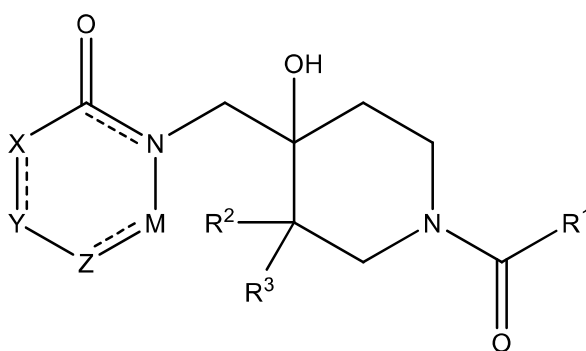


The established and ever growing connections between USP19 and numerous proteins involved in human pathologies indicate that small molecule inhibitors of USP19 may have broad therapeutic applications beneficial to human health. Insofar as is known however, no inhibitors targeting USP19 have been reported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

SUMMARY

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



(I)

wherein

R^1 is NR^aR^b or $NR^aCH_2R^b$, wherein R^a and R^b are independently selected from H, methyl, ethyl, propyl, CF_3 , optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted pyridinyl, pyrazole, imidazole, furan, benzodioxol, optionally substituted oxadiazole, thiazole, and thiophene, wherein the optional substituents are independently selected from halo, methyl, cyclopropyl and CN, optionally wherein R^1 is $NR^aCH_2R^b$ and the methylene group is substituted with CF_3 ; or wherein R^1 is NR^aR^b and R^a and R^b together form an optionally substituted C3-C9 heterocycle together with the N to which they are attached;

R^2 and R^3 are independently selected from H, and C1-C6 alkyl, or together form a C3-C6 cycloalkyl or C3-C6 heterocycloalkyl with the carbon to which they attached;

X is CR^{4a},

wherein R^{4a} is selected from H, optionally substituted C1-C6 alkyl and halo;

Y is CR⁵,

wherein R⁵ is selected from H, halo, optionally substituted C1-C6 alkyl,

optionally substituted C3-C6 cycloalkyl, optionally substituted C5-C8 aryl, optionally substituted C6-C9 arylalkyl, optionally substituted C3-C8 heteroaryl, CH₂OH, NR'R'', NS(O)R'R'', SO₂R', C(O)R', COR', C(O)OR', C(O)NR'R'', OR', wherein R' and R'' are independently selected from H, C1-C6 alkyl, C5-C8 aryl, C6-C9 arylalkyl, and C3-C8 heteroaryl;

Z is N or CR⁷,

wherein R⁷ is selected from H, halo, C1-C6 alkyl, C2-C6 alkene, C2-C6 alkyne, C3-C6 cycloalkyl, optionally substituted C3-C6 heterocycloalkyl, C5-C8 aryl, C6-C9 arylalkyl, C3-C8 heteroaryl, CN, C(O)OR^c, CONR^cR^d, NR^cR^d, NS(O)R^cR^d, S(O)(R^c)NR^d, SOR^c, SO₂R^c, and SR^c, wherein R^c and R^d are independently H, C1-C6 alkyl, C3-C6 cycloalkyl, C5-C6 aryl, C6-C9 arylalkyl, C3-C6 heteroaryl, CN, COOH, or COCH₃ or R^c and R^d together form an optionally substituted C3-C7 heterocycle together with the heteroatom to which they are attached;

M is CH or C-CH₃;

and

the ring including X, Y and Z is aromatic;

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

In a second aspect, the present disclosure provides a compound according to formula (I) as defined in claim 1 selected from:

N-Benzyl-4-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-hydroxy-*N*-methylpiperidine-1-carboxamide

N-(Cyclohexylmethyl)-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide

N-Benzyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxamide

- 10-((5-(Dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N,N*-dimethyl-7-azaspiro[4.5]decane-7-carboxamide
- 5 *N*-Benzyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide
- 1-((10-Hydroxy-7-(3-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N,N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide
- 10 *N*-Cyclohexyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide
- 1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylthio)-4-phenylpyridin-2(1*H*)-one
- 15 1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylsulfinyl)-4-phenylpyridin-2(1*H*)-one
- 20 1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylsulfonyl)-4-phenylpyridin-2(1*H*)-one
- 1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(*S*-methylsulfonimidoyl)-4-phenylpyridin-2(1*H*)-one
- 25 1-((10-Hydroxy-7-((*R*)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(*S*-methylsulfonimidoyl)-4-phenylpyridin-2(1*H*)-one
- 5-((Dimethyl(oxo)- λ^6 -sulfaneylidene)amino)-1-((10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 30 *N*-Benzyl-10-hydroxy-10-((2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 *N*-Benzyl-8-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxamide
- 40 *N*-Benzyl-4-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxamide
- 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(2,2,2-trifluoroethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 45 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-2-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-((4-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxamide
- 50

