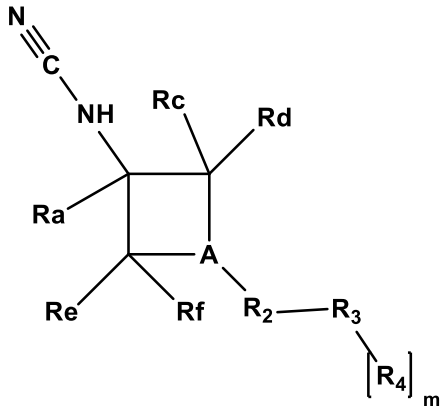
(Nakamura, et al., Mol Biol Cell. **2008**, 19(5), 1903-1911; Bingol, et al., Nature 2014, 510(7505):370-5). Therefore, inhibition of USP30 could present a novel treatment paradigm for PD, by promoting mitochondrial turnover.

[0009] USP30 inhibition could also benefit patients with other indications which involve mitochondria function, including but not limited to, neurodegenerative diseases, motor neuron diseases, metabolic disorders, , cardio-vascular diseases, psychiatric diseases, osteoarthritis, and cancer. For example, mitochondria play a central role in apoptotic cell death. The key event in this process is BAX/BAK-dependent mitochondrial outer-membrane permeabilization. USP30 regulates BAX/BAK-dependent apoptosis, and its depletion sensitizes cancer cells to ABT-737, a BCL-2 inhibitor/BH3-mimetic (Liang, et al., EMBO reports **2015**, 16, 618-627). These studies suggest a utility for a USP30 inhibitor in anti-cancer therapy.

[0010] There remains a need for USP30 inhibitor compounds. Such compounds would be useful, for example, in the development of new therapies for Parkinson's disease.

SUMMARY

[0010a] In a first aspect of the present disclosure, there is provided a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

A is N or CR_b;

R_a is selected from the group consisting of hydrogen and (C_1-C_6) alkyl;

R_b is selected from the group consisting of hydrogen, halogen, OH, (C_1-C_6) alkyl optionally substituted with one or more R_5, and (C_1-C_6) alkoxy optionally substituted with one or more R_5; or

R_b and X together form a (C_3-C_6) spirocyclic cycloalkyl or (C_3-C_6) spirocyclic heterocycloalkyl;

each of R_c, R_d, R_e and R_f is independently selected from the group consisting of hydrogen, halogen, -OR_5 and (C_1-C_6) alkyl optionally substituted with one or more R_5;

R_2 is selected from the group consisting of C(O)N(X) and N(X)C(O);

X is independently chosen from hydrogen, alkyl, and heteroalkyl, wherein the alkyl and heteroalkyl can optionally cyclize with R_b or R_3;

R_3 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) heteroalkyl, aryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups, and heteroaryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups;

R_4 is independently chosen from alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, cycloalkoxy, heteroalkoxy, haloalkoxy, carboxyalkyl, heterocarboxyalkyl, cyclic, heterocyclic, aryl, and heteroaryl, wherein any rings are optionally substituted with 1 or 2 Y groups;

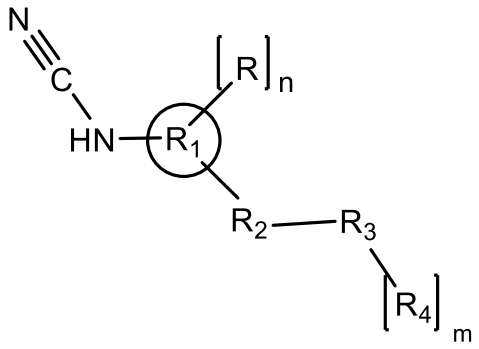
R_5 is selected from the group consisting of hydrogen, halogen, OH, (C_1-C_3) alkyl, and (C_1-C_3) alkoxy;

R is independently chosen from hydrogen, OH, CN, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, (C_3-C_6) cycloalkyl, (C_3-C_6) heterocycloalkyl, (C_3-C_6) cycloalkyloxy, and (C_1-C_6) alkoxyalkyl;

Y is independently chosen from hydrogen, OH, CN, $N(X)_2$, (C_1-C_6) alkyl, (C_1-C_6) heteroalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, (C_3-C_6) cycloalkyl, (C_3-C_6) heterocycloalkyl, (C_5-C_8) aryl, (C_4-C_8) heteroaryl, and (C_4-C_8) heteroaryl substituted with (C_1-C_3) alkyl; and

m is 0, 1, or 2.

[0010b] In another aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is independently chosen from hydrogen, OH, CN, (C_1-C_6) alkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, and (C_3-C_6) heterocycloalkyl groups;

n is 0, 1, or 2;

wherein, if n is 2, the R groups can combine to form a fused ring system with R_1;

R_1 is chosen from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and pyrrolidine;

R_2 is chosen from amides, reverse amides, and ureas;

X is independently chosen from hydrogen, alkyl groups, and heteroalkyl groups, wherein the alkyl and heteroalkyl groups can optionally cyclize with R, R_1, or R_3 or with another X group when multiple X groups are present;

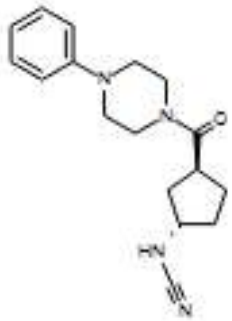
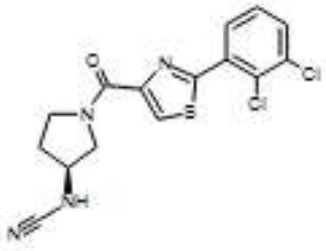
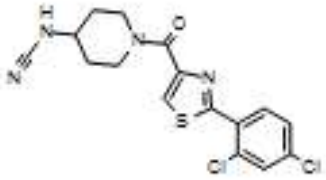
R_3 is chosen from hydrogen, halogens, alkyl groups, heteroalkyl groups, haloalkyl groups, alkoxy groups, heteroalkoxy groups, haloalkoxy groups, carbonylalkyl groups, carbonylheteroalkyl groups, cyclic groups, heterocyclic groups, aryl groups, and heteroaryl groups, wherein any rings are optionally substituted with 1 or 2 R groups;

R_4 is independently chosen from alkyl groups, heteroalkyl groups, haloalkyl groups, alkoxy groups, cycloalkoxy groups, heteroalkoxy groups, haloalkoxy groups, carboxyalkyl groups, heterocarboxyalkyl groups, cyclic groups, heterocyclic groups, aryl groups and heteroaryl groups, wherein any rings are optionally substituted with 1 or 2 Y groups;

Y is independently chosen from hydrogen, OH, CN, $N(X)_2$, (C_1-C_6) alkyl groups, (C_1-C_6) heteroalkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, (C_3-C_6) heterocycloalkyl groups, (C_5-C_8) aryl groups, and (C_4-C_8) heteroaryl groups; and

m is 0, 1, or 2.

