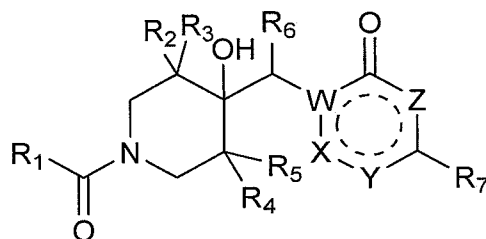


muscle wasting is also associated with other serious illnesses such as HIV/AIDS, heart failure, rheumatoid arthritis and chronic obstructive pulmonary disease (Wiles B. *et al.*, *Mol. Biol. Cell* (2015), 26, 913-923). Muscle wasting is also a prominent feature of aging. Beyond the above pathological conditions, USP19 may also have implications in the pathogenesis of degenerative diseases including but not restricted to Parkinson's disease and other prion-like transmission disorders by regulating important substrates such as α -synuclein or polyglutamine-containing proteins, Ataxin3, Huntington (He W. *et al.*, *PLoS ONE* (2016), 11, e0147515; Bieri G. *et al.*, *Neurobiol Dis.* (2017), doi: 10.1016/j.nbd.2017.03.007). The regulation of coronin 2A (CORO2A) through the activity of USP19 has been shown to affect the transcriptional repression activity of the retinoic acid receptor (RAR), suggesting that USP19 may also be involved in the regulation of RAR-mediated adipogenesis (Lim K. *et al.*, *Oncotarget* (2016), 7, 34759-34772).

The established and ever growing connections between USP19 and numerous proteins involved in human pathologies indicate that small molecule inhibitors of USP19 may have broad therapeutic applications beneficial to human health. Insofar as is known however, no inhibitors targeting USP19 have been reported and the identification of such inhibitors with drug-like potential therefore remains of prime importance and high priority.

SUMMARY

In a first aspect, the disclosure provides a compound of formula (I):



(I)

including a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, wherein:

R₁ is an optionally substituted alkyl, alkenyl, alkynyl, ether, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R₂ is H or an optionally substituted alkyl group,

R₃ is H or an optionally substituted alkyl group,

R₄ is H or an optionally substituted alkyl group,

R₅ is H or an optionally substituted alkyl group,

R₂ and R₄ may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl ring that includes the carbons to which they are attached,

R₄ and R₅ may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl ring that includes the carbon to which they are attached;

R₆ is H or an optionally substituted alkyl group;

W is C or N;

X is N or CR₈, wherein R₈ is H or optionally substituted C1-C6 alkyl,

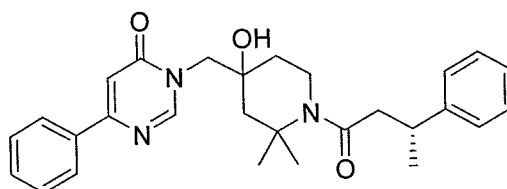
Y is N or CR₉

Z is CH, or NH,

wherein R₉ is H or optionally substituted alkyl, amido, amino, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, halo, carbonyl, ester, aminoalkyl, or cyano;

R₇ is hydrogen, halo, or an optionally substituted alkyl, alkenyl, alkynyl, amino, aryl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryl or heterocycloalkyl group;

or the compound



or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof.

In a second aspect, the disclosure provides a pharmaceutical composition comprising a compound according to the above and a pharmaceutically acceptable carrier or diluent.

USP19 has been associated with a number of diseases and conditions including (but not limited to) cancer and neoplastic conditions, as well as muscle atrophy including (but not limited to) cachexia and sarcopenia.

The compounds described herein are able to selectively inhibit USP19 activity. The compounds provided herein may therefore be suitable for the treatment and prevention of cancer and neoplastic conditions, immunological and inflammatory conditions for example by promoting

antiviral immune response, as well as for treatment and prevention of muscular atrophy, for example cachexia and sarcopenia, neurodegenerative diseases including Parkinson's disease and other prion-based disorders. The compounds may be used as monotherapy or as combination therapy with radiation and/or additional therapeutic agents.

5

Therefore, in a further aspect, the disclosure provides a compound according to the above or a pharmaceutical composition according to the above for use in therapy. The disclosure provides a compound according to the above or a pharmaceutical composition according to the above for use in a method of treating or preventing cancer. The disclosure provides a compound according to the above or a pharmaceutical composition according to the above for use in a method of treating or preventing muscular atrophy, optionally cachexia or sarcopenia. The disclosure provides a compound according to the above or a pharmaceutical composition according to the above for use in a method of treating or preventing Parkinson's Disease.

10

15 In a further aspect, the disclosure provides a compound according to the above or a pharmaceutical composition according to the above for use in a method of treating or preventing cancer, muscular atrophy or Parkinson's disease, optionally wherein the muscular atrophy is cachexia or sarcopenia.