- 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-3-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 *N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyridin-3-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyridin-4-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10 *N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyrrolidin-1-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((4-morpholino-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 15 *N*-Benzyl-10-hydroxy-10-((4-(1-methyl-1*H*-pyrazol-4-yl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((4-(1-methyl-1*H*-pyrazol-5-yl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 20 3-((10-Hydroxy-7-(2-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 25 3-((10-Hydroxy-7-((*R*)-2-methylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-isopropylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 30 3-((7-(3-Azabicyclo[3.1.0]hexane-3-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((*S*)-10-Hydroxy-7-((*S*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-(((*S*)-10-Hydroxy-7-((*R*)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((*S*)-10-Hydroxy-7-((*S*)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 3-(((*S*)-10-Hydroxy-7-((*S*)-2-phenylpyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 (*S*)-10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(thiophen-2-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- (*S*)-*N*-(4-Cyanobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 50

- (S)-N-(3-Fluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 (S)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-N-((5-Cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10 (S)-N-(Furan-2-ylmethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 6-Chloro-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 15 (S)-3-((10-Hydroxy-7-(3-(trifluoromethyl)azetidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 6-Cyclopropyl-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 20 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(pyrrolidin-1-yl)pyrimidin-4(3H)-one
- 25 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1H-pyrazol-5-yl)pyrimidin-4(3H)-one
- 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4(3H)-one
- 30 6-(Dimethylamino)-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 3-(((10S)-10-Hydroxy-7-(3-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 35 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 40 3-((7-(3-(Cyclopropylmethyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 3-((7-(3-Cyclobutylmorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 45 3-((10-Hydroxy-7-(3-(methoxymethyl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- N-(Furan-3-ylmethyl)-10-hydroxy-N-methyl-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
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- 3-((10-Hydroxy-7-(2-methylpyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
N-Cyclobutyl-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 3-((10-Hydroxy-7-(3-(thiophen-2-yl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-((10-Hydroxy-7-(6-oxa-1-azaspiro[3.4]octane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-((7-(3-Cyclopropylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 10-Hydroxy-*N*-(isothiazol-5-ylmethyl)-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 *N*-((3-Fluorocyclobutyl)methyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 3-((7-(2,2-Dimethylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-((7-(4-(Difluoromethyl)piperidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 *N*-(Furan-2-ylmethyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 45 3-((7-(2-Oxa-5-azabicyclo[4.1.0]heptane-5-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10-Hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-3-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 3-((10-Hydroxy-7-(2-(pyridin-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(3-(1*H*-Pyrrol-1-yl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- N*-(1-Cyclopropylethyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 3-((7-(3-Cyclopropylmorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(pyridin-4-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

- 3-((10-Hydroxy-7-(5-azaspiro[2.5]octane-5-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 5 *N*-(3-Cyanobenzyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 3-((7-(3-Cyclopropylazetidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-((7-(2,2-Difluoromorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- N*-(2-Fluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 15 *N*-(1-(Furan-3-yl)ethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 20 10-Hydroxy-*N*-((1-methylcyclopropyl)methyl)-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-(3-Cyanobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 *N*-(4-(Cyanomethyl)benzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-((5,6-Dihydro-2*H*-pyran-3-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 *N*-((1,3-Dihydroisobenzofuran-5-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 3-((10-Hydroxy-7-(4-oxa-1-azaspiro[5.5]undecane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(3-(Difluoromethyl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 3-((10-Hydroxy-7-(3-(trifluoromethyl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(2-Cyclopropylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 3-((10-Hydroxy-7-((*S*)-2-(isoxazol-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (2*S*)-1-(10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carbonyl)-*N,N*-dimethylpyrrolidine-2-carboxamide
- 50

- 3-((10-Hydroxy-7-((*S*)-2-(thiophen-2-ylmethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 5 3-((7-((*S*)-2-(1*H*-1,2,4-Triazol-5-yl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-((*S*)-2-(5-methyl-1*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-((10-Hydroxy-7-((*S*)-2-(4-isopropoxyloxazol-2-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(2-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-((10-Hydroxy-7-(2-(3-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(4-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 3-((10-Hydroxy-7-(2-(pyridin-3-yl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 25 3-((7-(2-Cyclopropylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(2-Cyclobutylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 30 3-((10-Hydroxy-7-(2-(methoxymethyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((*S*)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-(((*S*)-7-((*R*)-4-Acetyl-2-phenylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 2-((10-Hydroxy-7-((*R*)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-phenylpyridazin-3(2*H*)-one
- 3-(((*S*)-10-Hydroxy-7-((*R*)-4-methyl-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 6-Chloro-3-(((*S*)-7-((*R*)-3-(4-fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 1-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-*N,N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide
- 50