[0010c] In yet another aspect of the present disclosure, there is provided a compound selected from:

Compound 12-6		{[(1S,3S)-3-(4-phenylpiperazine-1-carbonyl)cyclopentyl]amino}carbonitrile;
Compound 12-8		{[(3S)-1-[2-(2,3-dichlorophenyl)-1,3-thiazole-4-carbonyl]pyrrolidin-3-yl]amino}carbonitrile; and
Compound 12-9		({1-[2-(2,4-dichlorophenyl)-1,3-thiazole-4-carbonyl]piperidin-4-yl}amino)carbonitrile

or a pharmaceutically acceptable salt thereof.

[0010d] In a further aspect of the present disclosure, there is provided a composition comprising the compound as disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0010e] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in a method of:

(a) treating a neurodegenerative disease; or

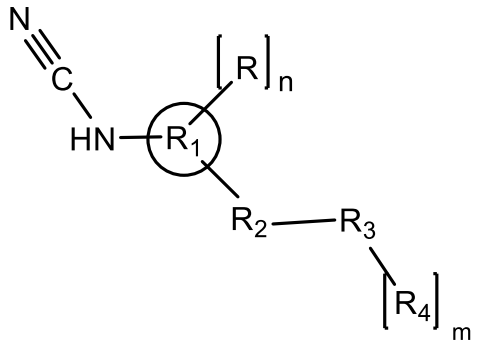
(b) inhibiting USP30 in a patient.

[0010f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for:

(a) treating a neurodegenerative disease; or

(b) inhibiting USP30 in a patient.

[0011] The present disclosure provides compounds of Formula (Ia):



(Ia)

and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein:

R is independently chosen from hydrogen, OH, CN, (C_1-C_6) alkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, and (C_3-C_6) heterocycloalkyl groups;

n is 0, 1, or 2;

wherein, if n is 2, the R groups can combine to form a fused ring system with R_1;

Y is independently chosen from hydrogen, OH, CN, $N(X)_2$, (C_1-C_6) alkyl groups, (C_1-C_6) heteroalkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, (C_3-C_6) heterocycloalkyl groups, (C_5-C_8) aryl groups, and (C_4-C_8) heteroaryl groups; and

m is 0, 1, or 2.

[0017] Another example of the present disclosure relates to a method of treating a disease or disorder associated with inhibition of Ubiquitin Specific Peptidase 30 (USP30). The method comprises administering to a patient in need of a treatment for diseases or disorders associated with inhibition of USP30 an effective amount of at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0018] Another example of the disclosure is directed to a method of inhibiting USP30. The method involves administering to a patient in need thereof an effective amount of at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0019] Another example of the disclosure relates to a method of treating neurodegenerative diseases. The method comprises administering to a patient in need thereof an effective amount of at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0020] Preferably the compounds of the disclosure are for use in a method of treating Parkinson's disease, wherein the method comprises administering to a patient in need therof an effective amount of at least one chemical entity of the disclosure or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof

[0021] Another example of the disclosure is directed to pharmaceutical compositions comprising at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0022] Another example of the present disclosure relates to at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, for use in the manufacture of a medicament for treating a disease associated with inhibiting USP30.

[0023] Another example of the present disclosure relates to the use of at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, in the treatment of a disease associated with inhibiting USP30.

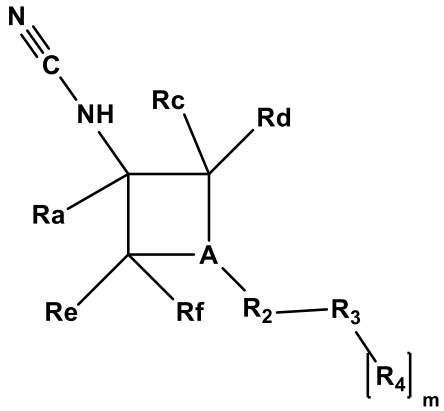
[0024] As summarized above, and as set forth in detail below, the present disclosure relates to chemical entities and compositions that are capable of inhibiting the activity of USP30. The disclosure also relates to methods of treating, preventing or ameliorating a disease or disorder in which USP30 plays a role by administering to a patient in need thereof a therapeutically effective amount of at least one chemical entity chosen from compounds of Formula (I), and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof. The methods of the present disclosure can be used in the treatment of a variety of USP30 dependent diseases and disorders by inhibiting the activity of USP30. Inhibition of USP30 as disclosed herein provides a novel approach to the treatment, prevention, or amelioration of diseases including, but not limited to, cancer.

DETAILED DESCRIPTION

[0025] The present disclosure describes compounds that inhibit USP30. Compounds that inhibit USP30 are useful in the development of novel therapies for the treatment of diseases or disorders associated with USP30 enzymes, such as the treatment of mitochondrial dysfunction diseases or disorders, neurodegenerative diseases, and in the treatment of cancer. Specifically, the present disclosure is concerned with chemical entities and compositions inhibiting USP30, methods of treating diseases or disorders associated with USP30, and methods of synthesis of these compounds. In some embodiments the compounds of the invention are USP30 inhibitors having an IC_{50} value of <10 μM and > 0.001 μM when tested in the Biochemical Assay of Example A herein. Preferably, the compounds of the invention are USP30 inhibitors having an IC_{50} value of <1 μM and > 0.001 μM when tested in the Biochemical Assay of Example A herein.

Claims:

1. A compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

A is N or CR_b;

R_a is selected from the group consisting of hydrogen and (C_1-C_6) alkyl;

R_b is selected from the group consisting of hydrogen, halogen, OH, (C_1-C_6) alkyl optionally substituted with one or more R_5, and (C_1-C_6) alkoxy optionally substituted with one or more R_5; or

R_b and X together form a (C_3-C_6) spirocyclic cycloalkyl or (C_3-C_6) spirocyclic heterocycloalkyl;

each of R_c, R_d, R_e and R_f is independently selected from the group consisting of hydrogen, halogen, -OR_5 and (C_1-C_6) alkyl optionally substituted with one or more R_5;

R_2 is selected from the group consisting of C(O)N(X) and N(X)C(O);

X is independently chosen from hydrogen, alkyl, and heteroalkyl, wherein the alkyl and heteroalkyl can optionally cyclize with R_b or R_3;

R_3 is selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) heteroalkyl, aryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups, and heteroaryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups;

R_4 is independently chosen from alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, cycloalkoxy, heteroalkoxy, haloalkoxy, carboxyalkyl, heterocarboxyalkyl, cyclic, heterocyclic, aryl, and heteroaryl, wherein any rings are optionally substituted with 1 or 2 Y groups;

R_5 is selected from the group consisting of hydrogen, halogen, OH, (C_1-C_3) alkyl, and (C_1-C_3) alkoxy;

R is independently chosen from hydrogen, OH, CN, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, (C_3-C_6) cycloalkyl, (C_3-C_6) heterocycloalkyl, (C_3-C_6) cycloalkyloxy, and (C_1-C_6) alkoxyalkyl;