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The disclosure provides a method of treating cancer or muscular atrophy comprising administering to a subject an effective amount of a compound according to the above or a pharmaceutical composition according to the above.

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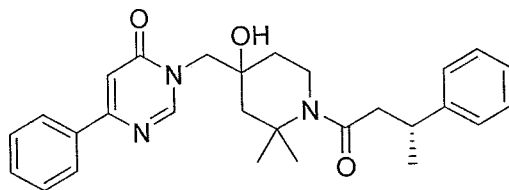
The disclosure provides a method of treating Parkinson's Disease comprising administering to a subject an effective amount of a compound according to the above or a pharmaceutical composition according to the above

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Other preferred embodiments of the compounds according to the disclosure appear throughout the specification and in particular in the examples. Particularly preferred are those named compounds having greater activity as tested. Compounds having higher activity are more preferred over those having lower activity.

35

Each aspect or embodiment as defined herein may be combined with any other aspect(s) or embodiment(s) unless clearly indicated to the contrary. In particular any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.



or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof.

5

2. A compound of claim 1, wherein R_1 is optionally substituted C1-C6 alkyl, optionally substituted C4-C10 alkylcycloalkyl, optionally substituted C7-C10 arylalkyl, optionally substituted C3-C6 cycloalkyl, or optionally substituted C3-C6 heteroaryl,

10 wherein the optional substituent is selected from C1-C6 alkyl, C2-C6 alkenyl, hydroxymethyl, methoxymethyl, benzyloxy methyl, phenyl, C3-C6 cycloalkyl, CF_3 , CHF_2 , OH, or halo.

3. A compound of claim 1 or claim 2, wherein R_1 is optionally substituted cyclohexylalkane, preferably optionally substituted cyclohexylethane; or optionally substituted alkylbenzene, preferably ethylbenzene; or optionally substituted 3,3,3-trifluoropropane,

15 wherein the optional substituent is selected from C1-C6 alkyl, C2-C6 alkenyl, hydroxymethyl, methoxymethyl, OH, or halo.

4. A compound of any one of claims 1-3 wherein R_1 is substituted and the substituent is C1-
20 C6 alkyl, optionally methyl.

5. A compound according to any one of claims 1-4, wherein R_7 is optionally substituted C6-C10 aryl, C1-C12 heteroaryl, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, amino, C1-C3 alkoxy, or halo,

25 wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C3-C6 cycloalkyl, C1-C6 heterocycloalkyl, C1-C6 alkoxy, halo-substituted C1-C6 alkoxy, amido, cyano or halo, optionally

wherein R_7 is optionally substituted phenyl, naphthalenyl, indazole, pyrimidine, thiophene, or pyrazole,

30 wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C3-C6 cycloalkyl or C1-C6 heterocycloalkyl, C1-C6 alkoxy, halo-substituted C1-C6 alkoxy, C1-C6 alkylamine, amido, cyano or halo.

6. A compound according to any one of claims 1-5, wherein R_2 , R_3 , R_4 , R_5 are independently selected from H and C1-C6 alkyl and optionally wherein R_2 and R_3 are H, and R_4 and R_5 are methyl.
- 5 7 A compound according to any one of claims 1-5 wherein R_4 and R_5 are joined to one another to form an optionally substituted C3-C6 cycloalkyl or C3-C6 heterocycloalkyl that includes the carbon to which they are attached and R_2 and R_3 are independently selected from H and C1-C6 alkyl and optionally wherein R_2 and R_3 are H and R_4 and R_5 are joined to one another to form a C3-C6 cycloalkyl that includes the carbon to which they are attached, optionally a C4 or C5 cycloalkyl that includes the carbon to which they are attached.
- 10 8. A compound according to any preceding claim wherein R_6 is H or C1-C6 alkyl.
- 15 9. A compound according to any one of claims 1-5, wherein R_2 and R_4 are joined to one another to form a C5 cycloalkyl that includes the carbons to which they are attached, and wherein R_3 , R_5 and R_6 are independently H or C1-C6 alkyl.
10. A compound according to any one of claims 1-9, wherein W is N and X is CR_8 , wherein R_8 is H or methyl.
- 20 11. A compound according to any one of claims 1-10, wherein Y is N or CR_9 , wherein R_9 is H, C1-C6 alkyl, $NR'R''$, $C(O)NR'R''$, cyano, carboxyl, halo, C1-C6 alkylamine, C3-C6 alkylester, optionally substituted C6-C10 aryl or optionally substituted C2-C6 heteroaryl, wherein the one or more heteroatoms are selected from N and O, and the one or more optional substituents of the aryl or heteroaryl are selected from C1-C6 alkyl, C1-C6 alkylamine, amido, and cyano, wherein R' and R'' are independently selected from H, C1-C6 alkyl optionally substituted with OH, C3-C7 cycloalkyl, C1-C7 heterocycloalkyl, C4-C7 alkylcycloalkyl, C3-C7 alkylheterocycloalkyl, benzyl, phenyl, and methoxy, or wherein R' and R'' are joined to one another to form a C2-C7 heterocycle that includes the N to which they are attached, wherein the heterocycle is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH_2OH -substituted, or acetyl-substituted.
- 25 30

