-5S. (9aS)-8-[5-(3-chlorophenyl)pyrimidin-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



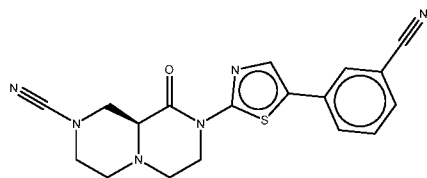
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 9.19 (s, 1H), 7.96 (s, 1H), 7.81 (d, $J = 7.2\text{Hz}$, 1H), 7.59 (d, $J = 8.0\text{Hz}$, 1H), 7.56-7.53 (m, 2H), 3.96-3.82 (m, 2H), 3.68-3.64 (m, 1H), 3.41-3.38 (m, 1H), 3.25-3.11 (m, 4H), 2.96-2.93 (m, 1H), 2.82-2.76 (m, 1H), 2.48-2.42 (m, 1H). LCMS (ES, m/z): 371 $[\text{M}+\text{H}]^+$.

[0212] Compound 1-6R. (9aR)-8-[5-(3-cyanophenyl)-1,3-thiazol-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



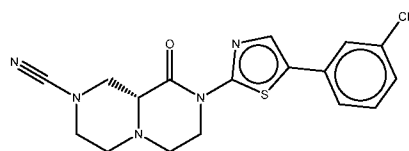
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.22 (s, 1H), 8.18 (s, 1H), 7.96 (d, $J = 8.0\text{Hz}$, 1H), 7.78 (d, $J = 7.6\text{Hz}$, 1H), 7.63 (t, $J = 8.0\text{Hz}$, 1H), 4.31-4.27 (m, 1H), 3.92-3.89 (m, 1H), 3.77-3.73 (m, 1H), 3.43-3.39 (m, 1H), 3.33-3.30 (m, 1H), 3.23-3.18 (m, 3H), 2.98-2.95 (m, 1H), 2.84-2.81 (m, 1H), 2.51-2.46 (m, 1H). LCMS (ES, m/z): 365 $[\text{M}+\text{H}]^+$.

[0213] Compound 1-6S. (9aS)-8-[5-(3-cyanophenyl)-1,3-thiazol-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



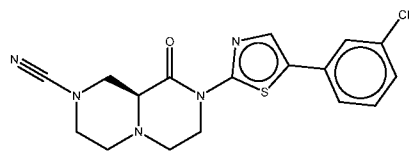
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.22 (s, 1H), 8.18 (s, 1H), 7.96 (d, $J = 8.0\text{Hz}$, 1H), 7.78 (d, $J = 7.6\text{Hz}$, 1H), 7.63 (t, $J = 8.0\text{Hz}$, 1H), 4.31-4.27 (m, 1H), 3.95-3.86 (m, 1H), 3.77-3.73 (m, 1H), 3.43-3.39 (m, 1H), 3.33-3.31 (m, 1H), 3.27-3.18 (m, 3H), 2.98-2.95 (m, 1H), 2.85-2.81 (m, 1H), 2.48-2.42 (m, 1H). LCMS (ES, m/z): 365 $[\text{M}+\text{H}]^+$.

[0214] Compound 1-7R. (9aR)-8-[5-(3-chlorophenyl)-1,3-thiazol-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



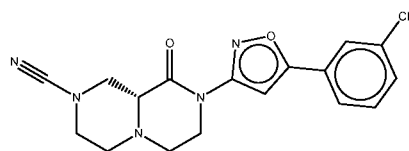
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.11 (s, 1H), 7.78 (s, 1H), 7.59 (d, $J = 7.6\text{Hz}$, 1H), 7.46 (t, $J = 8.0\text{Hz}$, 1H), 7.39 (d, $J = 8.4\text{Hz}$, 1H), 4.31-4.27 (m, 1H), 3.89-3.85 (m, 1H), 3.76-3.73 (m, 1H), 3.42-3.39 (m, 1H), 3.33-3.29 (m, 1H), 3.27-3.17 (m, 3H), 2.98-2.95 (m, 1H). LCMS (ES, m/z): 374, 376 $[\text{M}+\text{H}]^+$.

[0215] Compound 1-7S. (9aS)-8-[5-(3-chlorophenyl)-1,3-thiazol-2-yl]-9-oxo-octahydro-1H-[1,4]diazino[1,2-a]pyrazine-2-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.11 (s, 1H), 7.78 (s, 1H), 7.59 (d, $J = 8.0\text{Hz}$, 1H), 7.46 (t, $J = 8.0\text{Hz}$, 1H), 7.39 (d, $J = 8.0\text{Hz}$, 1H), 4.28-4.27 (m, 1H), 3.89-3.85 (m, 1H), 3.77-3.73 (m, 1H), 3.42-3.39 (m, 1H), 3.33-3.29 (m, 1H), 3.27-3.17 (m, 3H), 2.98-2.95 (m, 1H), 2.85-2.80 (m, 1H), 2.51-2.43 (m, 1H). LCMS (ES, m/z): 374, 376 $[\text{M}+\text{H}]^+$.

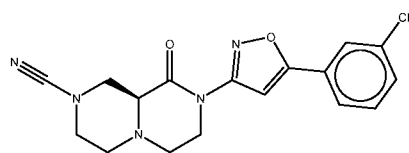
[0216] Compound 1-11R. (R)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 7.73 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.59-7.42 (m, 3H), 3.87-3.72 (m, 2H), 3.49-3.39 (m, 2H), 3.19-2.96 (m, 5 H), 2.89-2.82 (m, 1H), 2.56-2.49 (m, 1H)

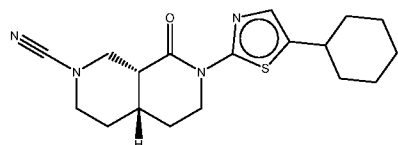
LCMS (ES, m/z): 358, 360 [M+H]⁺.

[0217] Compound 1-11S. (S)-8-(5-(3-chlorophenyl)isoxazol-3-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



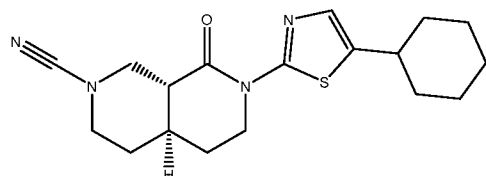
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 7.73 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.59-7.36 (m, 3H), 3.87-3.72 (m, 2H), 3.53-3.39 (m, 2H), 3.19-2.96 (m, 5 H), 2.89-2.82 (m, 1H), 2.56-2.49 (m, 1H). LCMS (ES, m/z): 358, 360 [M+H]⁺.

[0218] Compound 1-12S,R. (4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile



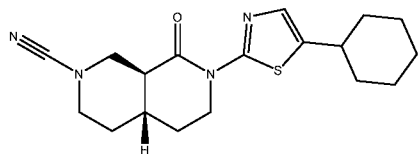
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 7.27 (s, 1H), 4.15-4.11 (m, 1H), 4.03-3.96 (m, 1H), 3.93-3.90 (m, 1H), 3.34-3.31 (m, 1H), 3.23-3.19 (m, 1H), 3.13-3.07 (m, 1H), 2.92-2.90 (m, 1H), 2.84-2.79 (m, 1H), 2.22-2.08 (m, 2H), 2.01-1.92 (m, 3H), 1.82-1.75 (m, 2H), 1.84-1.62 (m, 2H), 1.60-1.47 (m, 1H), 1.46-1.28 (m, 4H), 1.27-1.18 (m, 1H). LCMS (ES, m/z): 345 [M+H]⁺.