Y is independently chosen from hydrogen, OH, CN, $N(X)_2$, (C_1-C_6) alkyl, (C_1-C_6) heteroalkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, (C_3-C_6) cycloalkyl, (C_3-C_6) heterocycloalkyl, (C_5-C_8) aryl, (C_4-C_8) heteroaryl, and (C_4-C_8) heteroaryl substituted with (C_1-C_3) alkyl; and

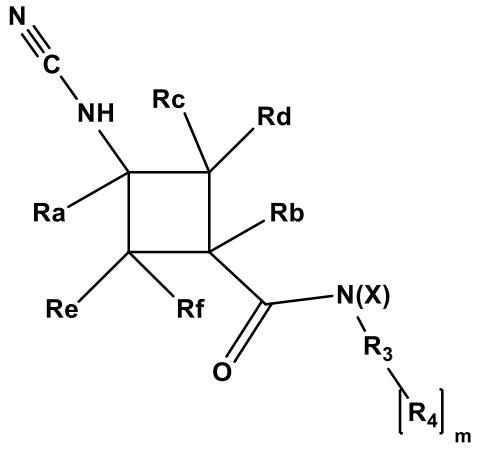
m is 0, 1, or 2.

2. The compound of claim 1, wherein each of R_c, R_d, R_e, and R_f is independently selected from the group consisting of hydrogen and (C_1-C_6) alkyl optionally substituted with one or more R_5.

3. The compound of claim 1 or claim 2, wherein R_3 is aryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups or heteroaryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups.

4. The compound of any one of claims 1 to 3, wherein R_4 is cycloalkyl optionally substituted with 1 or 2 Y groups or aryl optionally substituted with 1 or 2 Y groups.

5. The compound of claim 1, wherein the compound is of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein X is hydrogen.

7. The compound of claim 5 or claim 6, wherein each of R_c, R_d, R_e, and R_f is hydrogen.

8. The compound of any one of claims 5 to 7, wherein R_a is hydrogen.

9. The compound of any one of claims 5 to 8, wherein R_3 is:

(a) aryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups or heteroaryl having 1 to 3 aromatic rings and optionally substituted with 1 or 2 R groups; or

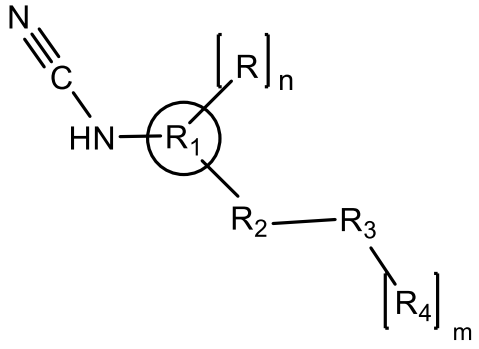
(b) heteroaryl having 1 aromatic ring containing two heteroatoms and optionally substituted with 1 or 2 R groups; or

(c) a thiazole ring.

10. The compound of any one of claims 5 to 9, wherein R_4 is a cyclic group optionally substituted with 1 or 2 Y groups or aryl optionally substituted with 1 or 2 Y groups.

11. The compound of any one of claims 5 to 10, wherein m is 0.

12. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is independently chosen from hydrogen, OH, CN, (C_1-C_6) alkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, and (C_3-C_6) heterocycloalkyl groups;

n is 0, 1, or 2;
wherein, if n is 2, the R groups can combine to form a fused ring system with R_1;

R_1 is chosen from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and pyrrolidine;

R_2 is chosen from amides, reverse amides, and ureas;

X is independently chosen from hydrogen, alkyl groups, and heteroalkyl groups, wherein the alkyl and heteroalkyl groups can optionally cyclize with R, R_1, or R_3 or with another X group when multiple X groups are present;

R_3 is chosen from hydrogen, halogens, alkyl groups, heteroalkyl groups, haloalkyl groups, alkoxy groups, heteroalkoxy groups, haloalkoxy groups, carbonylalkyl groups, carbonylheteroalkyl groups, cyclic groups, heterocyclic groups, aryl groups, and heteroaryl groups, wherein any rings are optionally substituted with 1 or 2 R groups;

R_4 is independently chosen from alkyl groups, heteroalkyl groups, haloalkyl groups, alkoxy groups, cycloalkoxy groups, heteroalkoxy groups, haloalkoxy groups, carboxyalkyl groups, heterocarboxyalkyl groups, cyclic groups, heterocyclic groups, aryl groups and heteroaryl groups, wherein any rings are optionally substituted with 1 or 2 Y groups;

Y is independently chosen from hydrogen, OH, CN, $N(X)_2$, (C_1-C_6) alkyl groups, (C_1-C_6) heteroalkyl groups, (C_1-C_6) alkoxy groups, (C_1-C_6) haloalkyl groups, (C_1-C_6) haloalkoxy groups, halogen, (C_3-C_6) cycloalkyl groups, (C_3-C_6) heterocycloalkyl groups, (C_5-C_8) aryl groups, and (C_4-C_8) heteroaryl groups; and

m is 0, 1, or 2.

13. The compound of claim 12, wherein R_2 is an amide.

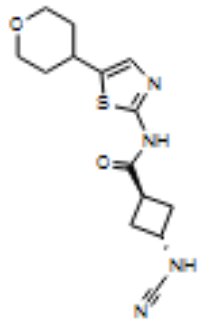
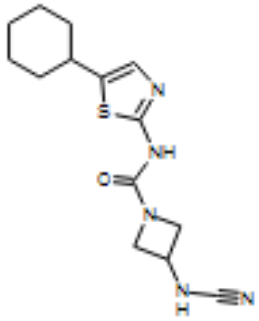
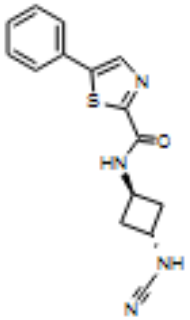
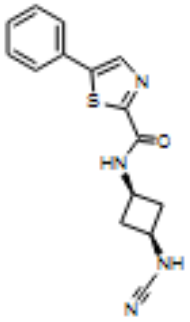
14. The compound of claim 12 or claim 13, wherein R_3 is chosen from aryl and heteroaryl rings.