- 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one
- 5 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one
- 1-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 10 1-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 1-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 15 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(pyrrolidin-1-yl)pyrimidin-4(3*H*)-one
- 20 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one
- 25 6-Cyclopropyl-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 3-(((S)-7-((R)-3-(1*H*-Benzo[d]imidazol-2-yl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 30 (S)-10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-((R)-2,2,2-trifluoro-1-phenylethyl)-7-azaspiro[4.5]decane-7-carboxamide
- (R)-3-((4-Hydroxy-1-(3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-((5-Hydroxy-2-((R)-3-phenylmorpholine-4-carbonyl)-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (R)-3-((4-Hydroxy-1-(2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 3-((5-Hydroxy-2-((R)-2-phenylpiperazine-1-carbonyl)-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 (S)-3-((10-Hydroxy-7-(2-phenylpyrazolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-methylpyrimidin-4(3*H*)-one
- 50

- (S)-N-(2,3-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 (S)-N-(2,6-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-N-(2,4-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10 (S)-N-(3,4-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 15 3-((9-Hydroxy-6-((*R*)-3-phenylmorpholine-4-carbonyl)-6-azaspiro[3.5]nonan-9-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((9-Hydroxy-6-((*R*)-2-phenylpiperazine-1-carbonyl)-6-azaspiro[3.5]nonan-9-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 (S)-N-((3,3-Difluorocyclobutyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-N-(1,1,1,3,3,3-Hexafluoropropan-2-yl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 (S)-10-Hydroxy-10-((2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-N-((*R*)-2,2,2-trifluoro-1-phenylethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 3-(((S)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (S)-N-((1-Fluorocyclopropyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 (S)-N-((1-Fluorocyclobutyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-N-(Cyclopropylmethyl)-10-hydroxy-N-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 40 6-(2-Fluorophenyl)-3-(((S)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 45 6-(3-Fluorophenyl)-3-(((S)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 6-(4-Fluorophenyl)-3-(((S)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 50 3-(((S)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3*H*)-one

- 6-(Dimethylamino)-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 5 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(methylamino)pyrimidin-4(3H)-one
- 3-(((S)-7-((R)-2-(3-Fluorophenyl)piperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 10 3-(((S)-5-Hydroxy-2-((R)-2-phenylpiperazine-1-carbonyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 15 3-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenyl-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 20 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-methoxypyrimidin-4(3H)-one
- 3-(((S)-5-Hydroxy-2-((R)-3-phenylmorpholine-4-carbonyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 25 4-Chloro-1-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyridin-2(1H)-one
- 4-Cyclopropyl-1-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyridin-2(1H)-one
- 30 1-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(1-methyl-1H-pyrazol-5-yl)pyridin-2(1H)-one
- 35 1-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one
- 1-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(pyrrolidin-1-yl)pyridin-2(1H)-one
- 40 5-Fluoro-1-(((10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1H)-one
- 3-Fluoro-1-(((10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1H)-one
- 45 (S)-3-(((10-Hydroxy-7-(3-phenylthiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 50 3-(((10S)-10-Hydroxy-7-(1-imino-1-oxido-3-phenyl-1 λ^6 -thiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one

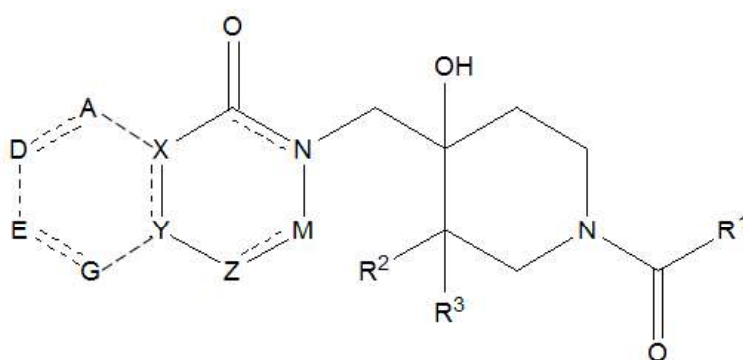
(S)-3-((7-(1,1-Dioxido-3-phenylthiomorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one

3-(((10S)-10-Hydroxy-7-(2-(4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one, and

3-(((10S)-10-Hydroxy-7-(1-oxido-3-phenylthiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one,

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

In a first example is provided a compound of formula (I):



(I)

15 wherein

R^1 is optionally substituted C1-C6 alkyl, optionally substituted C4-C10 alkylcycloalkyl, optionally substituted C6-C10 alkylaryl, optionally substituted C5-C8 aryl, optionally substituted C3-C8 heteroaryl, optionally substituted C3-C8 heterocycloalkyl, NR^aR^b , $NR^aCH_2R^b$, OR^a , or OCH_2R^a , wherein R^a and R^b are independently selected from H, C1-C6
20 alkyl, CF_3 , optionally substituted C3-C6 cycloalkyl, optionally substituted C5-C8 aryl, optionally substituted C6-C9 arylalkyl, and optionally substituted C2-C8 heteroaryl, or wherein R^1 is NR^aR^b and R^a and R^b together form an optionally substituted C2-C9 heterocycle together with the N to which they are attached;

25 R^2 and R^3 are independently selected from H, and C1-C6 alkyl, or together form a C3-C6 cycloalkyl or heterocycloalkyl with the carbon to which they are attached;