[0219] Compound 1-12R,R. (4aR,8aR)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile



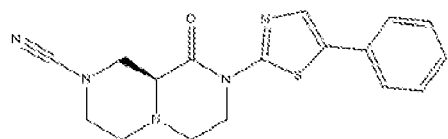
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 7.25 (s, 1H), 4.27-4.22 (m, 1H), 3.85-3.72 (m, 2H), 3.42-3.34 (m, 1H), 3.08-3.00 (m, 2H), 2.82-2.77 (m, 1H), 2.63-2.57 (m, 1H), 2.04-2.02 (m, 1H), 1.93-1.90 (m, 2H), 1.86-1.67 (m, 6H), 1.48-1.30 (m, 5H), 1.29-1.18 (m, 1H). LCMS (ES, m/z): 345 [M+H]⁺.

[0220] Compound 1-12S,S. (4aS,8aS)-7-(5-cyclohexylthiazol-2-yl)-8-oxooctahydro-2,7-naphthyridine-2(1H)-carbonitrile



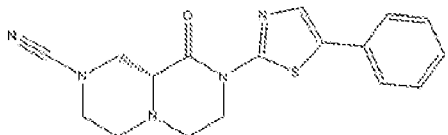
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.27 (s, 1H), 4.15-4.11 (m, 1H), 4.03-3.96 (m, 1H), 3.93-3.90 (m, 1H), 3.34-3.31 (m, 1H), 3.23-3.19 (m, 1H), 3.13-3.07 (m, 1H), 2.92-2.90 (m, 1H), 2.84-2.79 (m, 1H), 2.22-2.08 (m, 2H), 2.01-1.92 (m, 3H), 1.82-1.75 (m, 2H), 1.84-1.62 (m, 2H), 1.60-1.47 (m, 1H), 1.46-1.28 (m, 4H), 1.27-1.18 (m, 1H). LCMS (ES, m/z): 345 $[\text{M}+\text{H}]^+$.

[0221] Compound 1-14S. *(S)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



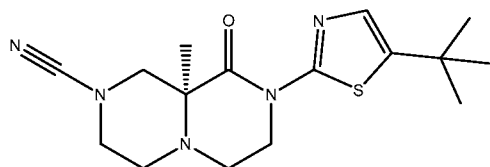
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.80 (s, 1H), 7.65 (d, $J = 7.2\text{Hz}$, 2H), 7.44 (t, $J = 7.6\text{Hz}$, 2H), 7.34 (t, $J = 7.2\text{Hz}$, 1H), 4.31-4.26 (m, 1H), 3.92-3.84 (m, 1H), 3.77-3.73 (m, 1H), 3.43-3.39 (m, 1H), 3.32-3.28 (m, 1H), 3.23-3.15 (m, 3H), 2.97-2.94 (m, 1H), 2.84-2.77 (m, 1H), 2.49-2.44 (m, 1H). LCMS (ES, m/z): 340 $[\text{M}+\text{H}]^+$.

[0222] Compound 1-14R. *(R)-9-oxo-8-(5-phenylthiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.80 (s, 1H), 7.65 (d, $J = 7.2\text{Hz}$, 2H), 7.46-7.42 (m, 2H), 7.34 (t, $J = 7.2\text{Hz}$, 1H), 4.30-4.26 (m, 1H), 3.92-3.84 (m, 1H), 3.77-3.73 (m, 1H), 3.43-3.39 (m, 1H), 3.32-3.28 (m, 1H), 3.23-3.15 (m, 3H), 2.97-2.94 (m, 1H), 2.84-2.77 (m, 1H), 2.49-2.44 (m, 1H). LCMS (ES, m/z): 340 $[\text{M}+\text{H}]^+$.

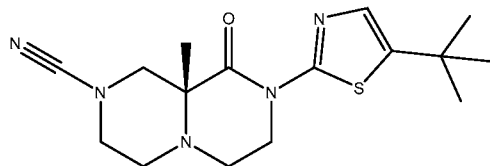
[0223] Compound 1-15S. (S)-8-(5-(tert-butyl)thiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



¹H-NMR (DMSO-d₆, 300 MHz) δ (ppm): 7.28 (s, 1H), 4.15-4.09 (m, 1H), 3.93-3.86 (m, 1H), 3.34-3.23 (m, 5H), 3.00-2.96 (m, 1H), 2.92-2.83 (m, 1H), 2.73-2.67 (m, 1H), 1.40 (s, 3H), 1.34 (s, 9H).

LCMS (ES, m/z): 334 [M+H]⁺.

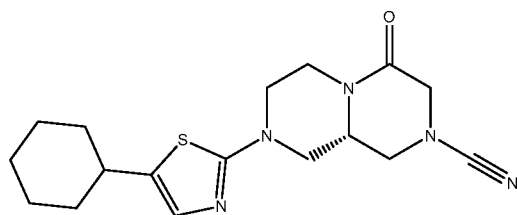
[0224] Compound 1-15R. (R)-8-(5-(tert-butyl)thiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



¹H-NMR (DMSO-d₆, 300 MHz) δ (ppm): 7.28 (s, 1H), 4.15-4.09 (m, 1H), 3.93-3.86 (m, 1H), 3.34-3.23 (m, 5H), 2.99-2.96 (m, 1H), 2.92-2.83 (m, 1H), 2.73-2.67 (m, 1H), 1.40 (s, 3H), 1.34 (s, 9H).

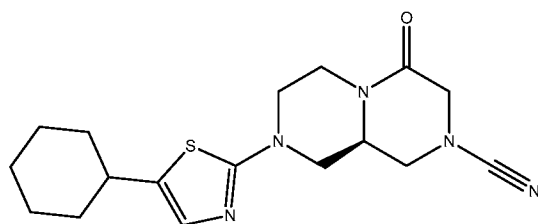
LCMS (ES, m/z): 334 [M+H]⁺.

[0225] Compound 3-1R. (R)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



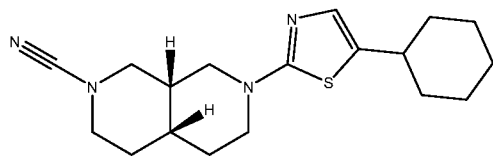
¹H-NMR (DMSO-d₆, 300 MHz) δ (ppm): 6.89 (s, 1H), 4.46-4.43 (m, 1H), 3.98-3.89 (m, 3H), 3.82-3.77 (m, 3H), 2.95-2.80 (m, 3H), 2.72-2.67 (m, 1H), 1.93-1.89 (m, 2H), 1.74-1.71 (m, 2H), 1.67-1.64 (m, 1H), 1.38-1.14 (m, 6H). LCMS (ES, m/z): 346 [M+H]⁺.

[0226] Compound 3-1S. (S)-8-(5-cyclohexylthiazol-2-yl)-4-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



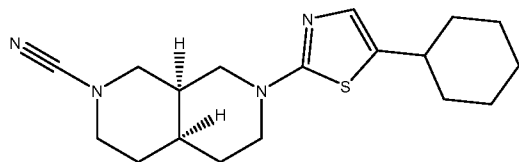
¹H-NMR (DMSO-d₆, 300 MHz) δ (ppm): 6.89 (s, 1H), 4.46-4.43 (m, 1H), 3.97-3.89 (m, 3H), 3.84-3.77 (m, 3H), 2.95-2.80 (m, 3H), 2.72-2.67 (m, 1H), 1.93-1.89 (m, 2H), 1.74-1.71 (m, 2H), 1.67-1.64 (m, 1H), 1.40-1.12 (m, 6H). LCMS (ES, m/z): 346 [M+H]⁺.