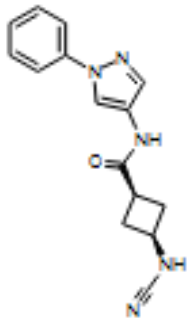
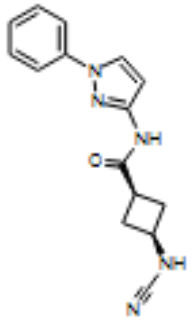
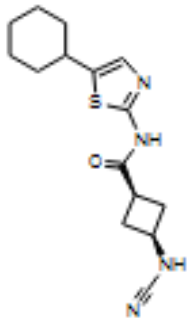
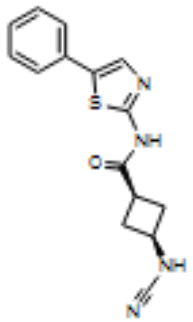
15. The compound of any one of claims 12 to 14, wherein R_4 is

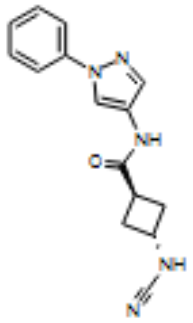
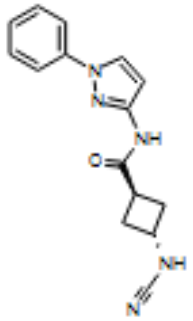
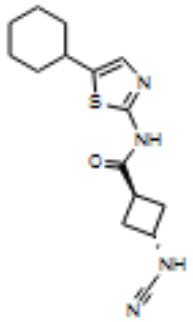
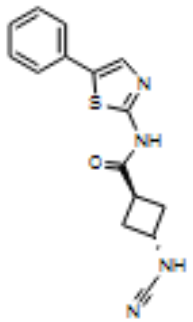
(a) chosen from cyclic and heterocyclic rings optionally substituted with 1 or 2 R; or

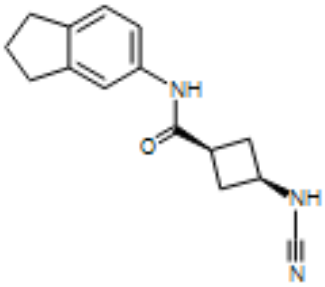
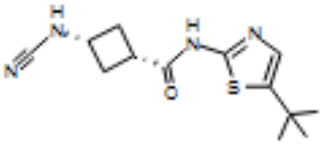
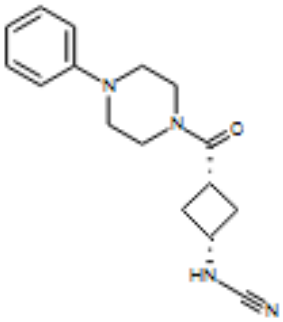
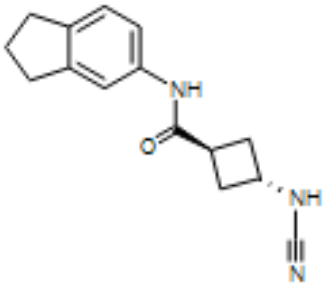
(b) chosen from aryl and heteroaryl rings optionally substituted with 1 or 2 R.

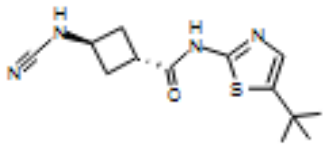
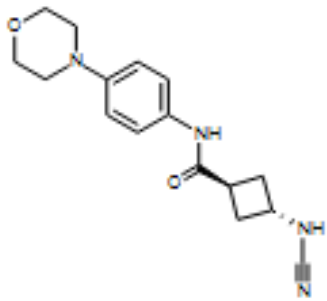
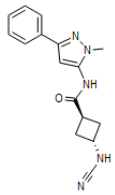
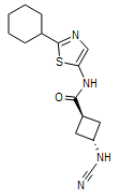
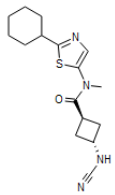
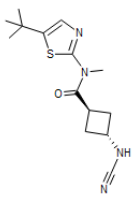
16. The compound of any preceding claim, selected from the following compounds:

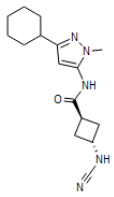
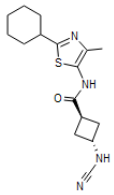
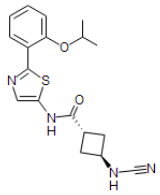
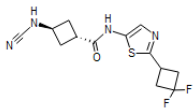
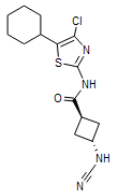
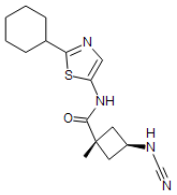
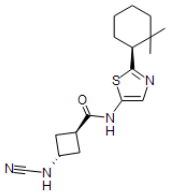
Compound 1-1		trans-3-(cyanoamino)-N-[5-(oxan-4-yl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide
Compound 2-1		3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)azetidine-1-carboxamide
Compound 3-1		5-phenyl-N-[(trans)-3-(cyanoamino)cyclobutyl]-1,3-thiazole-2-carboxamide
Compound 4-1		5-phenyl-N-[(cis)-3-(cyanoamino)cyclobutyl]-1,3-thiazole-2-carboxamide

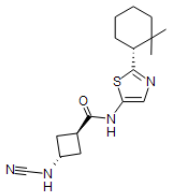
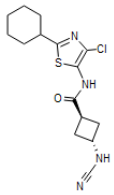
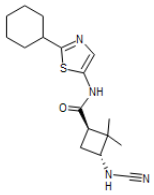
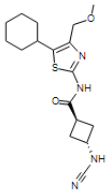
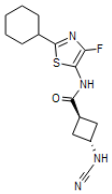
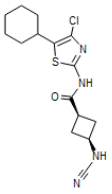
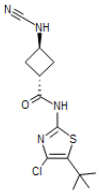
Compound 5-1		cis-3-(cyanoamino)-N-(1-phenyl-1H-pyrazol-4-yl)cyclobutane-1-carboxamide
Compound 5-2		cis-3-(cyanoamino)-N-(1-phenyl-1H-pyrazol-3-yl)cyclobutane-1-carboxamide
Compound 5-3		cis-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide
Compound 5-4		cis-3-(cyanoamino)-N-(5-phenyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide

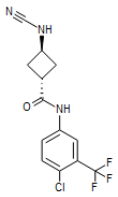
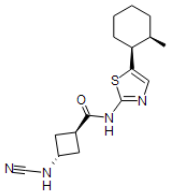
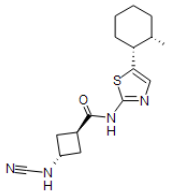
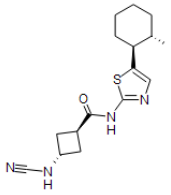
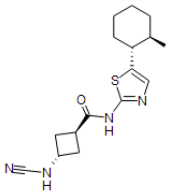
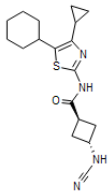
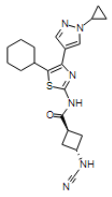
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Compound 5-6		trans-3-(cyanoamino)-N-(1-phenyl-1H-pyrazol-3-yl)cyclobutane-1-carboxamide
Compound 5-7		trans-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide
Compound 5-8		trans-3-(cyanoamino)-N-(5-phenyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide

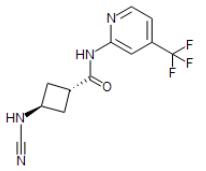
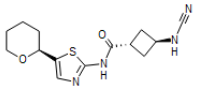
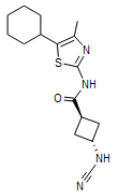
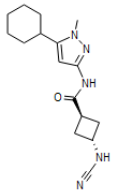
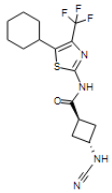
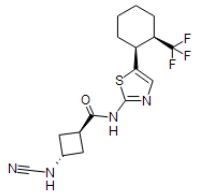
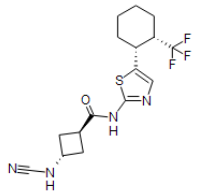
Compound 5-9		cis-3-(cyanoamino)-N-(2,3-dihydro-1H-inden-5-yl)cyclobutane-1-carboxamide
Compound 5-10		cis-N-(5-tert-butyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide
Compound 5-11		{[cis-3-(4-phenylpiperazine-1-carbonyl)cyclobutyl]amino}carbonitrile
Compound 5-12		trans-3-(cyanoamino)-N-(2,3-dihydro-1H-inden-5-yl)cyclobutane-1-carboxamide

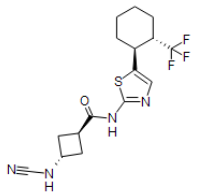
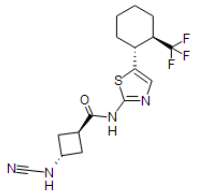
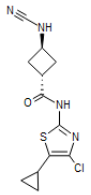
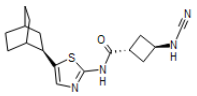
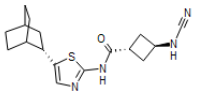
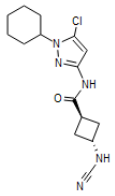
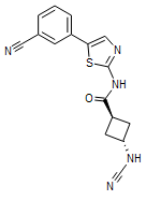
Compound 5-13		trans-N-(5-tert-butyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide
Compound 5-14		trans-3-(cyanoamino)-N-[4-(morpholin-4-yl)phenyl]cyclobutane-1-carboxamide
Compound 1-2		(1r,3r)-3-(cyanoamino)-N-(1-methyl-3-phenyl-1H-pyrazol-5-yl)cyclobutane-1-carboxamide;
Compound 1-3		(1r,3r)-3-(cyanoamino)-N-(2-cyclohexyl-1,3-thiazol-5-yl)cyclobutane-1-carboxamide;
Compound 1-4		(1r,3r)-3-(cyanoamino)-N-(2-cyclohexyl-1,3-thiazol-5-yl)-N-methylcyclobutane-1-carboxamide;
Compound 1-5		(1r,3r)-N-(5-tert-butyl-1,3-thiazol-2-yl)-3-(cyanoamino)-N-methylcyclobutane-1-carboxamide;

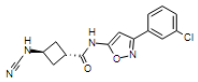
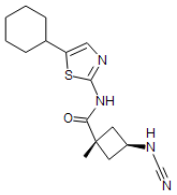
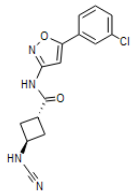
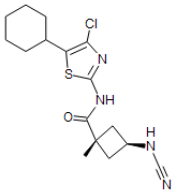
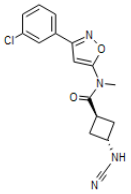
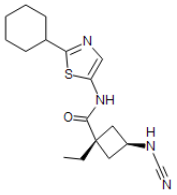
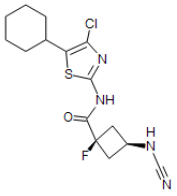
Compound 1-6		(1r,3r)-3-(cyanoamino)-N-(3-cyclohexyl-1-methyl-1H-pyrazol-5-yl)cyclobutane-1-carboxamide;
Compound 1-7		(1r,3r)-3-(cyanoamino)-N-(2-cyclohexyl-4-methyl-1,3-thiazol-5-yl)cyclobutane-1-carboxamide;
Compound 1-8		(1r,3r)-3-(cyanoamino)-N-{2-[2-(propan-2-yloxy)phenyl]-1,3-thiazol-5-yl}cyclobutane-1-carboxamide;
Compound 1-9		(1r,3r)-3-(cyanoamino)-N-[2-(3,3-difluorocyclobutyl)-1,3-thiazol-5-yl]cyclobutane-1-carboxamide;
Compound 1-10		(1r,3r)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-11		(1r,3s)-3-(cyanoamino)-N-(2-cyclohexyl-1,3-thiazol-5-yl)-1-methylcyclobutane-1-carboxamide;
Compound 1-12		(1r,3r)-3-(cyanoamino)-N-{2-[(1S)-2,2-dimethylcyclohexyl]-1,3-thiazol-5-yl}cyclobutane-1-carboxamide;

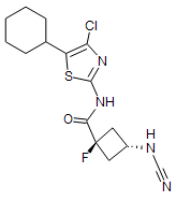
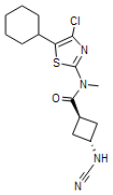
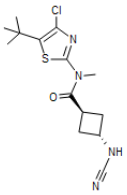
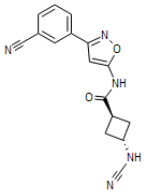
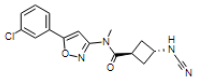
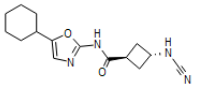
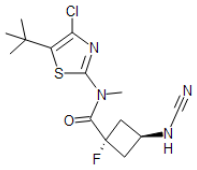
Compound 1-13		(1r,3r)-3-(cyanoamino)-N-{2-[(1R)-2,2-dimethylcyclohexyl]-1,3-thiazol-5-yl}cyclobutane-1-carboxamide;
Compound 1-14		(1r,3r)-N-(4-chloro-2-cyclohexyl-1,3-thiazol-5-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-15		(1R,3R)-3-(cyanoamino)-N-(2-cyclohexyl-1,3-thiazol-5-yl)-2,2-dimethylcyclobutane-1-carboxamide;
Compound 1-16		(1r,3r)-3-(cyanoamino)-N-[5-cyclohexyl-4-(methoxymethyl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide;
Compound 1-17		(1r,3r)-3-(cyanoamino)-N-(2-cyclohexyl-4-fluoro-1,3-thiazol-5-yl)cyclobutane-1-carboxamide;
Compound 1-18		(1s,3s)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-19		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;