X is absent, C, CR^{4a} , $CR^{4a}R^{4b}$, N, NR^{4a} , or $C=O$,

wherein R^{4a} and R^{4b} are independently selected from H, optionally substituted C1-C6

30 alkyl or halo;

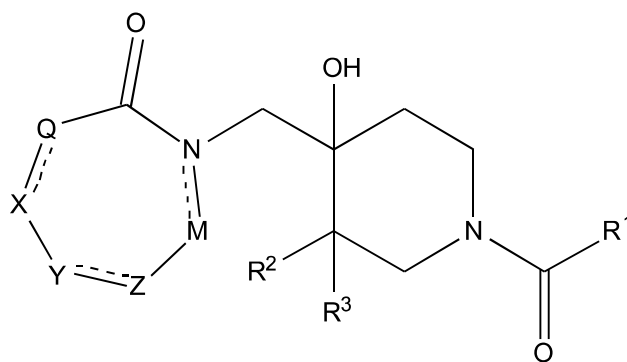
E is CR¹⁰, CHR¹⁰, N, NR¹⁰, S, or O,

wherein R¹⁰ is selected from H, halo, C1-C6 alkyl, C3-C6 cycloalkyl, C5-C8 aryl, C6-C9 arylalkyl, C4-C8 heteroaryl, SR^x, OR^x, NR^xR^y, and NS(O)R^xR^y, S(O)(R^x)NR^y, wherein R^x and R^y are independently selected from H, C1-C6 alkyl, CF₃, C3-C6 cycloalkyl, C5-C8 aryl, C6-C9 arylalkyl, C4-C8 heteroaryl, COOH, amido, cyano, C2-C6 alkene, C2-C6 alkyne, or wherein R^x and R^y together form an optionally substituted C4-C6 heterocycloalkyl together with the nitrogen to which they are attached;

or A, D, E and G are all absent, and X, Y, Z and M are defined above, and optionally wherein both X and M are absent, or optionally wherein Y and Z together form an optionally substituted C5-C6 aryl or C5-C6 heteroaryl fused ring or Z and M together form an optionally substituted C5-C6 aryl or C5-C6 heteroaryl fused ring;

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

In a second example is provided a compound according to formula (Ia):



(Ia)

wherein Q is selected from CR¹¹, CR¹¹R¹², NR¹¹ or O, where R¹¹ and R¹² are independently selected from H, OH, C1-C6 alkyl, CF₃, C3-C6 cycloalkyl, optionally substituted C5-C8 aryl, C4-C8 heteroaryl, or wherein R¹¹ and R¹² together form an optionally substituted C3-C5 carbocycle together with the C to which they are attached,

and wherein each of X, Y, Z and M are present and as defined above, wherein the ring QXYZM is aliphatic or aromatic, preferably aliphatic;

and wherein R¹, R², and R³ are as defined above;

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

In a third aspect is provided a pharmaceutical composition comprising a compound as described herein, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, 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. Knockout of USP19 by RNAi leads to p27^{Kip1} accumulation and inhibition of cell proliferation (Lu Y. *et al.*, *PLoS ONE* (2011), 6, e15936). USP19 was also found to interact with the inhibitors of apoptosis (IAPs) including c-IAP1 and c-IAP2 (Mei Y. *et al.*, *J. Biol. Chem.* (2011), 286, 35380-35387). Knockdown of USP19 decreases the total levels of these c-IAPs whilst overexpression increases the levels of both BIRC2/cIAP1 and BIRC3/cIAP2. Knockdown of USP19 also enhances TNF α -induced caspase activation and apoptosis in a BIRC2/c-IAP1 and BIRC3/c-IAP2 dependent manner. USP19 has also been recently implicated in the Wnt signalling pathway by stabilising the coreceptor LRP6 (Perrody E. *et al.*, *eLife* (2016), 5, e19083) and in the DNA repair processes, most particularly chromosomal stability and integrity, by regulating the HDAC1 and HDAC2 proteins (Wu M. *et al.*, *Oncotarget* (2017), 8, 2197-2208).

In vivo studies have also demonstrated that mice lacking the USP19 gene (USP19 KO mice) exhibited a decrease in fat mass when fed a high-fat diet (Coyne E. *et al.*, *Diabetologia* (2019), 62, 136-146, which is incorporated herein by reference). USP19 KO mice also exhibited greater glucose tolerance and higher insulin sensitivity when fed a high-fat diet.

USP19 is also implicated in muscular atrophy, muscle-wasting syndromes and other skeletal muscle atrophy disorders (Wing S., *Int. J. Biochem. Cell Biol.* (2013), 45, 2130-2135; Wing S. *et al.*, *Int. J. Biochem. Cell Biol.* (2016), 79, 426-468; Wiles B. *et al.*, *Mol. Biol. Cell* (2015), 26, 913-923; Combaret L. *et al.*, *Am. J. Physiol. Endocrinol. Metab.* (2005), 288, E693-700). This was supported for instance by studies which demonstrated that USP19-silencing induced the expression of myofibrillar proteins and promoted myogenesis (Sundaram P. *et*

al., *Am. J. Physiol. Endocrinol. Metab.* (2009), 297, E1283-90; Ogawa M. *et al.*, *J. Biol. Chem.* (2011), 286, 41455-41465; Ogawa M. *et al.*, *J. Endocrinol.* (2015), 225, 135-145).