[0227] Compound 4-1S,R. (4aS,8aR)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile



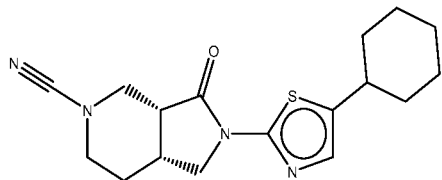
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 6.81 (s, 1H), 3.49-3.19 (m, 4H), 3.09-3.07 (m, 1H), 2.68-2.63 (m, 1H), 2.09-2.07 (m, 3H), 1.98-1.90 (m, 4H), 1.84-1.70 (m, 4H), 1.69-1.52 (m, 3H), 1.38-1.12 (m, 5H). LCMS (ES, m/z): 331 $[\text{M}+\text{H}]^+$.

[0228] Compound 4-1R,S. (4aR,8aS)-7-(5-cyclohexylthiazol-2-yl)octahydro-2,7-naphthyridine-2(1H)-carbonitrile



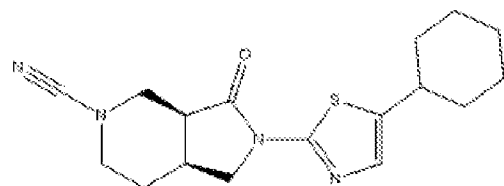
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 6.81 (s, 1H), 3.48-3.39 (m, 3H), 3.38-3.19 (m, 4H), 3.09-3.07 (m, 1H), 2.68-2.63 (m, 1H), 2.08-1.88 (m, 4H), 1.87-1.72 (m, 4H), 1.70-1.56 (m, 3H), 1.36-1.28 (m, 4H), 1.27-1.17 (m, 1H). LCMS (ES, m/z): 331 $[\text{M}+\text{H}]^+$.

[0229] Compound 5-1R,R. (3aR,7aR)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.22 (s, 1H), 3.95-3.93 (m, 1H), 3.78-3.75 (m, 1H), 3.66-3.62 (m, 1H), 3.40-3.38 (m, 1H), 3.36-3.26 (m, 1H), 3.04-3.01 (m, 2H), 2.85-2.81 (m, 1H), 2.66-2.62 (m, 1H), 1.98-1.85 (m, 3H), 1.83-1.67 (m, 3H), 1.47-1.31 (m, 5H), 1.30-1.19 (m, 1H). LCMS (ES, m/z): 331 $[\text{M}+\text{H}]^+$.

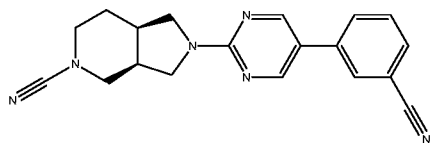
[0230] Compound 5-1S,S. (3aS,7aS)-2-(5-cyclohexylthiazol-2-yl)-3-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.22 (s, 1H), 3.95-3.93 (m, 1H), 3.78-3.75 (m, 1H), 3.66-3.62 (m, 1H), 3.40-3.38 (m, 1H), 3.35-3.26 (m, 1H), 3.04-3.01 (m, 2H), 2.85-2.81 (m, 1H), 2.66-2.62

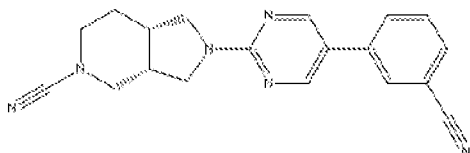
(m, 1H), 1.98-1.85 (m, 3H), 1.83-1.67 (m, 3H), 1.47-1.31 (m, 5H), 1.30-1.19 (m, 1H). LCMS (ES, m/z): 331 [M+H]⁺.

[0231] Compound 5-2R,R. (3aR,7aR)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile



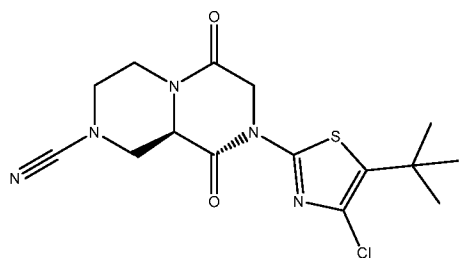
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 8.79 (s, 2H), 8.18 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 3.69-3.61 (m, 2H), 3.59-3.48 (m, 2H), 3.42-3.28 (m, 2H), 3.26-3.21 (m, 1H), 3.15-3.10 (m, 1H), 2.52-2.50 (m, 1H), 2.46-2.42 (m, 1H), 1.83-1.76 (m, 1H), 1.57-1.54 (m, 1H). LCMS (ES, m/z): 331 [M+H]⁺.

[0232] Compound 5-2S,S. (3aS,7aS)-2-(5-(3-cyanophenyl)pyrimidin-2-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carbonitrile



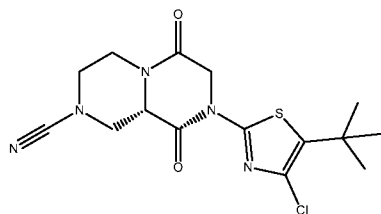
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 8.79 (s, 2H), 8.18 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 3.69-3.61 (m, 2H), 3.59-3.48 (m, 2H), 3.41-3.28 (m, 2H), 3.26-3.21 (m, 1H), 3.15-3.09 (m, 1H), 2.52-2.50 (m, 1H), 2.46-2.41 (m, 1H), 1.83-1.76 (m, 1H), 1.58-1.53 (m, 1H). LCMS (ES, m/z): 331 [M+H]⁺.

[0233] Compound 6-1R. (R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



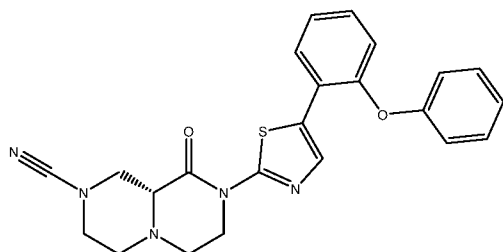
¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 4.63 (dd, J = 11.2, 3.6 Hz, 1H), 4.59-4.49 (m, 2H), 4.45-4.38 (m, 1H), 3.73 (dd, J = 12.4, 3.2 Hz, 1H), 3.52-3.49 (m, 1H), 3.39-3.34 (m, 1H), 3.13-3.09 (m, 1H), 2.92-2.87 (m, 1H), 1.43 (s, 9H). LCMS (ES, m/z): 368, 370 [M+H]⁺.

[0234] Compound 6-1S. (S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-6,9-dioxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



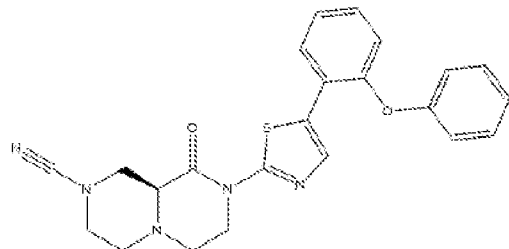
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 4.63 (dd, $J = 11.2, 3.6$ Hz, 1H), 4.59-4.49 (m, 2H), 4.45-4.38 (m, 1H), 3.73 (dd, $J = 12.4, 3.2$ Hz, 1H), 3.52-3.49 (m, 1H), 3.39-3.34 (m, 1H), 3.13-3.09 (m, 1H), 2.92-2.87 (m, 1H), 1.43 (s, 9H). LCMS (ES, m/z): 368, 370 $[\text{M}+\text{H}]^+$.