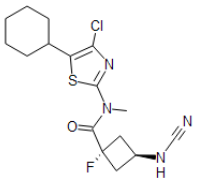
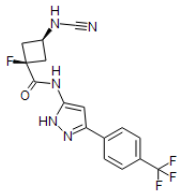
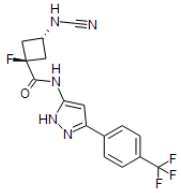
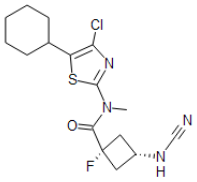
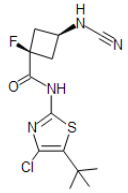
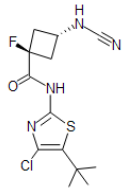
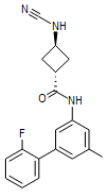
Compound 1-20		(1r,3r)-N-[4-chloro-3-(trifluoromethyl)phenyl]-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-21		(1r,3r)-3-(cyanoamino)-N-{5-[(1S,2R)-2-methylcyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-22		(1r,3r)-3-(cyanoamino)-N-{5-[(1R,2S)-2-methylcyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-23		(1r,3r)-3-(cyanoamino)-N-{5-[(1S,2S)-2-methylcyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-24		(1r,3r)-3-(cyanoamino)-N-{5-[(1R,2R)-2-methylcyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-25		(1r,3r)-3-(cyanoamino)-N-(5-cyclohexyl-4-cyclopropyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide;
Compound 1-26		(1r,3r)-3-(cyanoamino)-N-[5-cyclohexyl-4-(1-cyclopropyl-1H-pyrazol-4-yl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide;

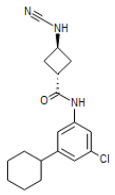
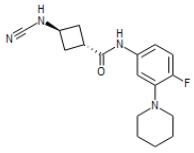
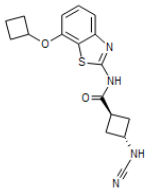
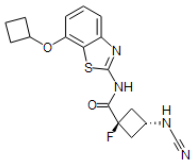
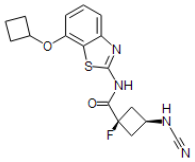
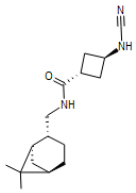
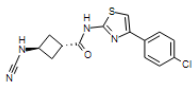
Compound 1-27		(1r,3r)-3-(cyanoamino)-N-[4-(trifluoromethyl)pyridin-2-yl]cyclobutane-1-carboxamide;
Compound 1-28		(1r,3r)-3-(cyanoamino)-N-{5-[(2S)-oxan-2-yl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-29		(1r,3r)-3-(cyanoamino)-N-(5-cyclohexyl-4-methyl-1,3-thiazol-2-yl)cyclobutane-1-carboxamide;
Compound 1-30		(1r,3r)-3-(cyanoamino)-N-(5-cyclohexyl-1-methyl-1H-pyrazol-3-yl)cyclobutane-1-carboxamide;
Compound 1-31		(1r,3r)-3-(cyanoamino)-N-[5-cyclohexyl-4-(trifluoromethyl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide;
Compound 1-32		(1r,3r)-3-(cyanoamino)-N-{5-[(1S,2R)-2-(trifluoromethyl)cyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-33		(1r,3r)-3-(cyanoamino)-N-{5-[(1R,2S)-2-(trifluoromethyl)cyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;

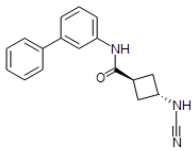
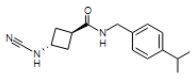
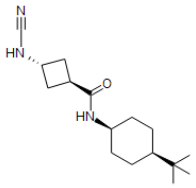
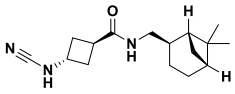
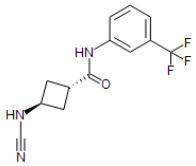
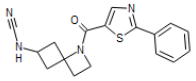
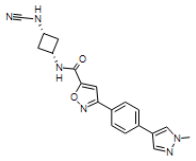
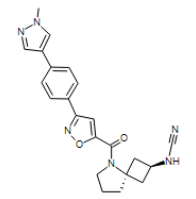
Compound 1-34		(1r,3r)-3-(cyanoamino)-N-{5-[(1S,2S)-2-(trifluoromethyl)cyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-35		(1r,3r)-3-(cyanoamino)-N-{5-[(1R,2R)-2-(trifluoromethyl)cyclohexyl]-1,3-thiazol-2-yl}cyclobutane-1-carboxamide;
Compound 1-36		(1r,3r)-N-(4-chloro-5-cyclopropyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-37		(1r,3r)-N-{5-[(2R)-bicyclo[2.2.2]octan-2-yl]-1,3-thiazol-2-yl}-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-38		(1r,3r)-N-{5-[(2S)-bicyclo[2.2.2]octan-2-yl]-1,3-thiazol-2-yl}-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-39		(1r,3r)-N-(5-chloro-1-cyclohexyl-1H-pyrazol-3-yl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-40		(1r,3r)-3-(cyanoamino)-N-[5-(3-cyanophenyl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide;

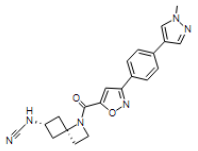
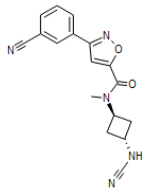
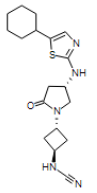
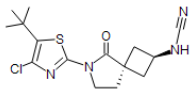
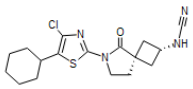
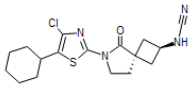
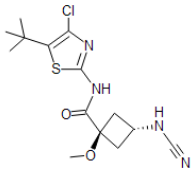
Compound 1-41		(1r,3r)-N-[3-(3-chlorophenyl)-1,2-oxazol-5-yl]-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-42		(1r,3s)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)-1-methylcyclobutane-1-carboxamide;
Compound 1-43		(1r,3r)-N-[5-(3-chlorophenyl)-1,2-oxazol-3-yl]-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-44		(1r,3s)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-1-methylcyclobutane-1-carboxamide;
Compound 1-45		(1r,3r)-N-[3-(3-chlorophenyl)-1,2-oxazol-5-yl]-3-(cyanoamino)-N-methylcyclobutane-1-carboxamide;
Compound 1-46		(1r,3s)-3-(cyanoamino)-N-(2-cyclohexyl-1,3-thiazol-5-yl)-1-ethylcyclobutane-1-carboxamide;
Compound 1-47		(1s,3s)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluorocyclobutane-1-carboxamide;

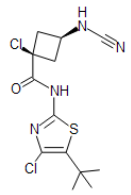
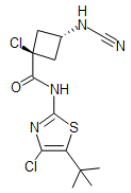
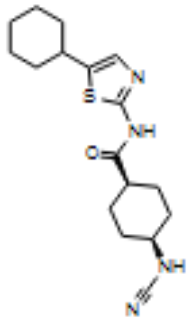
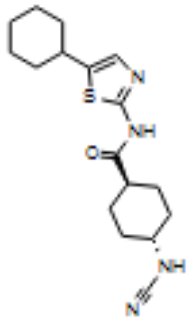
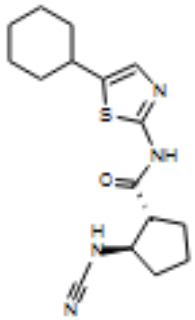
Compound 1-48		(1r,3r)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluorocyclobutane-1-carboxamide;
Compound 1-49		(1r,3r)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-N-methylcyclobutane-1-carboxamide;
Compound 1-50		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)-N-methylcyclobutane-1-carboxamide;
Compound 1-51		(1r,3r)-3-(cyanoamino)-N-[3-(3-cyanophenyl)-1,2-oxazol-5-yl]cyclobutane-1-carboxamide;
Compound 1-52		(1r,3r)-N-[5-(3-chlorophenyl)-1,2-oxazol-3-yl]-3-(cyanoamino)-N-methylcyclobutane-1-carboxamide;
Compound 1-53		(1r,3r)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-oxazol-2-yl)cyclobutane-1-carboxamide;
Compound 1-54		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluoro-N-methylcyclobutane-1-carboxamide;