Knockout studies have demonstrated that mice lacking the USP19 gene were resistant to muscle wasting in response to both glucocorticoids, a common systemic cause of muscle atrophy, as well as in response to denervation, a model of disuse atrophy (Bedard N. *et al.*, *FASEB J.* (2015), 29, 3889-3898, which is incorporated herein by reference).

The compounds according to the disclosure are able to selectively inhibit USP19 activity.

The compounds of the disclosure are therefore suitable for use in methods of treatment. Indications suitable for treatment with compounds of the disclosure include: the treatment and prevention of cancer and neoplastic conditions; immunological and inflammatory conditions for example by promoting antiviral immune response; treatment and prevention of muscular atrophy, for example cachexia and sarcopenia; treatment and prevention of obesity; treatment and prevention of insulin resistance, for example diabetes; treatment and prevention of neurodegenerative diseases including Parkinson's disease and other prion-based disorders.

In another aspect, the present disclosure provides a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt as described herein or a pharmaceutical composition as described herein for use in therapy. In yet another aspect, the present disclosure provides a use of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating muscular atrophy. Therefore, in a further example, is provided a compound according to the first or second example, or a pharmaceutical composition according to the third example, for use in therapy.

In a further example, is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing cancer. In certain preferred examples the cancer to be treated is breast cancer or neuroblastoma.

In a further example is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing muscular atrophy, optionally cachexia or sarcopenia.

In a further example is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing obesity.

In a further example is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing insulin resistance.

- 5 In a further example is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing type II diabetes.

- 10 In a further example is provided a compound according to the first or second example or a pharmaceutical composition according to the third example for use in a method of treating or preventing Parkinson's Disease.

- 15 In a further example is provided a method of treating cancer comprising administering to a subject an effective amount of a compound according to the first or second example or a pharmaceutical composition according to the third example.

- 20 In a further example is provided a method of treating muscular atrophy comprising administering to a subject an effective amount of a compound according to the first or second example or a pharmaceutical composition according to the third example.

- In a further example is provided a method of treating Parkinson's Disease comprising administering to a subject an effective amount of a compound according to the first or second example or a pharmaceutical composition according to the third example.

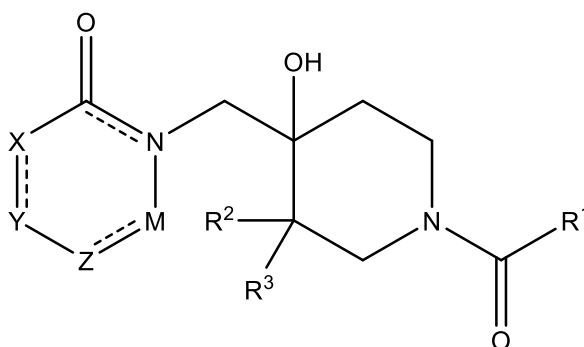
- 25 The compounds may be used as monotherapy or as combination therapy with radiation and/or additional therapeutic agents.

- 30 Other preferred examples of the compounds provided herein 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 example or example as defined herein may be combined with any other example(s) or example(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.

Claims:

1. A compound of formula (I):



(I)

wherein

R^1 is NR^aR^b or $NR^aCH_2R^b$, wherein R^a and R^b are independently selected from H, methyl, ethyl, propyl, CF_3 , optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted pyridinyl, pyrazole, imidazole, furan, benzodioxol, optionally substituted oxadiazole, thiazole, and thiophene, wherein the optional substituents are independently selected from halo, methyl, cyclopropyl and CN,

optionally wherein R^1 is $NR^aCH_2R^b$ and the methylene group is substituted with CF_3 ;

or

wherein R^1 is NR^aR^b and R^a and R^b together form an optionally substituted C3-C9 heterocycle together with the N to which they are attached;

R^2 and R^3 are independently selected from H, and C1-C6 alkyl, or together form a C3-C6 cycloalkyl or C3-C6 heterocycloalkyl with the carbon to which they attached;

X is CR^{4a} ,

wherein R^{4a} is selected from H, optionally substituted C1-C6 alkyl and halo;

Y is CR^5 ,

wherein R^5 is selected from H, halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C6 cycloalkyl, optionally substituted C5-C8 aryl, optionally substituted C6-C9 arylalkyl, optionally substituted C3-C8 heteroaryl, CH₂OH, NR'R'', NS(O)R'R'', SO₂R', C(O)R', COR', C(O)OR', C(O)NR'R'', OR', wherein R' and R'' are independently selected from H, C1-C6 alkyl, C5-C8 aryl, C6-C9 arylalkyl, and C3-C8 heteroaryl;