[0235] **Compound 1-113S. $^*(\text{S})$ -9-oxo-8-(5-(2-phenoxypyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



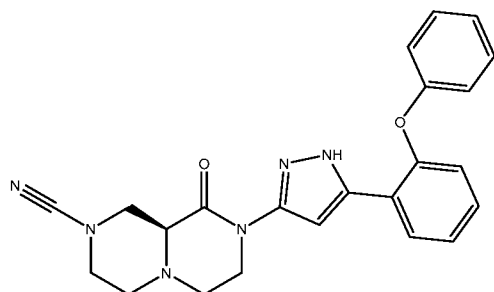
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.09 (s, 1H), 7.91 (d, $J = 6.8$ Hz, 1H), 7.42-7.33 (m, 3H), 7.26 (t, $J = 7.2$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.01-6.99 (m, 3H), 4.28-4.24 (m, 1H), 3.88-3.81 (m, 1H), 3.73-3.70 (m, 1H), 3.42-3.36 (m, 1H), 3.25-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.80-2.76. LCMS (ES, m/z): 432 $[\text{M}+\text{H}]^+$.

[0236] **Compound 1-113R. $^*(\text{R})$ -9-oxo-8-(5-(2-phenoxypyphenyl)thiazol-2-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



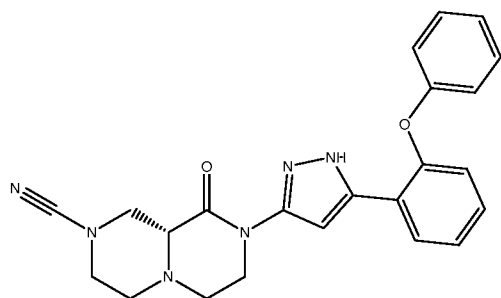
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.10 (s, 1H), 7.92 (d, $J = 6.8$ Hz, 1H), 7.42-7.34 (m, 3H), 7.26 (t, $J = 7.2$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.01-6.99 (m, 3H), 4.28-4.24 (m, 1H), 3.88-3.81 (m, 1H), 3.73-3.70 (m, 1H), 3.50-3.48 (m, 1H), 3.35-3.10 (m, 4H), 2.95-2.92 (m, 1H), 2.80-2.76 (m, 1H), 2.48-2.38 (m, 1H). LCMS (ES, m/z): 432 $[\text{M}+\text{H}]^+$.

[0237] **Compound 1-114S. (S) -9-oxo-8-(5-(2-phenoxypyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



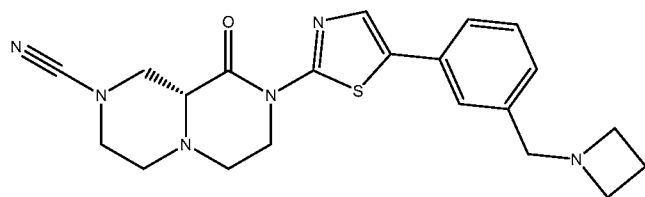
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 12.97 (br s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.41-7.36 (m, 3H), 7.27 (t, J = 7.2 Hz, 1H), 7.16-7.10 (m, 2H), 7.01-6.96 (m, 3H), 3.3.96-3.93 (m, 1H), 3.77-3.66 (m, 2H), 3.20-3.19 (m, 1H), 3.17-3.01 (m, 3H), 2.92-2.89 (m, 1H), 2.70-2.67 (m, 1H), 2.39-2.33 (m, 2H). LCMS (ES, m/z): 415 $[\text{M}+\text{H}]^+$.

[0238] Compound 1-114R. (R)-9-oxo-8-(5-(2-phenoxyphenyl)-1H-pyrazol-3-yl)octahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



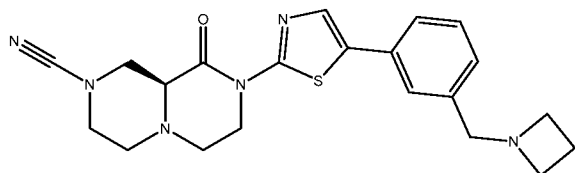
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 12.97 (br s, 1H), 7.80 (d, J = 6.8 Hz, 1H), 7.41-7.36 (m, 3H), 7.27 (t, J = 7.2 Hz, 1H), 7.16-7.11 (m, 2H), 7.01-6.96 (m, 3H), 3.96-3.92 (m, 1H), 3.76-3.66 (m, 2H), 3.38-3.34 (m, 1H), 3.20-3.19 (m, 1H), 3.17-3.03 (m, 3H), 2.92-2.89 (m, 1H), 2.70-2.67 (m, 1H), 2.38-2.33 (m, 1H). LCMS (ES, m/z): 415 $[\text{M}+\text{H}]^+$.

[0239] Compound 1-115R. (R)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



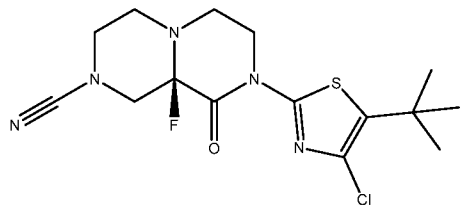
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.97 (s, 1H), 7.52-7.50 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 4.30-4.26 (m, 1H), 3.90-3.85 (m, 1H), 3.76-3.73 (m, 1H), 3.55 (s, 2H), 3.28-3.21 (m, 2H), 3.17-3.13 (m, 7H), 2.97-2.94 (m, 1H), 2.84-2.78 (m, 1H), 2.51-2.41 (m, 1H), 2.02-1.98 (m, 2H). LCMS (ES, m/z): 409 $[\text{M}+\text{H}]^+$.

[0240] **Compound 1-115S. (S)-8-(5-(3-(azetidin-1-ylmethyl)phenyl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



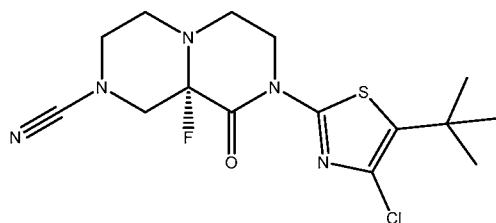
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.98 (s, 1H), 7.52-7.51 (m, 2H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 1H), 4.30-4.27 (m, 1H), 3.90-3.85 (m, 1H), 3.76-3.73 (m, 1H), 3.56 (s, 2H), 3.31-3.21 (m, 2H), 3.17-3.13 (m, 7H), 2.97-2.94 (m, 1H), 2.84-2.78 (m, 1H), 2.51-2.43 (m, 1H), 2.02-1.98 (m, 2H). LCMS (ES, m/z): 409 $[\text{M}+\text{H}]^+$.