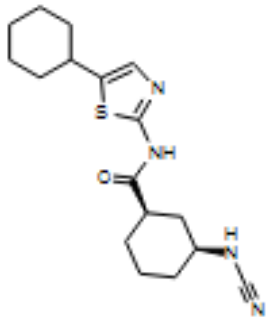
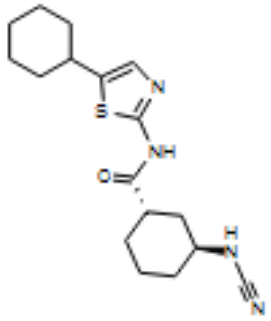
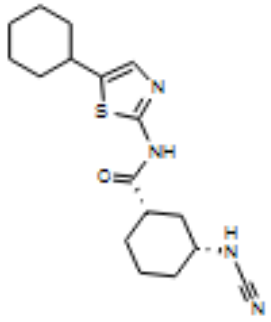
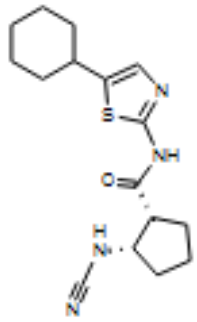
Compound 1-55		(1r,3r)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluoro-N-methylcyclobutane-1-carboxamide;
Compound 1-56		(1s,3s)-3-(cyanoamino)-1-fluoro-N-{3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}cyclobutane-1-carboxamide;
Compound 1-57		(1r,3r)-3-(cyanoamino)-1-fluoro-N-{3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}cyclobutane-1-carboxamide;
Compound 1-58		(1s,3s)-N-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluoro-N-methylcyclobutane-1-carboxamide;
Compound 1-59		(1s,3s)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluorocyclobutane-1-carboxamide;
Compound 1-60		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)-1-fluorocyclobutane-1-carboxamide;
Compound 1-61		(1r,3r)-3-(cyanoamino)-N-[3-(2-fluorophenyl)-5-methylphenyl]cyclobutane-1-carboxamide;

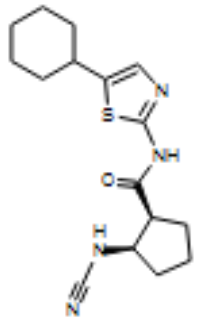
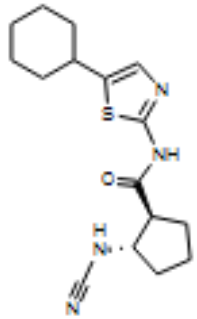
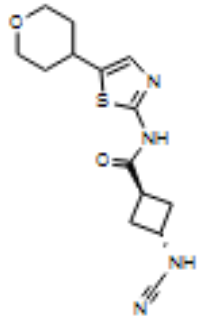
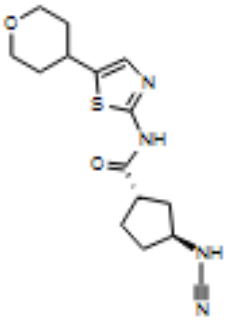
Compound 1-62		(1r,3r)-N-(3-chloro-5-cyclohexylphenyl)-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 1-63		(1r,3r)-3-(cyanoamino)-N-[4-fluoro-3-(piperidin-1-yl)phenyl]cyclobutane-1-carboxamide;
Compound 1-64		(1r,3r)-3-(cyanoamino)-N-(7-cyclobutoxy-1,3-benzothiazol-2-yl)cyclobutane-1-carboxamide;
Compound 1-65		(1r,3r)-3-(cyanoamino)-N-(7-cyclobutoxy-1,3-benzothiazol-2-yl)-1-fluorocyclobutane-1-carboxamide;
Compound 1-66		(1s,3s)-3-(cyanoamino)-N-(7-cyclobutoxy-1,3-benzothiazol-2-yl)-1-fluorocyclobutane-1-carboxamide;
Compound 1-67		(1r,3r)-3-(cyanoamino)-N-{[(1R,2R,5R)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl}cyclobutane-1-carboxamide;
Compound 1-68		(1r,3r)-N-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-3-(cyanoamino)cyclobutane-1-carboxamide;

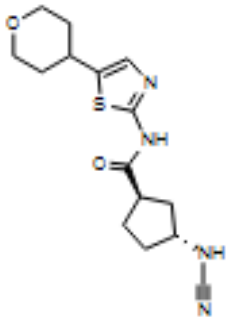
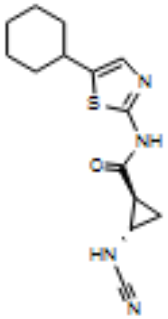
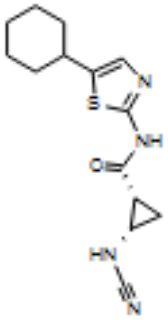
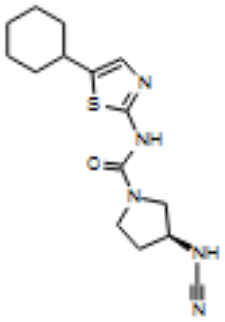
Compound 1-69		(1r,3r)-3-(cyanoamino)-N-(3-phenylphenyl)cyclobutane-1-carboxamide;
Compound 1-70		(1r,3r)-3-(cyanoamino)-N-{[4-(propan-2-yl)phenyl]methyl}cyclobutane-1-carboxamide;
Compound 1-71		(1r,3r)-3-(cyanoamino)-N-[(1s,4s)-4-tert-butylcyclohexyl]cyclobutane-1-carboxamide;
Compound 1-72		(1r,3r)-3-(cyanoamino)-N-{[(1R,2R,5R)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl}cyclobutane-1-carboxamide;
Compound 1-73		(1r,3r)-3-(cyanoamino)-N-[3-(trifluoromethyl)phenyl]cyclobutane-1-carboxamide;
Compound 3-2		{[1-(2-phenyl-1,3-thiazole-5-carbonyl)-1-azaspiro[3.3]heptan-6-yl]amino}carbonitrile;
Compound 3-3		3-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-N-[(1s,3s)-3-(cyanoamino)cyclobutyl]-1,2-oxazole-5-carboxamide;
Compound 3-4		{[(2r,4s)-5-{3-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-1,2-oxazole-5-carbonyl}-5-azaspiro[3.4]octan-2-yl]amino}carbonitrile;