Z is N or CR⁷,

wherein R⁷ is selected from H, halo, C1-C6 alkyl, C2-C6 alkene, C2-C6 alkyne, C3-C6 cycloalkyl, optionally substituted C3-C6 heterocycloalkyl, C5-C8 aryl, C6-C9 arylalkyl, C3-C8 heteroaryl, CN, C(O)OR^c, CONR^cR^d, NR^cR^d, NS(O)R^cR^d, S(O)(R^c)NR^d, SOR^c, SO₂R^c, and SR^c, wherein R^c and R^d are independently H, C1-C6 alkyl, C3-C6 cycloalkyl, C5-C6 aryl, C6-C9 arylalkyl, C3-C6 heteroaryl, CN, COOH, or COCH₃ or R^c and R^d together form an optionally substituted C3-C7 heterocycle together with the heteroatom to which they are attached;

M is CH or C-CH₃;

and

the ring including X, Y and Z is aromatic;

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

2. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt of claim 1, wherein R¹ is NR^aR^b and R^a and R^b form an optionally substituted heterocycle together with the N to which they are attached, wherein each of the one or more optional substituents of the heterocycle is independently selected from C1-C4 alkyl, halo, CF₃, hydroxyl, NH₂, NO₂, CH₂OH, CH₂OCH₃, phenyl, benzyl, and oxo.
3. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt of claim 1, wherein R¹ is NR^aR^b and R^a and R^b form a heterocycle together with the N to which they are attached, wherein the heterocycle is selected from pyrrolidinyl, pyrimidinyl, morpholino, piperazinyl, and thiomorpholino,

wherein the heterocycle is optionally substituted with one or more substituents independently selected from CH₂CF₃, oxo, thiophene, and phenyl optionally substituted with F or CF₃.

4. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 5 pharmaceutically acceptable salt of claim 3, wherein R^a and R^b together with the N to which they are attached form a morpholino group or a piperazinyl group, wherein the morpholino group or piperazinyl group is substituted with phenyl or fluoro-phenyl.
5. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 10 pharmaceutically acceptable salt of claim 1, wherein R¹ is NR^aCH₂R^b, wherein R^a is H or methyl and R^b is selected from cyclobutyl optionally substituted with F, cyclohexyl, phenyl optionally substituted with F, furan and thiophene,
 optionally wherein the methylene group is substituted with CF₃.
6. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 15 pharmaceutically acceptable salt of claim 5, wherein R^b is phenyl or fluoro-substituted phenyl.
7. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 pharmaceutically acceptable salt of any one of claims 1-6, wherein R² and R³ are
 20 independently selected from H, methyl and ethyl, or together form optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted pyrrolidine, optionally substituted tetrahydropyran or optionally substituted tetrahydrofuran together with the carbon to which they attached.
8. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 25 pharmaceutically acceptable salt according to claim 7, wherein R² and R³ are independently selected from H, and methyl.
9. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or
 30 pharmaceutically acceptable salt according to claim 7, wherein R² and R³ together form cyclohexyl, cyclopentyl or cyclobutyl together with the carbon to which they attached, preferably cyclopentyl.

10. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt of claim 1, wherein R^{4a} is H, R⁵ is Cl or phenyl optionally substituted with fluoro, and Z is N or CR⁷.
11. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt of claim 1, wherein Z is N or CR⁷, where R⁷ is H.
12. A compound according to formula (I) as defined in claim 1 selected from:

N-Benzyl-4-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-hydroxy-*N*-methylpiperidine-1-carboxamide

N-(Cyclohexylmethyl)-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide

N-Benzyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxamide

10-((5-(Dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N,N*-dimethyl-7-azaspiro[4.5]decane-7-carboxamide

N-Benzyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide

1-((10-Hydroxy-7-(3-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N,N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide

N-Cyclohexyl-10-((5-(dimethylcarbamoyl)-2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-10-hydroxy-*N*-methyl-7-azaspiro[4.5]decane-7-carboxamide

1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylthio)-4-phenylpyridin-2(1*H*)-one

1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylsulfinyl)-4-phenylpyridin-2(1*H*)-one

1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(methylsulfonyl)-4-phenylpyridin-2(1*H*)-one

1-((10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(*S*-methylsulfonimidoyl)-4-phenylpyridin-2(1*H*)-one

1-((10-Hydroxy-7-((*R*)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(*S*-methylsulfonimidoyl)-4-phenylpyridin-2(1*H*)-one

5-((Dimethyl(oxo)-λ⁶-sulfaneylidene)amino)-1-((10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one