[0241] **Compound 1-116R. (R)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



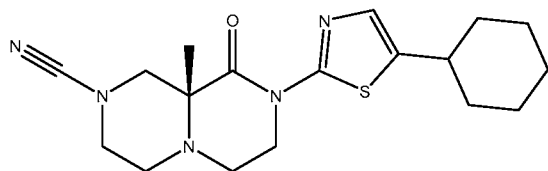
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 3.50-3.40 (m, 1H), 3.38-3.31 (m, 2H), 3.28-3.15 (m, 4H), 3.05-3.01 (m, 1H), 2.82-2.80 (m, 1H), 2.67-2.65 (m, 1H), 1.32 (s, 9H). LCMS (ES, m/z): 372, 374 $[\text{M}+\text{H}]^+$.

[0242] **Compound 1-116S. (S)-8-(5-(tert-butyl)-4-chlorothiazol-2-yl)-9a-fluoro-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



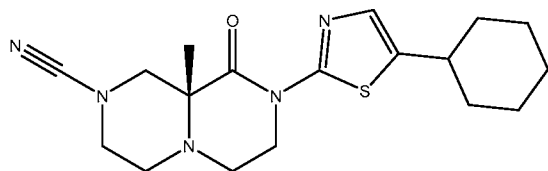
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 3.48-3.44 (m, 1H), 3.34-3.26 (m, 2H), 3.25-3.12 (m, 3H), 3.05-3.02 (m, 1H), 2.84-2.81 (m, 1H), 2.73-2.70 (m, 1H), 2.57-2.51 (m, 1H), 1.32 (s, 9H). LCMS (ES, m/z): 372, 374 $[\text{M}+\text{H}]^+$.

[0243] **Compound 1-117R. (R)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile**



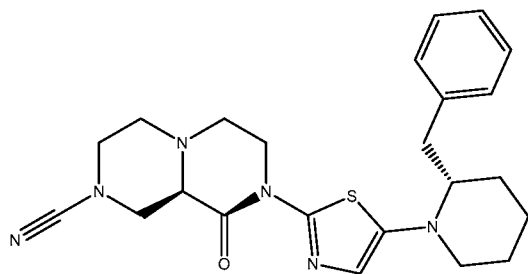
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.29 (s, 1H), 4.13-4.11 (m, 1H), 3.94-3.88 (m, 1H), 3.39-3.34 (m, 1H), 3.30-3.18 (m, 4H), 3.01-2.96 (m, 1H), 2.89-2.71 (m, 2H), 2.72-2.70 (m, 1H), 1.96-1.94 (m, 2H), 1.76-1.74 (m, 2H), 1.72-1.69 (m, 1H), 1.42-1.35 (m, 7H), 1.25-1.18 (m, 1H). LCMS (ES, m/z): 360 $[\text{M}+\text{H}]^+$.

[0244] Compound 1-117S. (S)-8-(5-cyclohexylthiazol-2-yl)-9a-methyl-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



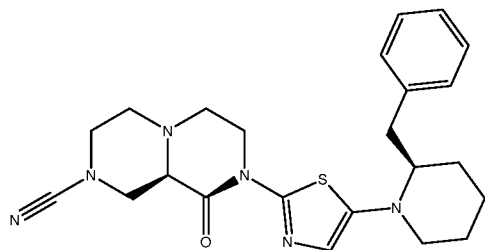
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.29 (s, 1H), 4.13-4.09 (m, 1H), 3.94-3.88 (m, 1H), 3.39-3.32 (m, 1H), 3.30-3.16 (m, 4H), 3.01-2.96 (m, 1H), 2.89-2.71 (m, 2H), 2.70-2.68 (m, 1H), 1.96-1.94 (m, 2H), 1.76-1.74 (m, 2H), 1.69-1.66 (m, 1H), 1.42-1.35 (m, 7H), 1.26-1.21 (m, 1H). LCMS (ES, m/z): 360 $[\text{M}+\text{H}]^+$.

[0245] Compound 1-118R,S. (R)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



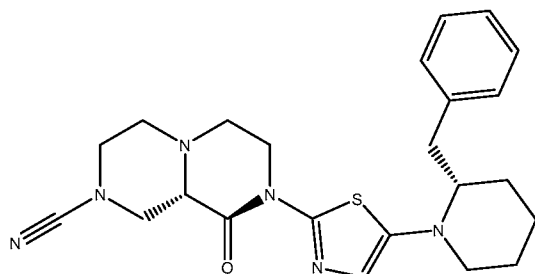
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.30-7.28 (m, 2H), 7.19-7.18 (m, 3H), 6.79 (s, 1H), 4.22-4.17 (m, 1H), 3.75-3.68 (m, 2H), 3.46-3.44 (m, 1H), 3.41-3.35 (m, 1H), 3.22-3.06 (m, 6H), 2.94-2.91 (m, 1H), 2.87-2.70 (m, 3H), 2.42-2.38 (m, 1H), 1.80-1.66 (m, 2H), 1.64-1.43 (m, 3H), 1.42-1.38 (m, 1H). LCMS (ES, m/z): 437 $[\text{M}+\text{H}]^+$.

[0246] Compound 1-118R,R. (R)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



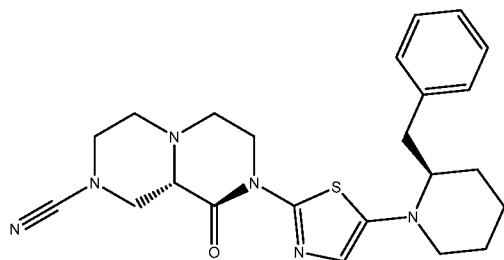
$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.30-7.28 (m, 2H), 7.19-7.17 (m, 3H), 6.79 (s, 1H), 4.14-4.12 (m, 1H), 3.81-3.70 (m, 2H), 3.45-3.42 (m, 1H), 3.40-3.35 (m, 1H), 3.22-3.06 (m, 6H), 2.94-2.91 (m, 1H), 2.87-2.70 (m, 3H), 2.42-2.38 (m, 1H), 1.78-1.66 (m, 2H), 1.64-1.43 (m, 3H), 1.42-1.38 (m, 1H). LCMS (ES, m/z): 437 $[\text{M}+\text{H}]^+$.

[0247] Compound 1-118S,S. (S)-8-(5-((S)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.32-7.28 (m, 2H), 7.21-7.17 (m, 3H), 6.79 (s, 1H), 4.14-4.12 (m, 1H), 3.80-3.69 (m, 2H), 3.43-3.40 (m, 1H), 3.39-3.35 (m, 1H), 3.23-3.04 (m, 6H), 2.94-2.91 (m, 1H), 2.88-2.70 (m, 3H), 2.42-2.38 (m, 1H), 1.78-1.66 (m, 2H), 1.64-1.43 (m, 3H), 1.42-1.38 (m, 1H). LCMS (ES, m/z): 437 $[\text{M}+\text{H}]^+$.

[0248] Compound 1-118S,R. (S)-8-(5-((R)-2-benzylpiperidin-1-yl)thiazol-2-yl)-9-oxooctahydro-2H-pyrazino[1,2-a]pyrazine-2-carbonitrile



$^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 7.32-7.28 (m, 2H), 7.21-7.17 (m, 3H), 6.79 (s, 1H), 4.14-4.12 (m, 1H), 3.80-3.69 (m, 2H), 3.43-3.40 (m, 1H), 3.39-3.35 (m, 1H), 3.23-3.04 (m, 6H), 2.94-2.91 (m, 1H), 2.88-2.70 (m, 3H), 2.42-2.38 (m, 1H), 1.78-1.66 (m, 2H), 1.64-1.43 (m, 3H), 1.42-1.38 (m, 1H). LCMS (ES, m/z): 437 $[\text{M}+\text{H}]^+$.