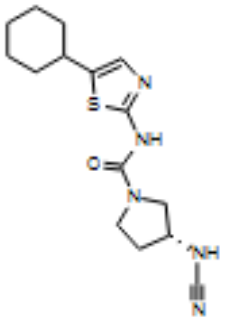
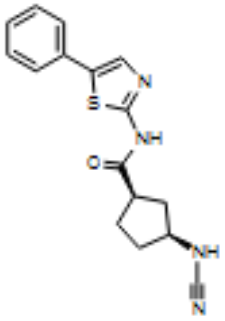
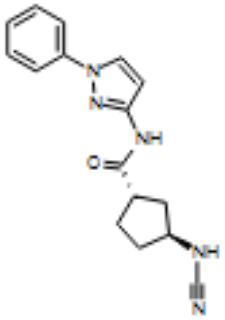
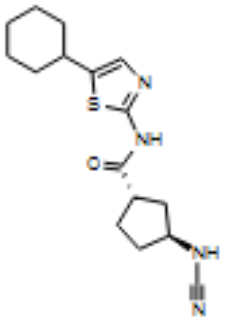
Compound 3-5		{[(4r,6s)-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-1,2-oxazole-5-carbonyl}-1-azaspiro[3.3]heptan-6-yl]amino}carbonitrile;
Compound 3-6		3-(3-cyanophenyl)-N-methyl-N-[(1r,3r)-3-(cyanoamino)cyclobutyl]-1,2-oxazole-5-carboxamide;
Compound 6-1		{[(1r,3r)-3-[(4S)-4-[(5-cyclohexyl-1,3-thiazol-2-yl)amino]-2-oxopyrrolidin-1-yl]cyclobutyl]amino}carbonitrile;
Compound 7-1		{[(2r,4s)-6-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-5-oxo-6-azaspiro[3.4]octan-2-yl]amino}carbonitrile;
Compound 7-2		{[(2s,4r)-6-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-5-oxo-6-azaspiro[3.4]octan-2-yl]amino}carbonitrile;
Compound 7-3		{[(2r,4s)-6-(4-chloro-5-cyclohexyl-1,3-thiazol-2-yl)-5-oxo-6-azaspiro[3.4]octan-2-yl]amino}carbonitrile;
Compound 8-1		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-3-(cyanoamino)-1-methoxycyclobutane-1-carboxamide;

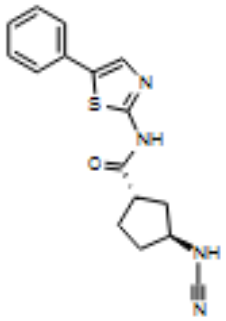
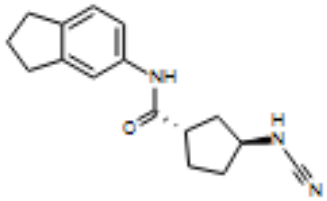
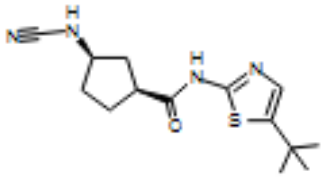
Compound 9-1		(1s,3s)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-1-chloro-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 9-2		(1r,3r)-N-(5-tert-butyl-4-chloro-1,3-thiazol-2-yl)-1-chloro-3-(cyanoamino)cyclobutane-1-carboxamide;
Compound 10-1		cis-4-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclohexane-1-carboxamide;
Compound 10-2		trans-4-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclohexane-1-carboxamide;
Compound 10-3		(1R,2R)-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;

Compound 10-4		(1R,3S)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclohexane-1-carboxamide;
Compound 10-5		(1S,3S)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclohexane-1-carboxamide;
Compound 10-6		(1S,3R)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclohexane-1-carboxamide;
Compound 10-7		(1R,2S)-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;

Compound 10-8		(1S,2R)-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;
Compound 10-9		(1S,2S)-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;
Compound 1-10		trans-3-(cyanoamino)-N-[5-(oxan-4-yl)-1,3-thiazol-2-yl]cyclobutane-1-carboxamide;
Compound 10-10		(1S,3S)-3-(cyanoamino)-N-[5-(oxan-4-yl)-1,3-thiazol-2-yl]cyclopentane-1-carboxamide;

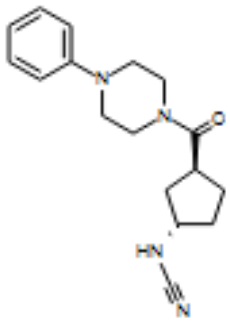
Compound 10-11		(1R,3R)-3-(cyanoamino)-N-[5-(oxan-4-yl)-1,3-thiazol-2-yl]cyclopentane-1-carboxamide;
Compound 11-1		trans-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopropane-1-carboxamide;
Compound 11-2		cis-2-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopropane-1-carboxamide;
Compound 2-2		(3S)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxamide;

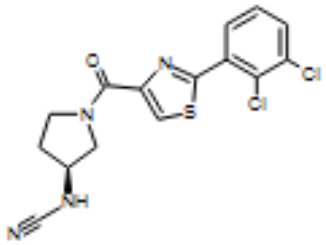
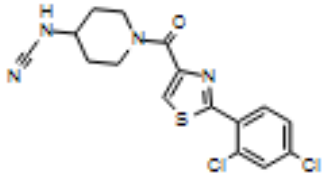
Compound 2-3		(3R)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxamide;
Compound 12-1		(1R,3S)-3-(cyanoamino)-N-(5-phenyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;
Compound 12-2		(1S,3S)-3-(cyanoamino)-N-(1-phenyl-1H-pyrazol-3-yl)cyclopentane-1-carboxamide;
Compound 12-3		(1S,3S)-3-(cyanoamino)-N-(5-cyclohexyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;

Compound 12-4		(1S,3S)-3-(cyanoamino)-N-(5-phenyl-1,3-thiazol-2-yl)cyclopentane-1-carboxamide;
Compound 12-5		(1S,3S)-3-(cyanoamino)-N-(2,3-dihydro-1H-inden-5-yl)cyclopentane-1-carboxamide;
Compound 12-7		(1S,3R)-N-(5-tert-butyl-1,3-thiazol-2-yl)-3-(cyanoamino)cyclopentane-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

17. A compound selected from:

Compound 12-6		{[(1S,3S)-3-(4-phenylpiperazine-1-carbonyl)cyclopentyl]amino}carbonitrile;

Compound 12-8		{[(3S)-1-[2-(2,3-dichlorophenyl)-1,3-thiazole-4-carbonyl]pyrrolidin-3-yl]amino}carbonitrile; and
Compound 12-9		({1-[2-(2,4-dichlorophenyl)-1,3-thiazole-4-carbonyl]piperidin-4-yl}amino)carbonitrile

or a pharmaceutically acceptable salt thereof.

18. A composition comprising the compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. A compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, for use in a method of:

(a) treating a neurodegenerative disease; or

(b) inhibiting USP30 in a patient.

20. Use of a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for:

(a) treating a neurodegenerative disease; or

(b) inhibiting USP30 in a patient.