12. A compound according to any one of claims 1-11, wherein Y is N or CR₉, wherein R₉ is phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; carboxyl; C(O)NR'R''; or NR'R'';

wherein R' and R'' are independently selected from H, C1-C6 alkyl, C3-C7 cycloalkyl, C3-C7 heterocycloalkyl wherein the heteroatom is N or O, or wherein R' and R'' are joined to one another to form a C2-C7 heterocycloalkyl that includes the N to which they are attached, wherein the heterocycloalkyl is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH₂OH-substituted, or acetyl-substituted.

10 13. A compound according to claim 1, wherein

R₁ is selected from optionally substituted ethylcyclohexane, optionally substituted ethylbenzene, and optionally substituted 3,3,3-trifluoropropane, wherein the optional substituent is one or more of methyl, ethyl, propyl, propenyl, hydroxymethyl and methoxymethyl,

R₂ and R₃ are independently selected from H, methyl,

15 R₄ and R₅ are independently selected from H, methyl, or are are joined to one another to form a C3-C6 cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached, optionally a C4 or C5 cycloalkyl that includes the carbon to which they are attached

R₆ is H or methyl,

20 R₇ is selected from optionally substituted phenyl, indazole, thiophene, or pyrazole, wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C3-C6 cycloalkyl, C1-C6 heterocycloalkyl, C1-C6 alkoxy, halo-substituted C1-C6 alkoxy, C1-C6 alkylamine, amido, cyano or halo,

W is N or C

X is CH or N

25 Z is C or NH

Y is N or CR₉, wherein R₉ is phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; C(O)NR'R''; or NR'R'';

wherein R' and R'' are independently selected from H, C1-C6 alkyl, C3-C7 cycloalkyl, C3-C7 heterocycloalkyl wherein the heteroatom is N or O, or wherein R' and R'' are joined to one another to form a C2-C7 heterocycloalkyl that includes the N to which they are attached, wherein the heterocycloalkyl is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH₂OH-substituted, or acetyl-substituted.

35 14. A compound according to claim 12 or 13, wherein Y is CR₉, wherein R₉ is C(O)NR'R'' and wherein wherein R' and R'' are joined to one another to form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine that includes the N to which they are attached,

wherein the piperidine, pyrrolidine, piperazine or morpholine is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH₂OH-substituted, or acetyl-substituted.

- 5 15. A compound according to claim 1 that is:
- (*R*)-5-Bromo-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 10 6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one
- 3-((1-(3-Cyclobutylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one
- 15 3-((1-(3-Cyclopentylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one
- (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(2-methyl-3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one
- 20 (*R*)-*N*-(3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)phenyl)acetamide
- (*R*)-3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzamide
- 25 (*R*)-5-(Furan-2-yl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridin-2(1*H*)-one
- 30 (*R*)-4-Chloro-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one
- (*R*)-4-(Dimethylamino)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one
- 35 (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenyl-4-(prop-1-en-2-yl)pyridine-2(1*H*)-one
- (*R*)-Ethyl 1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate
- 40 (*R,S*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(2-methyl-1,2,3,4-tetrahydronaphthalene-2-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide
- 45 (*R,S*)-1-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one
- (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(1-methyl-1*H*-indazol-7-yl)pyrimidin-4(3*H*)-one
- 50 (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3*H*)-one

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one

5 1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one

1-(((*R*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N,N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide

10 1-(((*R*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one

1-(((*R*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one

15 1-(((*R*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one

20 1-(((*R*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one

Ethyl 1-(((*R*)-7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate

25 1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid,

or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof.

30

16. A compound according to any one of claims 1-15 that is an inhibitor of USP19, preferably human USP19.

35 17. A pharmaceutical composition comprising a compound according to any one of claims 1-16 and a pharmaceutically acceptable carrier or diluent.

18. A compound according to any one of claims 1-16 or a pharmaceutical composition according to claim 17 for use in therapy.

40 19. A compound according to any one of claims 1-16 or a pharmaceutical composition according to claim 17 for use in a method of treating or preventing cancer, muscular atrophy or Parkinson's Disease, optionally wherein the muscular atrophy is cachexia or sarcopenia.