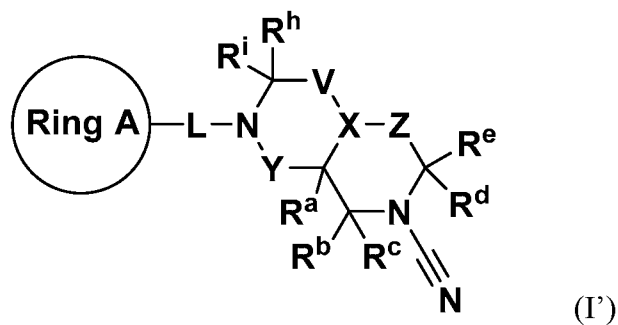
Equivalents

[0249] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. The foregoing description and Examples detail certain embodiments and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the embodiment may be practiced in many ways and should be construed in accordance with the appended claims and any equivalents thereof.

[0250] As used herein, the term “about” refers to a numeric value, including, for example, whole numbers, fractions, and percentages, whether or not explicitly indicated. The term about generally refers to a range of numerical values (e.g., +/- 5-10% of the recited range) that one of ordinary skill in the art would consider equivalent to the recited value (e.g., having the same function or result). When terms such as at least and about precede a list of numerical values or ranges, the terms modify all of the values or ranges provided in the list. In some instances, the term about may include numerical values that are rounded to the nearest significant figure.

CLAIMS

1. A compound of Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

V is selected from a bond, C(O), and CR^fR^g;

X is selected from N and CR^x;

Y is selected from a bond, C(O), and CR^jR^k;

Z is selected from C(O) and CR^jR^k;

L is -(CH₂)_n;

n is 0, 1, 2, or 3,

wherein each methylene unit of L is optionally substituted with one or two C₁-C₆ alkyl, and

wherein if n is 2 or 3, then one methylene unit of L is optionally replaced with a heteroatom selected from nitrogen, oxygen, and sulfur;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, -OR, -NR₂, -CN, -SR, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₆ cycloalkyl, or optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

or R^b and R^c, or R^d and R^e, or R^f and R^g, or R^h and Rⁱ, or R^j and R^k, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₆ cycloalkyl or an optionally substituted 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

wherein an optionally substituted R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x group may be substituted with one or more R¹;

Ring A is selected from C₃-C₁₃ cycloalkyl, 3- to 13-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, C₁₀ aryl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, optionally substituted C₁₀ aryl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from oxo, halogen, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, -(CH₂)_m(C₃-C₁₀cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), -(CH₂)_m(phenyl), -(CH₂)_m(C₁₀aryl), and -(CH₂)_m(5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur);

each R is independently selected from hydrogen, C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

each R' is independently selected from C₁-C₆ aliphatic, C₁-C₆ haloaliphatic, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur; and

each m is independently 0, 1, or 2.

2. The compound of claim 1, wherein: Y is selected from C(O) and CR^jR^k;

n is 0, 1, or 2,

wherein each methylene unit of L is optionally substituted with one C₁-C₆ alkyl, and

wherein if n is 2, then one methylene unit of L is optionally replaced with an oxygen;

each occurrence of R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x is independently selected from hydrogen, halogen, and C₁-C₆ alkyl;

Ring A is selected from C₃-C₁₀ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, -OR, -CN, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_m(C₃-C₁₀cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(C₆aryl);

each R is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, and phenyl; and

each m is independently 0 or 1.

3. The compound of claim 1 or 2, wherein:

Y is selected from C(O) and CR^jR^k;

n is 0;

R^a is selected from hydrogen, halogen, and C₁-C₆ alkyl;

R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen;

Ring A is 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(C₆aryl);

each R is phenyl; and

each m is 1.

4. The compound of any one of claims 1-3, wherein:

V is selected from C(O) and CR^fR^g;

X is N;

Y is C(O);

n is 0;

R^a is hydrogen;

R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^x are each hydrogen;

Ring A is 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein Ring A is optionally substituted with one or more W;

each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl, wherein an optionally substituted W group may be substituted with one or more R^l;

each R^l is independently selected from halogen, -OR, -CN, and -(CH₂)_m(phenyl);

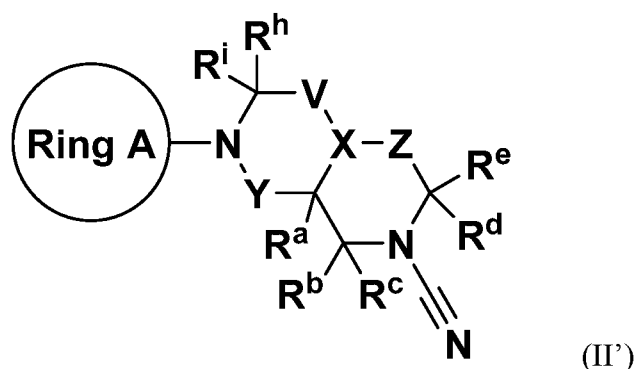
each R is phenyl; and

each m is 1.

5. The compound of any one of claims 1-4, wherein L is selected from -(CH₂)₀-, -CH₂-, -CH₂CH₂-, -CH₂CH(CH₃)-, and -CH₂CH(CH₃)O-.

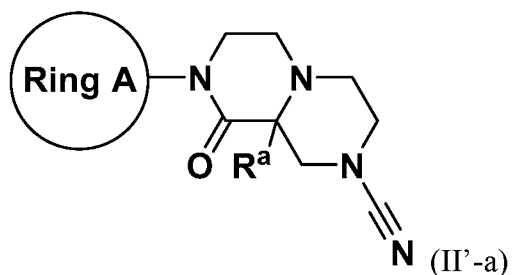
6. The compound of any one of claims 1-5, wherein n is 0.

7. The compound of any one of claims 1-6, wherein the compound is of formula (II'):



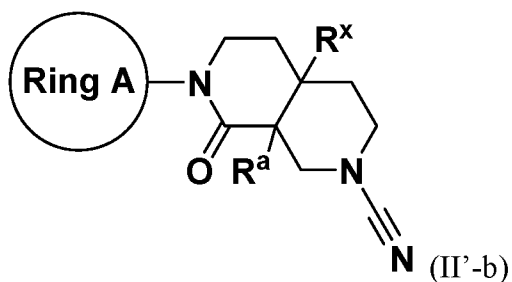
or a pharmaceutically acceptable salt thereof.