- N*-Benzyl-10-hydroxy-10-((2-oxo-4-phenylpyridin-1(2*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 *N*-Benzyl-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-8-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-8-hydroxy-5-azaspiro[2.5]octane-5-carboxamide
- 10 *N*-Benzyl-4-((4-(2-fluorophenyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-4-hydroxy-3,3-dimethylpiperidine-1-carboxamide
- 15 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(2,2,2-trifluoroethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-2-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 20 *N*-Benzyl-10-((4-chloro-6-oxopyrimidin-1(6*H*)-yl)methyl)-10-hydroxy-7-azaspiro[4.5]decane-7-carboxamide
- 10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-3-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 *N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyridin-3-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyridin-4-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 *N*-Benzyl-10-hydroxy-10-((6-oxo-4-(pyrrolidin-1-yl)pyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-Benzyl-10-hydroxy-10-((4-morpholino-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 *N*-Benzyl-10-hydroxy-10-((4-(1-methyl-1*H*-pyrazol-4-yl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 40 *N*-Benzyl-10-hydroxy-10-((4-(1-methyl-1*H*-pyrazol-5-yl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 45 3-((10-Hydroxy-7-(2-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-((*R*)-2-methylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 50 3-((10-Hydroxy-7-(2-isopropylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

- 3-((7-(3-Azabicyclo[3.1.0]hexane-3-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 5 3-(((S)-10-Hydroxy-7-((S)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-(((S)-10-Hydroxy-7-((S)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-(((S)-10-Hydroxy-7-((S)-2-phenylpyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (S)-10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(thiophen-2-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 20 (S)-*N*-(4-Cyanobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-*N*-(3-Fluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 (S)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-*N*-((5-Cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 (S)-*N*-(Furan-2-ylmethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 6-Chloro-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- (S)-3-((10-Hydroxy-7-(3-(trifluoromethyl)azetidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 6-Cyclopropyl-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(pyrrolidin-1-yl)pyrimidin-4(3*H*)-one
- 45 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one

- 3-(((S)-10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one
- 5 6-(Dimethylamino)-3-(((S)-10-hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 3-(((10*S*)-10-Hydroxy-7-(3-(trifluoromethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(3-(Cyclopropylmethyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-((7-(3-Cyclobutylmorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 3-((10-Hydroxy-7-(3-(methoxymethyl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- N*-(Furan-3-ylmethyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 25 3-((10-Hydroxy-7-(2-methylpyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
N-Cyclobutyl-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 3-((10-Hydroxy-7-(3-(thiophen-2-yl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(6-oxa-1-azaspiro[3.4]octane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-((7-(3-Cyclopropylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 10-Hydroxy-*N*-(isothiazol-5-ylmethyl)-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-((3-Fluorocyclobutyl)methyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 45 3-((7-(2,2-Dimethylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(4-(Difluoromethyl)piperidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 50

- N*-(Furan-2-ylmethyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 3-((7-(2-Oxa-5-azabicyclo[4.1.0]heptane-5-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 10-Hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-(pyridin-3-ylmethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 15 3-((10-Hydroxy-7-(2-(pyridin-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(3-(1*H*-Pyrrol-1-yl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 *N*-(1-Cyclopropylethyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 3-((7-(3-Cyclopropylmorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 25 3-((10-Hydroxy-7-(2-(pyridin-4-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 30 3-((10-Hydroxy-7-(5-azaspiro[2.5]octane-5-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- N*-(3-Cyanobenzyl)-10-hydroxy-*N*-methyl-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 3-((7-(3-Cyclopropylazetidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(2,2-Difluoromorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 *N*-(2-Fluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-(1-(Furan-3-yl)ethyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 45 10-Hydroxy-*N*-((1-methylcyclopropyl)methyl)-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- N*-(3-Cyanobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 50 *N*-(4-(Cyanomethyl)benzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide

- N*-((5,6-Dihydro-2*H*-pyran-3-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 *N*-((1,3-Dihydroisobenzofuran-5-yl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10 3-((10-Hydroxy-7-(4-oxa-1-azaspiro[5.5]undecane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(3-(Difluoromethyl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-((10-Hydroxy-7-(3-(trifluoromethyl)morpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-(2-Cyclopropylpyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 3-((10-Hydroxy-7-((*S*)-2-(isoxazol-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (2*S*)-1-(10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carbonyl)-*N,N*-dimethylpyrrolidine-2-carboxamide
- 25 3-((10-Hydroxy-7-((*S*)-2-(thiophen-2-ylmethyl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((7-((*S*)-2-(1*H*-1,2,4-Triazol-5-yl)pyrrolidine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 30 3-((10-Hydroxy-7-((*S*)-2-(5-methyl-1*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 35 3-((10-Hydroxy-7-((*S*)-2-(4-isopropylloxazol-2-yl)pyrrolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(2-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 40 3-((10-Hydroxy-7-(2-(3-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(4-methoxyphenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 3-((10-Hydroxy-7-(2-(pyridin-3-yl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