8. The compound of any one of claims 1-7, wherein the compound is of formula (II'-a):



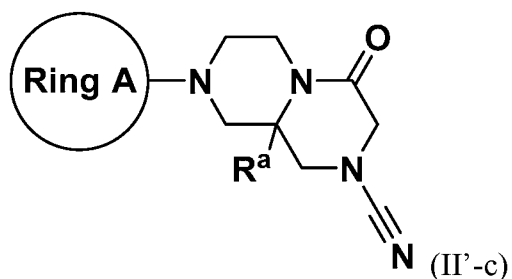
or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-7, wherein the compound is of formula (II'-b):



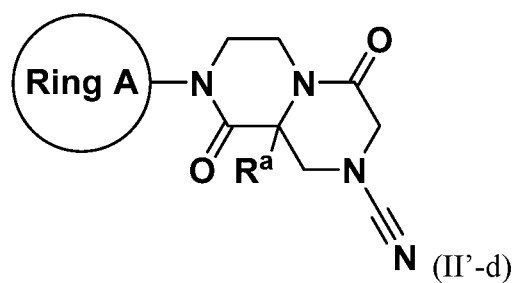
or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims 1-7, wherein the compound is of formula (II'-c):



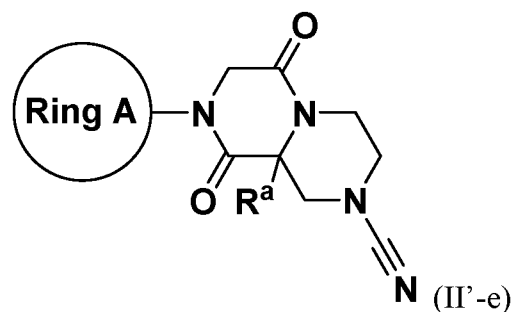
or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1-7, wherein the compound is of formula (II'-d):



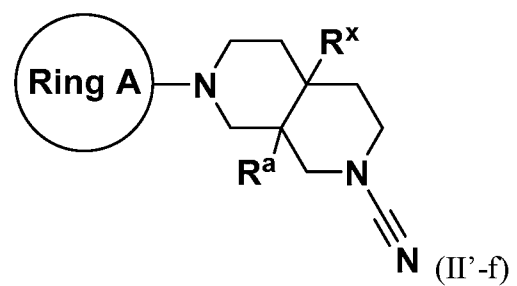
or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-7, wherein the compound is of formula (II'-e):



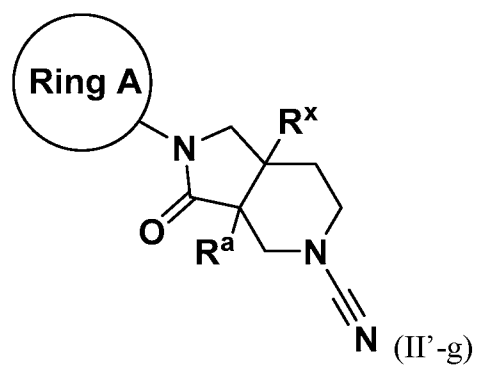
or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-7, wherein the compound is of formula (II'-f):



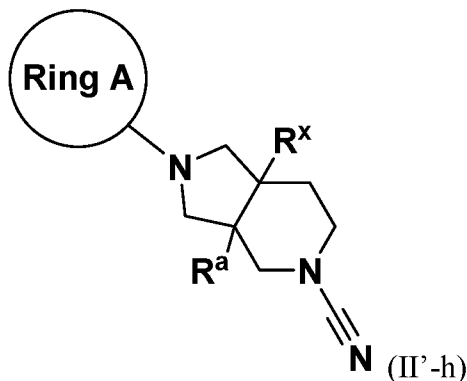
or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-7, wherein the compound is of formula (II'-g):



or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1-7, wherein the compound is of formula (II'-h):



or a pharmaceutically acceptable salt thereof.

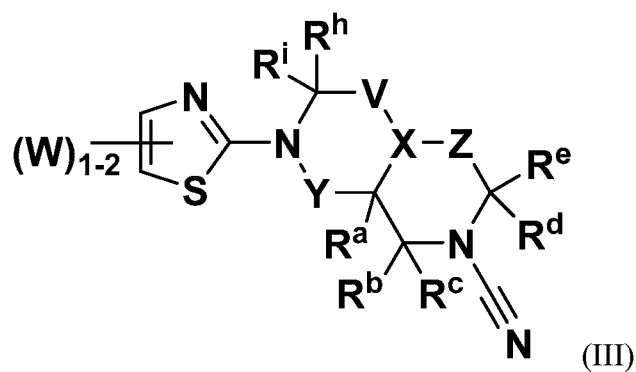
16. The compound of any one of claims 1, 2, and 5-15, wherein Ring A is selected from C₃-C₁₀ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, phenyl, and 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, wherein Ring A is optionally substituted with one or more W.

17. The compound of any one of claims 1-3 and 5-16, wherein Ring A is optionally substituted 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

18. The compound of any one of claims 1-17, wherein Ring A is optionally substituted 5-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

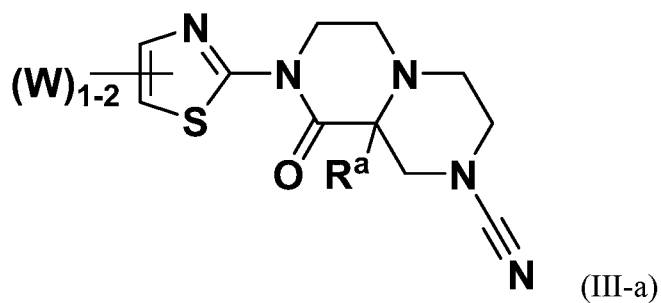
19. The compound of any one of claims 1-18, wherein Ring A is optionally substituted thiazolyl or pyrazolyl.

20. The compound of any one of claims 1-19, wherein the compound is of formula (III):



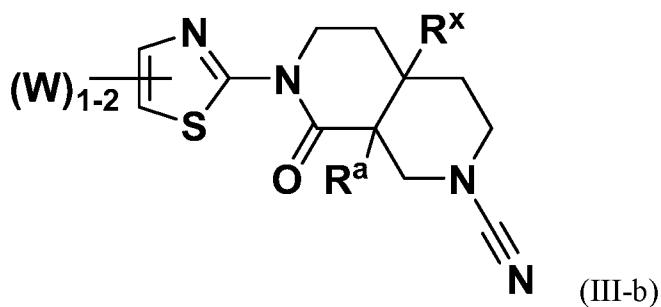
or a pharmaceutically acceptable salt thereof.

21. The compound of any one of claims 1-8 and 16-20, wherein the compound is of formula (III-a):



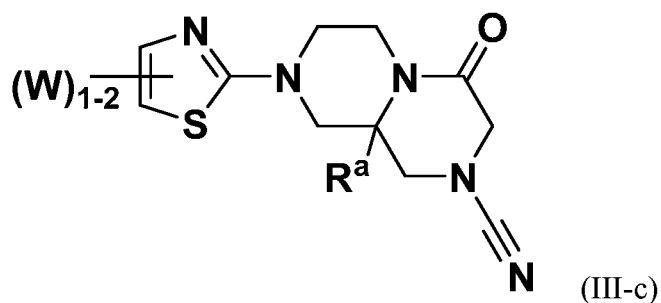
or a pharmaceutically acceptable salt thereof.

22. The compound of any one of claims 1-7, 9, and 16-20, wherein the compound is of formula (III-b):



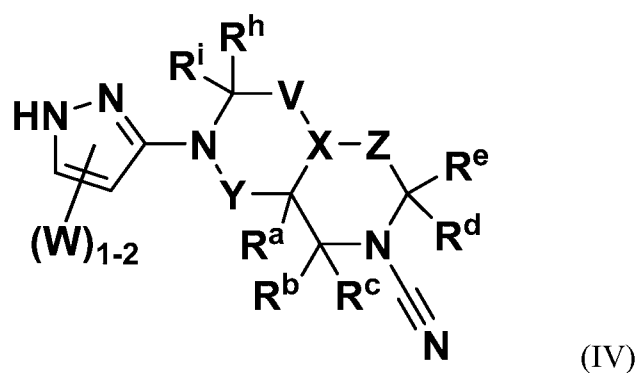
or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 1-7, 10, and 16-20, wherein the compound is of formula (III-c):



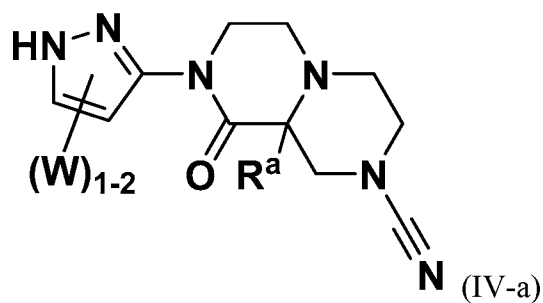
or a pharmaceutically acceptable salt thereof.

24. The compound of any one of claims 1-19, wherein the compound is of formula (IV):



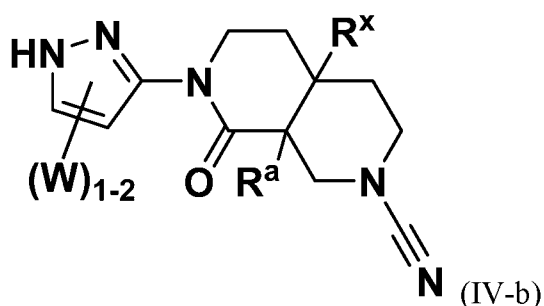
or a pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 1-8, 16-20, and 24 wherein the compound is of formula (IV-a):



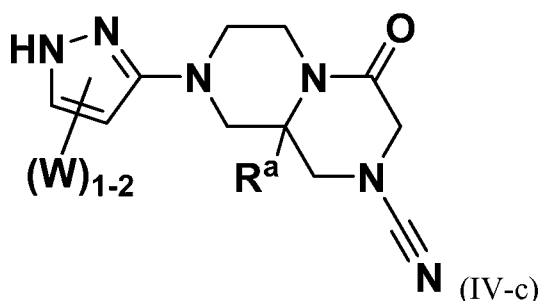
or a pharmaceutically acceptable salt thereof.

26. The compound of any one of claims 1-7, 9, 16-20, and 24 wherein the compound is of formula (IV-b):



or a pharmaceutically acceptable salt thereof.

27. The compound of any one of claims 1-7, 10, 16-20, and 24, wherein the compound is of formula (IV-c):



or a pharmaceutically acceptable salt thereof.

28. The compound of any one of claims 1, 2, and 5-28, wherein each occurrence of R^a , R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x is independently selected from hydrogen, halogen, and C_1 - C_6 alkyl.

29. The compound of any one of claims 1-3 and 5-28, wherein R^a is selected from hydrogen, halogen, and C_1 - C_6 alkyl.

30. The compound of any one of claims 1-29, wherein each occurrence of R^b , R^c , R^d , R^e , R^f , R^g , R^h , R^i , R^j , R^k , and R^x are each hydrogen.

31. The compound of any one of claims 1-30, wherein R^a is hydrogen.

32. The compound of any one of claims 1, 2, and 5-31, wherein each W is independently selected from halogen, -OR, -CN, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms

selected from nitrogen, oxygen, and sulfur, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur.

33. The compound of any one of claims 1-32, wherein each W is independently selected from halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl.

34. The compound of any one of claims 1-33, wherein each W is independently selected from halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, optionally substituted 5- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and optionally substituted phenyl.

35. The compound of any one of claims 1-34, wherein each W is independently selected from chloro, tert-butyl, cyclohexyl, 2-benzylpiperidinyl, phenyl, 3-cyanophenyl, 3-chlorophenyl, 2-phenoxyphenyl, and 3-(azetidin-1-ylmethyl)phenyl.

36. The compound of any one of claims 1, 2, and 5-35, wherein each R¹ is independently selected from halogen, -OR, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_m(C₃-C₁₀ cycloalkyl), -(CH₂)_m(3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl).

37. The compound of any one of claims 1-3 and 5-36, wherein each R¹ is independently selected from halogen, -OR, -CN, -(CH₂)_m(3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur), and -(CH₂)_m(phenyl).

38. The compound of any one of claims 1-37, wherein each R¹ is independently halogen, -OR, -CN, and -(CH₂)_m(phenyl).

39. The compound of any one of claims 1, 2, and 5-38, wherein each R is independently selected from hydrogen, C₁-C₆ alkyl, and phenyl.

40. The compound of any one of claims 1-39, wherein each R is phenyl.
41. The compound of any one of claims 1 and 5-40, wherein each R' is C₁-C₆ alkyl.
42. The compound of any one of claims 1, 2, and 5-41, wherein each m is 0 or 1.
43. The compound of any one of claims 1-42, wherein each m is 1.
44. A compound selected from Table B, or a pharmaceutically acceptable salt thereof.
45. A compound selected from Table C, or a pharmaceutically acceptable salt thereof.
46. A pharmaceutical composition comprising the compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
47. A method of inhibiting USP30 in a human, comprising administering the compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 46.
48. A method of treating a disease, disorder, or condition associated with USP30, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 46.
49. A method of treating a neurodegenerative or neurologic disease, disorder, or condition, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 46.
50. A method of treating a disease, disorder, or condition associated with mitochondrial dysfunction, comprising administering to a patient in need thereof a therapeutically effective amount

of the compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 46.

51. The method of any one of claims 48-50, wherein the disease, disorder, or condition is Parkinson's disease.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/032619

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D487/04 A61P25/28 A61K31/4985
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2018/134352 A1 (LEO PHARMA AS [DK]) 26 July 2018 (2018-07-26) claims 1,12,16; examples 1-3,21-23,28,29 -----	1-3,5-7, 13,15, 16, 28-30,46
A	WO 2016/156816 A1 (MISSION THERAPEUTICS LTD [GB]) 6 October 2016 (2016-10-06) claim 1 -----	1-51
A	WO 2017/103614 A1 (MISSION THERAPEUTICS LTD [GB]) 22 June 2017 (2017-06-22) claim 1 -----	1-51
A	WO 2018/060742 A1 (MISSION THERAPEUTICS LTD [GB]) 5 April 2018 (2018-04-05) claim 1 -----	1-51



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 July 2019

Date of mailing of the international search report

16/07/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/032619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018134352	A1	26-07-2018	NONE
WO 2016156816	A1	06-10-2016	AU 2016240033 A1 09-11-2017 BR 112017020900 A2 10-07-2018 CA 2976741 A1 06-10-2016 CN 107484415 A 15-12-2017 CO 2017011172 A2 16-01-2018 EP 3277677 A1 07-02-2018 JP 2018510183 A 12-04-2018 KR 20170131654 A 29-11-2017 RU 2017134901 A 30-04-2019 SG 11201706542T A 30-10-2017 US 2018086708 A1 29-03-2018 WO 2016156816 A1 06-10-2016
WO 2017103614	A1	22-06-2017	AU 2016373533 A1 05-07-2018 BR 112018007208 A2 16-10-2018 CA 3008747 A1 22-06-2017 CN 108368089 A 03-08-2018 CO 2018006299 A2 10-07-2018 EP 3390391 A1 24-10-2018 JP 2019504009 A 14-02-2019 KR 20180095625 A 27-08-2018 SG 11201804934P A 30-07-2018 WO 2017103614 A1 22-06-2017
WO 2018060742	A1	05-04-2018	CN 109790169 A 21-05-2019 WO 2018060742 A1 05-04-2018