- 3-((7-(2-Cyclopropylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 5 3-((7-(2-Cyclobutylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-((10-Hydroxy-7-(2-(methoxymethyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 10 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 3-(((S)-7-((R)-4-Acetyl-2-phenylpiperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 2-((10-Hydroxy-7-((R)-3-phenylmorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-phenylpyridazin-3(2*H*)-one
- 20 3-(((S)-10-Hydroxy-7-((R)-4-methyl-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 6-Chloro-3-(((S)-7-((R)-3-(4-fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 25 1-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-*N,N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide
- 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one
- 30 3-(((S)-7-((R)-3-(4-Fluorophenyl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one
- 1-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 35 1-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 40 1-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one
- 45 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(pyrrolidin-1-yl)pyrimidin-4(3*H*)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one
- 50

- 6-Cyclopropyl-3-(((*S*)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one
- 5 3-(((*S*)-7-((*R*)-3-(1*H*-Benzo[*d*]imidazol-2-yl)morpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (*S*)-10-Hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-*N*-((*R*)-2,2,2-trifluoro-1-phenylethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 10 (*R*)-3-((4-Hydroxy-1-(3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 15 3-((5-Hydroxy-2-((*R*)-3-phenylmorpholine-4-carbonyl)-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (*R*)-3-((4-Hydroxy-1-(2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 20 3-((5-Hydroxy-2-((*R*)-2-phenylpiperazine-1-carbonyl)-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (*S*)-3-((10-Hydroxy-7-(2-phenylpyrazolidine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 25 3-(((*S*)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-methylpyrimidin-4(3*H*)-one
- (*S*)-*N*-(2,3-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 30 (*S*)-*N*-(2,6-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 35 (*S*)-*N*-(2,4-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (*S*)-*N*-(3,4-Difluorobenzyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 40 3-((9-Hydroxy-6-((*R*)-3-phenylmorpholine-4-carbonyl)-6-azaspiro[3.5]nonan-9-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- 45 3-((9-Hydroxy-6-((*R*)-2-phenylpiperazine-1-carbonyl)-6-azaspiro[3.5]nonan-9-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one
- (*S*)-*N*-((3,3-Difluorocyclobutyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6*H*)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide

- (S)-N-(1,1,1,3,3,3-Hexafluoropropan-2-yl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 5 (S)-10-Hydroxy-10-((2-oxo-4-phenylpyridin-1(2H)-yl)methyl)-N-((R)-2,2,2-trifluoro-1-phenylethyl)-7-azaspiro[4.5]decane-7-carboxamide
- 3-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-3-phenylmorpholine-4-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 10 (S)-N-((1-Fluorocyclopropyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- (S)-N-((1-Fluorocyclobutyl)methyl)-10-hydroxy-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 15 (S)-N-(Cyclopropylmethyl)-10-hydroxy-N-methyl-10-((6-oxo-4-phenylpyrimidin-1(6H)-yl)methyl)-7-azaspiro[4.5]decane-7-carboxamide
- 20 6-(2-Fluorophenyl)-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 6-(3-Fluorophenyl)-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 25 6-(4-Fluorophenyl)-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3H)-one
- 30 6-(Dimethylamino)-3-(((S)-10-hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3H)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-(methylamino)pyrimidin-4(3H)-one
- 35 3-(((S)-7-((R)-2-(3-Fluorophenyl)piperazine-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 40 3-((5-Hydroxy-2-((R)-2-phenylpiperazine-1-carbonyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 3-(((S)-4-Hydroxy-3,3-dimethyl-1-((R)-2-phenylpiperazine-1-carbonyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 45 3-(((S)-10-Hydroxy-7-((R)-2-phenyl-4-(2,2,2-trifluoroethyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3H)-one
- 3-(((S)-10-Hydroxy-7-((R)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-methoxypyrimidin-4(3H)-one
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3-((5-Hydroxy-2-((*R*)-3-phenylmorpholine-4-carbonyl)-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

5 4-Chloro-1-(((*S*)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyridin-2(1*H*)-one

4-Cyclopropyl-1-(((*S*)-10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyridin-2(1*H*)-one

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1-(((*S*)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(1-methyl-1*H*-pyrazol-5-yl)pyridin-2(1*H*)-one

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1-(((*S*)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2(1*H*)-one

1-(((*S*)-10-Hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-(pyrrolidin-1-yl)pyridin-2(1*H*)-one

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5-Fluoro-1-((10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one

3-Fluoro-1-((10-hydroxy-7-((*R*)-2-phenylpiperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenylpyridin-2(1*H*)-one

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(*S*)-3-((10-Hydroxy-7-(3-phenylthiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

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3-(((10*S*)-10-Hydroxy-7-(1-imino-1-oxido-3-phenyl-1 λ^6 -thiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

(*S*)-3-((7-(1,1-Dioxido-3-phenylthiomorpholine-4-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one

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3-(((10*S*)-10-Hydroxy-7-(2-(4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one, and

3-(((10*S*)-10-Hydroxy-7-(1-oxido-3-phenylthiomorpholine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one,

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

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12 or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or

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pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

14. A compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-12 or a pharmaceutical composition according to claim 13 for use in therapy.
- 5 15. Use of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-12 or a pharmaceutical composition according to claim 13 in the manufacture of a medicament for treating muscular atrophy.